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Prolactin: Structure, Function, and Regulation of Secretion

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Freeman, Marc E., Béla Kanyicska, Anna Lerant, and György Nagy. Prolactin: Structure, Function, and Regulation of Secretion. *Physiol Rev* 80: 1523–1631, 2000.—Prolactin is a protein hormone of the anterior pituitary gland that was originally named for its ability to promote lactation in response to the suckling stimulus of hungry young mammals. We now know that prolactin is not as simple as originally described. Indeed, chemically, prolactin appears in a multiplicity of posttranslational forms ranging from size variants to chemical modifications such as phosphorylation or glycosylation. It is not only synthesized in the pituitary gland, as originally described, but also within the central nervous system, the immune system, the uterus and its associated tissues of conception, and even the mammary gland itself. Moreover, its biological actions are not limited solely to reproduction because it has been shown to control a variety of behaviors and even play a role in homeostasis. Prolactin-releasing stimuli not only include the nursing stimulus, but light, audition, olfaction, and stress can serve a stimulatory role. Finally, although

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it is well known that dopamine of hypothalamic origin provides inhibitory control over the secretion of prolactin, other factors within the brain, pituitary gland, and peripheral organs have been shown to inhibit or stimulate prolactin secretion as well. It is the purpose of this review to provide a comprehensive survey of our current understanding of prolactin's function and its regulation and to expose some of the controversies still existing.

I. INTRODUCTION

Prolactin is a polypeptide hormone that is synthesized in and secreted from specialized cells of the anterior pituitary gland, the lactotrophs. The hormone was given its name based on the fact that an extract of bovine pituitary gland would cause growth of the crop sac and stimulate the elaboration of crop milk in pigeons or promote lactation in rabbits (1477). However, we now appreciate that prolactin has over 300 separate biological activities (184) not represented by its name. Indeed, not only does prolactin subserve multiple roles in reproduction other than lactation, but it also plays multiple homeostatic roles in the organism. Furthermore, we are now aware that synthesis and secretion of prolactin is not restricted to the anterior pituitary gland, but other organs and tissues in the body have this capability. Indeed, the multiple roles and sources of prolactin had led Bern and Nicoll (154) to suggest renaming it "omnipotin" or "versatilin."

In this review we integrate the burgeoning information on prolactin's structure (sect. II), synthesis and release from varying sources (sect. III), the intracellular mechanism of its action (sect. IV), its major biological functions (sect. V), and the patterns (sect. VI) and regulation of its secretion (sect. VII).

II. PROLACTIN CHEMISTRY AND MOLECULAR BIOLOGY

A. Prolactin: Gene, Primary Structure, and Species Specificity

Based on its genetic, structural, binding and functional properties, prolactin belongs to the prolactin/growth hormone/placental lactogen family [group I of the helix bundle protein hormones (195, 791)]. Genes encoding prolactin, growth hormone, and placental lactogen evolved from a common ancestral gene by gene duplication (1311). The divergence of the prolactin and growth hormone lineages occurred ~400 million years ago (357, 358). In the human genome, a single gene, found on chromosome 6, encodes prolactin (1363). The prolactin gene is 10 kb in size and is composed of 5 exons and 4 introns (357, 1772). Transcription of the prolactin gene is regulated by two independent promoter regions. The proximal 5,000-bp region directs pituitary-specific expression (160), while a more upstream promoter region is responsible for extrapituitary expression (159). The human prolactin cDNA is 914 nucleotides long and contains a 681-nucleotide open reading frame encoding the prolactin prohormone of 227 amino acids. The signal peptide contains 28 amino acids; thus the mature human prolactin is composed of 199 amino acids (1640).

The prolactin molecule is arranged in a single chain of amino acids with three intramolecular disulfide bonds between six cysteine residues (Cys^{4}-Cys^{11}, Cys^{58}-Cys^{174}, and Cys^{191}-Cys^{199} in humans) (357). The sequence homology can vary from the striking 97% among primates to as low as 56% between primates and rodents (1640). In rats (358) and mice (968), pituitary prolactin consists of 197 amino acids, whereas in sheep (1036), pigs (1035), cattle (1851), and humans (1624) it consists of 199 amino acids with a molecular mass of ~23,000 Da.

B. Secondary and Tertiary Structure of Prolactin

Studies on the secondary structure of prolactin have shown that 50% of the amino acid chain is arranged in α-helices, while the rest of it forms loops (169). Although it was predicted earlier (1311), there are still no direct data about the three-dimensional structure of prolactin. The tertiary structure of prolactin was predicted by homology modeling approach (635), based on the structural similarities between prolactin and other helix bundle proteins, especially growth hormone (2, 438). According to the current three-dimensional model, prolactin contains four long α-helices arranged in antiparallel fashion (2, 438).

C. Prolactin Variants

Although the major form of prolactin found in the pituitary gland is 23 kDa, variants of prolactin have been characterized in many mammals, including humans. Prolactin variants can be results of alternative splicing of the primary transcript, proteolytic cleavage and other post-translational modifications of the amino acid chain.

1. Alternative splicing

Alternative splicing of prolactin mRNA has been proposed as one source of the variants (1639, 1640). Indeed, evidence suggestive of the existence of an alternatively spliced prolactin variant of 137 amino acids has been described in the anterior pituitary (501, 1882). In addition,

alternative splicing involving retention of introns is also possible. However, alternative splicing is not considered a major source of prolactin variants.

2. Proteolytic cleavage

Of the cleaved forms that have been characterized, 14-, 16-, and 22-kDa prolactin variants have been most widely studied. The 14-kDa NH_2-terminal fragment is a posttranslational product of the prolactin gene that is processed in the hypothalamus and shares biological activity with the 16-kDa fragment (335, 1765). Both seem to possess a unique biological activity, which will be described later. The 16-kDa fragment [prolactin-(1—148)] was first described in rat pituitary extracts (1207) and has subsequently been found in mouse (1642) and human (1643) pituitary glands as well as in human plasma (1643). The 16-kDa prolactin is a product of kallikrein enzymatic activity. Kallikrein is an estrogen-induced, trypsin-like serine protease that is found in the Golgi cisternae and secretory granules of lactotrophs (1433). This enzyme will cleave rat prolactin in a thiol-dependent manner. Thiol alters the conformation of prolactin such that kallikrein recognizes it as a substrate. Treatment of native prolactin with carboxypeptidase-B results in a 22-kDa prolactin fragment [prolactin-(1—173)]. Surprisingly, this synthetic fragment can be detected in pituitary extracts by Western blot using an antiserum produced specifically against the 22-kDa prolactin fragment (45). It seems that the production and release of these proteolytic fragments from the pituitary gland is specific to female rats and sensitive to inhibition by dopamine (45). Although these and other fragments have been found in pituitary gland and serum, more work is required to determine their physiological significance since the possibility remains that they may be preparative artifacts (1640).

3. Other posttranslational modifications

Besides proteolytic cleavage, the majority of prolactin variants can be the result of other posttranslational processing of the mature molecule in the anterior pituitary gland or the plasma. These include dimerization and polymerization, phosphorylation, glycosylation, sulfation, and deamidation (1702).

A) DIMERIZATION AND POLYMERIZATION: MACROPROLACTINS. Dimerization and polymerization of prolactin or aggregation with binding proteins, such as immunoglobulins, by covalent and noncovalent bonds may result in high-molecular-weight forms. In general, the high-molecular-weight forms have reduced biological activity (1640). The role of prolactin-IgG macromolecular complexes in the detection and differential diagnosis of different prolactinemias is targeted primarily in clinical studies (299).

B) PHOSPHORYLATION. Phosphorylation of prolactin occurs within the secretory vesicle of lactotrophs just before exocytosis and involves esterification of hydroxyl groups of serine and threonine residues (670). Phosphorylated prolactin isoforms have been isolated from bovine (224) and murine (1337) pituitary glands. Phosphorylated isoforms of prolactin may constitute as much as 80% of total pituitary prolactin in cattle (938). Although phosphoprolactin has been shown to be secreted in vitro, it is not known if it is secreted into the plasma in vivo. The significance of phosphorylated and nonphosphorylated prolactins has been reviewed in detail (736). Phosphorylated prolactin has much lower biological activity than nonphosphorylated prolactin (1859). However, phosphorylated prolactin may subserve a unique role as an autocrine regulator of prolactin secretion since it suppresses the release of nonphosphorylated prolactin from GH_3 cells (768). Phosphorylation of prolactin as well as the relative ratio of phosphorylated to nonphosphorylated isoforms seems to be regulated throughout the estrous cycle (769), although the physiological relevance of this finding is not yet appreciated. However, novel data indicate that phosphorylated prolactin acts as an antagonist to the signal transduction pathways (362) and proliferative activities initiated by unmodified prolactin on Nb2 lymphoma cells (315). Further investigation is needed to determine the significance of phosphorylated prolactin in primary cells and tissues.

C) GLYCOSYLATION. Glycosylated prolactin has been found in the pituitary glands of a wide variety of mammalian, amphibian, and avian species (1640). The degree of glycosylation varies from 1 to 60% among species and may also vary between reproductive states within species (1640). The linkage of the carbohydrate moiety may be either through nitrogen (*N*-glycosylation) or oxygen (*O*-glycosylation). The carbohydrate residues of the oligosaccharide chain may contain varying ratios of sialic acid, fucose, mannose, and galactose that differ considerably between species, physiological, and pathological states (1640). Like other prolactin variants, glycosylation also lowers biological activity (1127, 1641) as well as receptor binding and immunologic reactivity of prolactins (740). Glycosylation also alters the metabolic clearance rate of prolactin (1641). Taken together, glycosylation of prolactin may play a role either in regulation of the biological activity or clearance of the molecule.

III. SITES OF SYNTHESIS AND SECRETION OF PROLACTIN

A. Anterior Pituitary Gland

1. Morphology of lactotrophs

The cells of the anterior pituitary gland which synthesize and secrete prolactin were initially described by

light microscopy using conventional staining techniques (753). These cells, designated lactotrophs or mammotrophs, comprise 20–50% of the cellular population of the anterior pituitary gland depending on the sex and physiological status of the animal. Lactotrophs were subsequently identified unequivocally by immunocytochemistry in the anterior pituitary gland of the mouse (109), rat (110, 1287), and human (111, 725, 1387) using species-specific prolactin antibodies. Ontogenetically, lactotrophs descend from the Pit-1-dependent lineage of pituitary cells, together with somatotrophs and thyrotrophs (348, 643, 1382, 1599).

The morphology and distribution of lactotrophs have been best described in the rat (1768), where prolactin-containing cells are sparsely distributed in the lateroventral portion of the anterior lobe and are present as a band adjacent to the intermediate lobe (1287). Their shapes are heterogeneous, appearing as either polyhedral or angular but at times rounded or oval (429). With the use of either velocity sedimentation at unit gravity (1650) or discontinuous Percoll gradients (1813) to separate cell populations, it has been shown that lactotrophs vary based on their secretory granule size and content (1650) as well as on the amount of prolactin and prolactin mRNA present (1813).

2. Functional heterogeneity of lactotrophs

Aside from morphological heterogeneity, lactotrophs display functional heterogeneity as well. Development of the reverse hemolytic plaque assay (572, 576, 1300) led to a more precise description of functional heterogeneity in lactotrophs (1090). Although prolactin is largely found and secreted from a distinct cell type in the pituitary gland, the lactotroph, both prolactin and growth hormone can also be secreted from the intermediate cell population called mammosomatotrophs (572, 574, 576, 1300). These bifunctional cells, which predominate in the pituitary of neonatal rats (770), differentiate into lactotrophs in the presence of estrogen (191). Mammosomatotrophs also differentiate into lactotrophs in pups in the presence of a maternal signal that appears in early lactation (1427) and is delivered to the pups through the mother's milk (1429).

There also appears to be functional heterogeneity among lactotrophs with regard to their regional distribution within the anterior lobe (1246) as well as to the nature of their responsiveness to secretagogues (188); that is, lactotrophs from the outer zone of the anterior lobe respond greater to thyrotrophin releasing hormone (TRH) than those of the inner zone, adjacent to the intermediate lobe of the pituitary gland (188). On the other hand, dopamine-responsive lactotrophs (84) are more abundant in the inner than the outer zone of the anterior pituitary. Surprisingly, functional heterogeneity is also reflected in the discordance between prolactin gene transcription and prolactin release in some lactotroph populations (296, 1562). Taken together, it is clear that lactotrophs are not homogeneous in their morphology, hormonal phenotype, distribution, or function.

B. Brain

The first observation that prolactin is produced in the brain was by Fuxe et al. (594) who found prolactin immunoreactivity in hypothalamic axon terminals. Prolactin immunoreactivity was subsequently found in the telencephalon in the cerebral cortex, hippocampus, amygdala, septum (433), caudate putamen (502, 737), brain stem (433, 737), cerebellum (1589), spinal cord (737, 1630), choroid plexi, and the circumventricular organs (1741).

1. Hypothalamus

Prolactin immunoreactivity is found within numerous hypothalamic areas in a variety of mammals (29, 677, 678, 737, 1321, 1630, 1741). Within the rat hypothalamus, prolactin immunoreactivity is detectable in the dorsomedial, ventromedial (676), supraoptic, and paraventricular (735) nuclei. Several approaches have been taken to prove that prolactin found in the hypothalamus is synthesized locally, independent of prolactin synthesis in the pituitary gland. Indeed, hypophysectomy has no effect on the amount of immunoreactive prolactin in the male hypothalamus and only diminishes but does not abolish the quantity of immunoreactive prolactin in the female rat hypothalamus (433).

With the use of conventional peptide mapping (434) and sequencing of a polymerase chain reaction (PCR) product of hypothalamic cDNA from intact and hypophysectomized rats (1882), it has been established that the primary structure of prolactin of hypothalamic and pituitary origin is identical. Thus it seems that the prolactin gene expressed in the rat hypothalamus is identical to the prolactin gene of the anterior pituitary (501, 1882).

Although the role of prolactin of hypothalamic origin in the central nervous system (CNS) is not apparent, it should be noted that the hypothalamus contains the appropriate proteolytic enzymes to cleave 23-kDa prolactin into 16- and 14-kDa fragments (435). We do not know if prolactin of neural origin exerts its central effect as a neurotransmitter, neuromodulator, or a central cytokine regulating vascular growth and/or glial functions. To ascribe a role for prolactin of neural origin is troublesome, in part, because it is difficult to differentiate between the effects of prolactin of pituitary versus hypothalamic origin in the CNS. One cause of these difficulties is that pituitary prolactin from the circulation bypasses the blood-brain barrier and enters the CNS through the choroid plexi of the brain ventricles. Coincidentally, choroid plexi have a very high density of prolactin receptors (prolactin-Rs) as demonstrated by autoradiography (1113,

1853, 1854), immunocytochemistry (1495), standard receptor binding assays (1242), reverse transcriptase PCR, and ribonuclease protection assay (590). Interestingly, prolactin enhances the expression of its own receptors in the choroid plexus (1113). Aside from passage from the blood to the cerebrospinal fluid by way of the choroid plexus, pituitary prolactin may also reach the brain by retrograde blood flow from the anterior pituitary to the hypothalamus (1192, 1351). Therefore, because the actions of prolactin in the CNS can be due to the hormone of pituitary or hypothalamic origin, in this review we refer to its effects in the CNS without attributing a source.

2. Regulation of hypothalamic prolactin synthesis

Some well-established stimulators of pituitary prolactin secretion also affect hypothalamic prolactin production. For example, ovarian steroids modulate hypothalamic synthesis and release of prolactin (436, 437). Approximately 33% of the prolactin immunoreactive neurons in the medial basal hypothalamus can be labeled with [^{3}H]estradiol (436), suggesting that these neurons have estrogen receptors. Ovariectomy lowers hypothalamic prolactin content, whereas estrogen replacement elevates it (436, 437). Of the known hypophysiotrophic factors, angiotensin II stimulates release of prolactin from hypothalamic fragments (437), and intracerebroventricular injection of vasoactive intestinal peptide will increase the amount of hypothalamic prolactin mRNA (212). However, other established stimulators of pituitary prolactin secretion such as TRH are without effect (437). Obviously, much more work is needed to establish the control of hypothalamic prolactin synthesis and release.

C. Placenta, Amnion, Decidua, and Uterus

The placenta, in addition to its bidirectional fetomaternal metabolic transport functions, has a wide array of endocrine functions as well. Among its many secretory products are a family of placental lactogens found in the rat (354, 393, 537, 744, 1487–1489, 1491, 1651), mouse (1605, 1896), hamster (874, 1662–1664), cow (46, 1612), pig (568), and human (728). The rat placenta produces a bewildering array of prolactin-like molecules that bear structural similarity to pituitary prolactin (1058, 1652). These placental lactogens (PL) or prolactin-like proteins (PLP) have been variously identified as PL-I, PL-II, PL-Im (mosaic), PL-Iv (variant) (349, 1487, 1490), or PLP-A, -B, -C, -D, -E, -F, and -G (356, 392, 851). In addition, the placenta contains a lactogen known as proliferin (PLF) (1056) and proliferin-related protein (PRP) (1057).

The decidua, on the other hand, produces a prolactin-like molecule, that is indistinguishable from pituitary prolactin in human (35, 342, 1475, 1707), but is somewhat dissimilar in rat (688). A novel member of this family is prolactin-like protein J (1752), which is produced by the decidua during early pregnancy. Each of these prolactin-like molecules can bind to the prolactin-R (755, 860), and their secretion is regulated by local decidual (638, 689, 729–731, 1745, 1746), but not hypothalamic (637) prolactin-releasing factors (PRF). Progesterone has also been identified as a potent stimulator of decidual prolactin production (1143). In addition to stimulatory factors, a substance with inhibitory activity is found in decidual conditioned media (731). This substance decreases basal decidual prolactin release and competes with the decidual PRF (731). Recently, the N5 endometrial stromal cell line, which expresses the prolactin gene driven by the extrapituitary promoter, has been identified as a possible model system to study decidual prolactin gene expression (210). Ample evidence indicates that decidual prolactin diffuses into the amniotic fluid (1473, 1474, 1476, 1501). Although the function of amniotic prolactin is uncertain, it has been suggested that it may serve an osmoregulatory (1781), maturational (864), or immune (732) role in the embryo/fetus.

Finally, the nonpregnant uterus has been shown to be a source of prolactin as well. Indeed, a decidual-like prolactin, indistinguishable from pituitary prolactin (611), has been identified in the myometrium of nonpregnant rats (1855). Interestingly, although progesterone stimulates the production of decidual prolactin, it appears to be a potent inhibitor of myometrial prolactin production (611). The physiological role for myometrial prolactin has yet to be identified.

D. Mammary Gland and Milk

Prolactin can be detected in epithelial cells of the lactating mammary gland (1326) as well as in the milk itself (680). There is little doubt that a portion of the prolactin found in the milk originates in the pituitary gland and reaches the mammary gland through the circulation. Thus some of the prolactin found in milk is taken up rather than produced by the mammary epithelial cells. Indeed, a significant amount of radiolabeled prolactin introduced into the circulation appears in milk (685, 1253). Apparently, prolactin reaches the milk by first crossing the mammary epithelial cell basement membrane, attaches to a specific prolactin binding protein within the mammary epithelial cell, and is ultimately transported by exocytosis through the apical membrane into the alveolar lumen (1352, 1583).

In addition to uptake of prolactin from the blood, the mammary epithelial cells of lactating animals are capable of synthesizing prolactin. The presence of prolactin mRNA (992, 1682) as well as synthesis of immunoreactive prolactin by mammary epithelial cells of lactating rats has been described (1063, 1064). It is possible that de novo

synthesis of mammary prolactin requires a systemic trophic factor since the amount of both prolactin mRNA and immunoreactive prolactin declines over 24–48 h in mammary gland explants (992). The mammary gland may also act as a posttranslational processing site for prolactin. In both human (499) and rat (888, 889) milk, the number of prolactin variants far exceeds that found in serum. Indeed, the mammary gland is the site of formation of the important 16-kDa variant of prolactin mentioned previously (332). Although prolactin, produced locally by mammary epithelial cells promotes proliferation, the 16-kDa cleaved prolactin variant inhibits local angiogenesis, which makes this proteolytic step a possible target of breast cancer research (636).

The physiological role for milk-borne prolactin has only been described in the rat, which is born immature relative to many other mammals. Indeed, during a brief window of neonatal life, the gastrointestinal tract lacks the ability to digest protein and likewise possesses the ability to absorb intact protein. This is particularly important since the rat pituitary gland is relatively quiescent during this period. Approximately 20% of the prolactin ingested in milk passes to the neonatal circulation (686). It has been shown that milk prolactin participates in the maturation of the neuroendocrine (1596, 1629) and immune (687, 702) systems.

E. The Immune System

A great deal of evidence suggests that lymphocytes can be a source of prolactin as well (599, 882, 1214, 1516). Indeed, immune-competent cells from thymus and spleen as well as peripheral lymphocytes contain prolactin mRNA and release a bioactive prolactin that is similar to pituitary prolactin (445, 612, 613, 1214–1216, 1523). Not only is an immunoreactive 22-kDa prolactin found in murine (1214) and human (1886) immune-competent cells, but size variants of prolactin have been described as well (1215, 1398, 1523, 1592).

Although the control of pituitary prolactin secretion differs from that of lymphocytic origin, there is abundant evidence that lymphocytes contain dopamine receptors that may be involved in the regulation of lymphocytic prolactin production/release (432). Pharmacological characterization of lymphocytic dopamine receptors suggests that rather than the classical D_2 type receptors found on lactotrophs, both the D_4 and D_5 predominate on lymphocytes (186, 187, 1361, 1470, 1545, 1824). Moreover, mRNA for the D_1, D_3, and D_5 receptors have been identified in rat lymphocytes (283).

The question remains of the role for pituitary and lymphocytic prolactin in the immune response. It is interesting to note that pituitary prolactin gene expression (1601), bioassayable serum prolactin (1601), immunoassayable serum prolactin (1505), and lymphocyte number (1505, 1601) are elevated during acute skin allograft rejection in mice. Administration of bromocryptine, a D_2 receptor agonist, or antilymphocytic serum diminishes circulating levels of prolactin in grafted animals and prolongs graft survival (1294, 1505). Because bromocryptine has little direct effect on lymphocytic prolactin secretion (1294), such data suggest that pituitary prolactin may modulate the elaboration of lymphocytic prolactin and that suppression of pituitary prolactin is thus a requirement for graft survival (1131). Indeed, such a role for prolactin in transplant rejection warrants further investigation.

F. Prolactin-Secreting Cell Lines

To study the synthesis, processing and secretion of prolactin at the cellular and molecular level, cell lines derived from pituitary tumors have been developed. The first cell line was a mammosomatotroph (MtT/W5) isolated from a radiation-induced pituitary tumor produced in a Wistar-Furth rat (1724, 1907). Because these cell lines secreted mostly growth hormone, they were designated as GH cells. It was subsequently found that some of the subclones were pluripotent and heterogeneous (1721, 1722). For example, GH_3 cells may release growth hormone only (somatotrophs), prolactin only (mammotrophs), both hormones (mammosomatotrophs), or neither hormone (189, 192). Similarly, the GH_1 and GH_4C_1 cell lines produce both prolactin and growth hormone but in varying ratios (1721).

The most obvious advantage of using cell lines rather than primary pituitary lactotrophs is that clonal cells are usually immortal, can be easily stored, and thus provide a perpetual supply of cells without sacrificing animals and purifying primary pituitary cultures. To critically use these cells, one should recognize their dissimilarity to primary cultures of pituitary cells. For example, unlike pituitary cells, the vast majority of the prolactin synthesized by GH cell lines is rapidly released and not stored (1722); thus there is no intracellular degradation of prolactin (381). Moreover, GH cells lack functional dopamine receptors, and thus they are resistant to the prolactin-inhibiting actions of dopamine (538). This can be viewed as either an advantage or a disadvantage. Because cell lines lack the complete receptor repertoire of a normal pituitary cell, one must be careful when drawing conclusions that apply to normal lactotrophs on the basis of data collected from cell lines. On the other hand, with knowledge of the defect borne by cell lines, one can study the role of an absent phenotype in control of cellular function. For example, one can transfect GH_4C_1 cells with a dopamine receptor gene, thus isolating and examining the role of that particular dopamine receptor subtype in lactotroph function (22, 244, 249, 491, 666, 1784, 1807, 1924).

Not all clonal lactotroph lines deviate as markedly from primary cells. For example, the MMQ cell line derived from the estrogen-induced rat pituitary tumor 7315a secretes prolactin exclusively, expresses functional dopamine D_2 receptors (881), and behaves in a manner similar to (but not the same as) that of normal lactotrophs (567, 699).

IV. PROLACTIN RECEPTORS

A. Prolactin Receptor: Gene, Splicing Variants, and Isoforms

The prolactin-R is a single membrane-bound protein that belongs to class 1 of the cytokine receptor superfamily (131, 132, 926, 997). Just like their respective ligands, prolactin and growth hormone receptors share several structural and functional features despite their low (30%) sequence homology (632, 633). Each contains an extracellular, transmembrane, and intracellular domain (1899). The gene encoding the human prolactin-R is located on chromosome 5 and contains at least 10 exons (131, 132). Transcriptional regulation of the prolactin-R gene is accomplished by three different, tissue-specific promoter regions. Promoter I is specific for the gonads, promoter II for the liver, and promoter III is "generic," present in both gonadal and nongonadal tissues (812). Numerous prolactin-R isoforms have been described in different tissues (24, 386, 1031). These isoforms are results of transcription starting at alternative initiation sites of the different prolactin-R promoters as well as alternative splicing of noncoding and coding exon transcripts (809, 812). Although the isoforms vary in the length and composition of their cytoplasmic domains, their extracellular domains are identical (184, 926, 1031). The three major prolactin-R isoforms described in rats are the short (291 amino acids), intermediate (393 amino acids), and long (591 amino acids) forms (184). In mice, one long and three short forms have been described (338, 386). In addition to the membrane-bound receptors, soluble prolactin-binding proteins were also described in mammary epithelial cells (158) and milk (1430). These soluble forms contain 206 NH_2-terminal amino acids of the extracellular domain of the prolactin-R (159). The soluble prolactin binding proteins are also products of the same prolactin-R gene, but it is still uncertain whether they are results of alternative splicing of the primary transcript or products of proteolytic cleavage of the mature receptor (or both) (184).

B. Activation of Prolactin-R and the Associated Signal Transduction Pathways

1. Prolactin-R domains and receptor activation

a) EXTRACELLULAR DOMAIN: LIGAND-INDUCED DIMERIZATION. The extracellular domain of all rat and human prolactin-R isoforms consists of 210 amino acids (196, 197) and shows sequence similarities with other cytokine receptors (cytokine receptor homology domain, CRH) (1872). The extracellular domain can be further divided into NH_2-terminal D1 and membrane-proximal D2 subdomains (926, 1872). Both D1 and D2 show analogies with the fibronectin type III molecule, which drives the receptor-ligand interactions in the majority of cytokine receptors (1872). The most conserved features of the extracellular domain are two pairs of disulfide bonds (between Cys^{12}-Cys^{22} and Cys^{51}-Cys^{62}) in the D1 domain and a "WS motif" (Tpr-Ser-x-Trp-Ser) in the D2 domain (1872). The disulfide bonds and the WS motif are essential for the proper folding and trafficking of the receptor, although they are not responsible for binding the ligand itself (632). Activation of the prolactin-R involves ligand-induced sequential receptor dimerization (184) (Fig. 1). Each prolactin molecule contains two binding sites (site 1 involves helices 1 and 4, while site 2 encompasses helices 1 and 3). First, prolactin's binding site 1 interacts with a prolactin-R molecule (634). The formation of this initial hormone-receptor complex is the prerequisite for the interaction of binding site 2 on the same prolactin molecule with a second prolactin-R (184). Disruptive mutation of prolactin binding site 2 is detrimental to prolactin-R activation, which can be initiated only when a trimeric complex (2 receptors, 1 hormone) is formed (184, 634).

b) INTRACELLULAR DOMAIN: ACTIVATION OF JAK2 AND RECEPTOR PHOSPHORYLATION. *I) Transmembrane and intracellular domains.* The role of the 24-amino acid-long transmembrane domain in the activation of prolactin-R is unknown (184). The intracellular domain, however, is a key player in the initiation of the signal transduction mechanisms associated with the prolactin-R (184). The intracellular domains are different in length and composition among the various prolactin-R isoforms and show little sequence similarities with other cytokine receptors (184). However, there are two relatively conserved regions termed box 1 and box 2 (1260). Box 1 (Fig. 1) is a membrane-proximal, proline-rich motif necessary for the consensus folding of the molecule recognized by the transducing molecules (184). Box 2 is less conserved and is missing in the short isoform of the prolactin receptor (632, 926).

II) Activation of Jak2. Although the intracellular domain of the prolactin-R is devoid of any intrinsic enzymatic activity, ligand-mediated activation of prolactin-R results in tyrosine phosphorylation of numerous cellular proteins (1479), including the receptor itself (926, 1267). The membrane proximal region of the intracellular domain is constitutively (i.e., not induced by ligand binding) associated with a tyrosine kinase termed Janus kinase 2 (Jak2) (266, 834, 1013). Phosphorylation of Jak2 occurs within 1 min after prolactin binding, suggesting a major upstream role for Jak2 (1014)(Fig. 1). Experimental data suggest two major prerequisites for Jak2 activation: *1*)

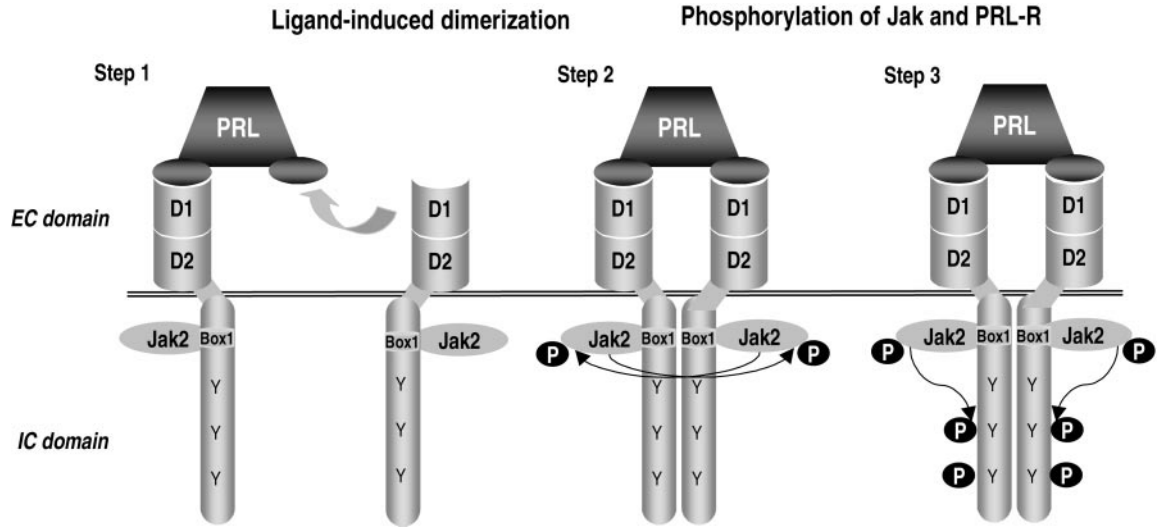

FIG. 1. Mechanism of prolactin receptor activation. Activation of prolactin-R involves ligand-induced sequential receptor dimerization (184) driven by the prolactin molecule containing two binding sites. First, prolactin's binding site 1 interacts with a prolactin-R molecule (*step 1*). The extracellular (EC) domain of all prolactin-R isoforms consists of NH_2-terminal D1 and membrane-proximal D2 subdomains (926), both of which show analogies with the fibronectin type III molecule driving the receptor-ligand interactions in cytokine receptors (1872). The formation of the initial hormone-receptor complex induces the interaction of binding site 2 on the same prolactin molecule with a second prolactin-R (184) (*step 2*). Although the intracellular (IC) domains of prolactin-R isoforms differ in length and composition, there are two conserved regions, termed box 1 and box 2 (1260). Both the presence of the proline-rich box 1 (1014) and strict homodimeric stoichiometry of prolactin-R dimers (550) are necessary for the activation of the tyrosine kinase termed Janus kinase2 (Jak2), constituitively associated with the IC domain of the prolactin-R (1013). Jak2 kinases transphosphorylate each other (550) (*step 2*) and phosphorylate (P) the Tyr residues (Y) of the prolactin-R itself (*step 3*) (1514). Although phosphorylation of Jak2 is a key event in the activation of all prolactin-R isoforms, Tyr phosphorylation of the receptor itself does not occur upon activation of the short form of the prolactin-R, despite the presence of four Tyr residues in its intracellular domain (660).

presence of the proline-rich box 1 motif in the intracellular domain of the prolactin-R (1014) and *2*) homodimeric stoichiometry of the ligand-induced prolactin-R dimers (307, 549, 550). Although the association of Jak2 with prolactin-R has been undoubtedly proven (266, 1013, 1515), the exact structure of their association is not known. Although box 1 of the intracellular domain adopts the typical SH3 (src kinase homology domain 3) folding (1464), no matching SH3 region is found in the sequence of Jak2, implying either the presence of an adapter protein or a mechanism different from the well-known SH3-SH3 binding (1357a). Activation of Jak2 occurs by transphosphorylation upon receptor dimerization, which brings two Jak2 molecules close to each other (550). Experiments with chimeric receptors suggest that mere juxtaposition of box 1 regions does not guarantee Jak2 activation (306). Exact homology of the rest of the intracellular domain is also required, suggesting the significance of the COOH-terminal residues (550).

III) Phosphorylation of the prolactin-R. Jak2 kinases transphosphorylate each other and are involved in the phosphorylation of Tyr residues of the prolactin-R itself (1514) (Fig. 1). Phosphotyrosines are of interest since they are potential binding/docking sites for transducer molecules containing SH2 domains. Although phosphorylation of Jak2 occurs in all active prolactin-R isoforms, Tyr phosphorylation of the receptor itself does not occur upon activation of the short form of the prolactin-R, despite the presence of four Tyr residues in its intracellular domain (660). Certain cellular functions, like proliferation, mediated by the short form of the prolactin-R, can take place without prolactin-R phosphorylation (1906). The long form of the prolactin-R also contains numerous Tyr residues, many of which are phosphorylated upon prolactin-R activation (1412).

2. *Signal transduction pathways associated with the prolactin-R*

A) STAT PROTEINS. The signal transducer and activator of transcription (STAT) protein family has been shown to be a major transducer in cytokine receptor signaling (834). The STAT family currently consists of eight members. Four of them, STAT1, STAT3, and especially STAT5a and STAT5b, have been identified as transducer molecules of the prolactin-R (631, 852). STAT contain five conserved features: a DNA-binding domain, an SH3-like domain, an SH2-like domain, and an NH_2- and a COOH-terminal transactivating domain (552). According to the consensus model of STAT activation (184, 552), a phos-

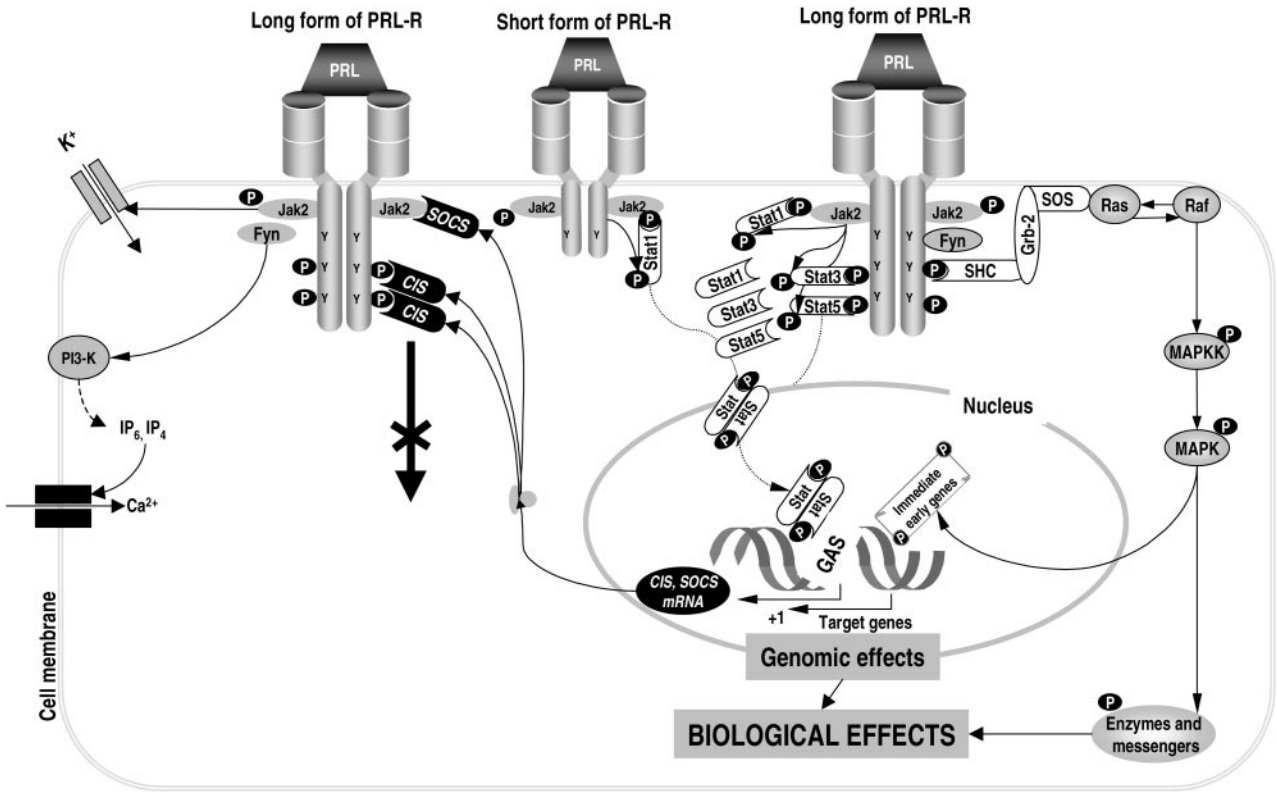

FIG. 2. Signal transduction pathways initiated by activation of the prolactin (PRL) receptor. Jak/STAT pathway: members of the signal transducer and activator of transcription (STAT) protein family (834), STAT1, STAT3, STAT5a, and STAT5b are the central transducer molecules of the signal transduction pathways initiated by prolactin-R (PRL-R) activation (631, 852). STAT contain a DNA-binding domain, an SH3-like domain, an SH2-like domain, and an NH_2- and a COOH-terminal transactivating domain (552). A phosphorylated Tyr residue (Y) of the activated long prolactin-R isoform interacts with the SH2 domain of a STAT. STAT, while docked at the receptor, is phosphorylated by the receptor-associated Jak kinase. Then, phosphorylated STAT dissociates from the receptor and hetero- or homodimerizes through its phosphotyrosine residues with the SH2 domain of another phosphorylated STAT molecule. Finally, the STAT dimer translocates to the nucleus and activates a STAT DNA-binding motif in the promoter of a target gene (184), termed GAS (γ-interferon activated sequence) (791). The tyrosine residues of the short form of prolactin receptor are not phosphorylated by Jak2, but the phosphotyrosine of Jak2 can serve as docking site for Stat1 (184). MAPK cascade: activation of the prolactin-R also activates the mitogen-activated protein kinase (MAPK) cascade (1417), which is involved in the activation of a wide range of transcription factors/immediate early genes by phosphorylation. Phosphotyrosine residues of the activated long prolactin-R isoform serve as docking sites for adapter proteins (Shc/Grb2/SOS) connecting the receptor to the Ras/Raf/MAPK cascade (382). Novel data indicate communication between the Jak/STAT and MAPK pathways (698). Ion channels: box 1 of the intracellular domain of prolactin-R is also involved in the activation of a tyrosine kinase-dependent, calcium-sensitive K^+ channels through Jak2 (1435). The COOH terminal of prolactin-R's intracellular domain is involved in the production of the intracellular messengers [inositol 1,3,4,5-tetrakisphosphate (IP_4) and inositol hexakisphosphate (IP_6)] that open voltage-independent Ca^{2+} channels (1452, 1659). Src kinases: prolactin also induces the activation of members of the Src kinase family, c-*src* (150, 1658) and Fyn (20), which are involved in the Tyr phosphorylation of phosphatidylinositol 3-kinase (PI3K) (152, 1453). Downregulation: Jak/STAT pathways can be inhibited by SOCS (suppressors of cytokine signaling) which inhibit Jak kinases (503, 762, 1289, 1312, 1411, 1672) or CIS (cytokine-inducible SH2-containing protein), which compete with STAT for docking sites on prolactin receptor (1144, 1914).

phorylated Tyr residue of the activated cytokine receptor interacts with the SH2 domain of STAT (Fig. 2). Then STAT, while docked at the receptor, is phosphorylated by the receptor-associated Jak kinase. The phosphorylated STAT dissociates from the receptor and hetero- or homodimerizes through its phosphotyrosine residues with the SH2 domain of another phosphorylated STAT molecule (184) (Fig. 2). Finally, the STAT dimer translocates to the nucleus and activates a STAT DNA-binding motif in the promoter of a target gene (184, 291). The consensus DNA motif recognized by STAT1, STAT3, and STAT5 homo- or heterodimers is termed GAS (γ-interferon activated sequence) (791) (Fig. 2). GAS consists of a palindromic sequence: TTCxxxGAA (791). Numerous promoters contain the GAS consensus motif, and multiple cytokines have been shown to activate these promoters in vitro (548, 658). It has been proposed that STAT interact with other signal transducers (e.g., glucocorticoid receptor) to initiate a cell- and cytokine-specific response (1687, 1688).

Of the STAT1, STAT3, and STAT5 proteins, STAT5 (earlier known as mammary gland factor, MGF) is recognized as the most important transducer of the long and intermediate isoforms of the prolactin-R (1060). STAT5 has two isoforms, STAT5a and STAT5b, encoded by two different genes, with 95% sequence homology and differences only in the COOH-terminal domain. Both isoforms possess a Tyr-694, which is phosphorylated by Jak2 (659). In addition to Tyr phosphorylation, activation of STAT involves serine/threonine phosphorylation as well. The major difference between STAT5a and -b isoforms lies in their serine/threonine phosphorylation sites (133). Protein kinase C (PKC)-α and casein kinase II have been proposed as serine/threonine kinases activating STAT5 (133). Novel data indicate that STAT5 may fulfill inhibitory roles in regulation of gene transcription (1088).

B) OTHER SIGNALING PATHWAYS. *I) Ras/Raf/MAP kinase pathway.* Although Jak/STAT are the most important pathways initiated by activation of the prolactin-R, a number of reports implicate activation of the mitogen-activated protein (MAP) kinase cascade as well (242, 345, 383, 384, 518, 1307, 1323, 1417). Phosphotyrosine residues of the prolactin-R can serve as docking sites for adapter proteins (Shc/Grb2/SOS) connecting the receptor to the Ras/Raf/MAPK cascade (291, 382) (Fig. 2). Although initially the Jak/Stat and MAPK pathways were regarded as independent or parallel pathways, there are data suggesting that these pathways are interconnected (698).

II) Other kinases: c-src and Fyn. Several recent reports indicate prolactin-induced activation of members of the Src kinase family, c-*src* (150, 267, 1658) and Fyn (31a) (Fig. 2). Recently, prolactin-induced rapid Tyr phosphorylation of insulin receptor substrate-1 (IRS-1) and a subunit of the phosphatidylinositol (PI) 3′-kinase (103, 152, 1453) have been described. Both IRS-1 and PI 3′-kinase seem to be associated with the prolactin-R complex. It has been proposed that prolactin-induced activation of PI 3′-kinase is mediated by Fyn (31a) (Fig. 2).

III) Intracellular ion concentration. At least two events and two regions of the prolactin-R are involved in prolactin-induced ionic changes. Box 1 of the intracellular domain of the prolactin-R is involved in the activation of tyrosine kinase-dependent K^+ channels by Jak2 (1435), whereas the COOH terminal of the intracellular domain is involved in the production of the intracellular messengers {inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4] and inositol hexakisphosphate ($InsP_6$)} that open voltage-independent Ca^{2+} channels (351, 1452, 1659) (Fig. 2).

C) DOWNREGULATION OF PROLACTIN-R SIGNAL: TYR PHOSPHATASES AND INHIBITOR PROTEINS. Because activation of prolactin-R results in Tyr phosphorylation of multiple signal molecules, it is expected that inactivation of signaling pathways involves Tyr phosphatases (184). Experimental data indicate that SH2 containing Tyr phosphatases SHP-1 and SHP-2 play less of a role in downregulation of prolactin signaling than in GH or other cytokines (23, 147, 490, 1411, 1445, 1770).

A newly revealed facet of cytokine receptor signaling is identification of SH2-containing protein families inhibiting the Jak/STAT pathways. These protein families are referred to as cytokine-inducible SH2-containing protein (CIS) (1042, 1144, 1914) and suppressors of cytokine signaling (SOCS) (503, 762, 1289, 1312, 1672). Their main mechanism of action in prolactin receptor signaling has been recently characterized (1411). The data indicate that prolactin induces acute and transient expression of SOCS-1 and SOCS-3 (1411). SOCS-1 and SOCS-3 switch off the prolactin receptor-mediated signaling by inhibiting the catalytic activity of Jak2 and activation of STAT proteins (1411). The CIS and SOCS-2 genes respond with prolonged activity to prolactin administration, and SOCS-2 seems to restore the cells' sensitivity to prolactin receptor stimulation probably by suppressing SOC-1's inhibitory effect (1411).

C. Distribution of Prolactin-R

1. Subcellular distribution: surface targeting, internalization, and nuclear translocation of prolactin-R

For proper surface targeting, glycosylation of the asparagyl residues (Asn^{35}, Asn^{80}, Asn^{108}) of the extracellular domain of the prolactin-R is crucial, although not an absolute requirement for prolactin-R activation (256). Although prolactin-R is mainly a cell-surface receptor, deglycosylated forms of prolactin-R can accumulate in the Golgi apparatus (256). Nitric oxide activates *N*-acetylglucosamine transferase, which is responsible for glycosylation of these intracellular receptors and promotes migration of these newly glycosylated receptors to the cell surface (183).

Earlier, endocytosis of prolactin and prolactin-R had been shown in several cell types (149, 447, 877). Surprisingly, even translocation of prolactin (1451) and prolactin-R to the nucleus has been demonstrated in different cell types (344, 1028, 1450). Nuclear translocation of prolactin-R can be accompanied by nuclear actions like stimulation of PKC (241, 343, 1449). Because activation of "classical" cytokine signaling pathways (Jak/STAT, MAP kinase) (1404) do not require nuclear translocation of prolactin-R, the mechanism and in vivo importance of prolactin-R internalization and nuclear actions still remain to be determined.

2. Distribution of prolactin-R in the mammalian body

It is not surprising that prolactin-R and its message are found in the mammary gland and the ovary, two of the best-characterized sites of prolactin actions in mammals

(1268). What may be truly surprising is that the receptor and its mRNA are also found in numerous parts of the CNS. The distribution of mRNA for the long form of the prolactin-R has been characterized in the rat brain (112). Abundant message is found in the choroid plexus, bed nucleus of the stria terminalis, amygdala, the central gray of the midbrain, thalamus, hypothalamus, cerebral cortex, and olfactory bulb (586, 587). Recently, prolactin binding sites have been described in the area postrema, which is one of the main chemosensitive areas of the brain lacking the blood-brain barrier (1112). Prolactin receptors are also present in a wide range of peripheral organs like the pituitary gland, heart, lung, thymus, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle, and skin (184, 1268).

V. BIOLOGICAL ACTIONS OF PROLACTIN

Our goal in this section is to summarize the most relevant actions of prolactin in the mammalian body. An extensive summary of prolactin's effects in different vertebrate species and organ systems can be found in the recent review written by Kelly et al. (184).

A. Reproduction

Prolactin is best known for the multiple effects it exerts on the mammary gland. However, it also exerts effects on other targets important to the reproduction of the mammalian species. In some mammals, particularly rodents, prolactin is also important for the maintenance and secretory activity of the corpus luteum. It also affects other actions related to reproduction such as mating and maternal behaviors.

1. Lactation

The varied effects of prolactin on the mammary gland include growth and development of the mammary gland (mammogenesis), synthesis of milk (lactogenesis), and maintenance of milk secretion (galactopoiesis).

Although it has long been accepted that prolactin is involved in the development of the mammary gland (154), recent elegant techniques have confirmed such findings. Indeed, targeted disruption of the prolactin gene (prolactin knockout) (790) or knockout of the prolactin receptor (1358) results in abnormal mammogenesis characterized by complete absence of lobuloalveolar units in adult homozygous females. Prolactin knockout heterozygotes appear to have nearly normal mammogenesis that is indistinguishable from wild type (790). Transplantation of mammary epithelium from prolactin receptor knockouts into mammary fat pads of wild-type mice revealed that prolactin affects mammary morphogenesis in two different ways: it controls ductal side branching and terminal end bud regression in virgin animals via indirect mechanisms, but acts directly on the mammary epithelium to produce lobuloalveolar development during pregnancy (223). Lactogenesis clearly requires pituitary prolactin, since hypophysectomy during pregnancy prevents subsequent lactation (1306). Due to impairment of mammogenesis, both prolactin knockout (790) and prolactin receptor knockout (1358) homozygous mice fail to produce milk. Interestingly, although the heterozygous prolactin knockouts have normal mammogenesis (790), the F_1 generation heterozygous prolactin receptor knockouts are unable to lactate for their first litter (1358). However, milk is delivered perfectly normally to the F_1's second litter (1358). The phenotype of the F_2 generation was similar (1358). With further reproductive cycles, mammogenesis in both the F_1 and F_2 generations proceeds sufficiently to support lactation, indicating that the defect in heterozygotes is one affecting the rate of mammary gland development. These experiments further indicate that two functional alleles of the prolactin receptor are required for full lactation.

Although there are dramatic differences between mammals in the hormonal requirements for galactopoiesis, the common absolute requirement is prolactin. Aqueous extracts of anterior pituitary gland containing prolactin (1093) initiate lactation in pseudopregnant rabbits (1694). Replacement of prolactin to hypophysectomized rabbits will fully restore lactation (364). On the other hand, while hypophysectomy of rats and mice stops lactation (1587), the replacement cocktail should minimally consist of prolactin and glucocorticoid or adrenocorticotrophin to maintain sufficient nurturing of the pups (173). Addition of growth hormone permits the maintenance of maximal lactation (1094).

It should be noted that none of these actions is solely due to prolactin, but the hormone is merely a player in an orchestra of hormones and growth factors that affect the mammary gland. A great deal of evidence from hypophysectomized-ovariectomized-adrenalectomized rodents suggests that the mammary gland's lobuloalveolar growth and development in vivo requires prolactin, estrogen, progesterone, and glucocorticoids (837). During pregnancy, the extensive branching of the ducts and development of the alveoli is a function of progesterone and prolactin or placental lactogen (837). There is evidence that insulin, growth hormone, thyroid hormone, parathyroid hormone, calcitonin, several growth factors, and even oxytocin may also play a role in galactopoiesis in various mammals (1779).

In the process of lactogenesis, prolactin stimulates uptake of some amino acids, the synthesis of the milk proteins casein and α-lactalbumin, uptake of glucose, and synthesis of the milk sugar lactose as well as milk fats (118, 1779).

Controlled exclusively by promoter III of the rat prolactin-R gene (812), the mammary gland expresses mainly the long form of prolactin-R (1268). The activation of promoter III involves binding of C/ERBβ (CCAAT-enhancer binding protein) and Sp1 (recognizing GC boxes of DNA) transcription factors to their respective binding elements and activation of a downstream sequence element resembling the consensus AP2 binding site (812). As in vitro studies indicate (750) and in vivo studies confirm (854), prolactin-R in the mammary gland is phosphorylated upon prolactin binding (1868) and activates the Jak2/STAT5 pathway responsible for both mammo- and lactogenesis. STAT5 (especially STAT5a) activated by the long form of the prolactin-R induces transcription of milk protein genes (151). Null mutation of the STAT5a or STAT5b gene is detrimental to tubuloalveolar development of the mammary gland and results in inability to lactate in homozygous (−/−) females (184). The signal transduction pathways over which prolactin induces mammary gland growth and development have been extensively studied in vitro and reviewed recently (750).

2. Luteal function

Actions of prolactin on luteal function depend on species and the stage of the estrous cycle. In rodents, prolactin can either be luteotrophic after mating or luteolytic in the absence of a mating stimulus.

In most rodents, prolactin acts as a luteotrophic hormone by maintaining the structural and functional integrity of the corpus luteum for 6 days after mating (1232). This "luteotrophic" action of prolactin, which has been best described in the rat, is characterized by enhanced progesterone secretion (580). Progesterone is essential for the implantation of the fertilized ovum (along with estrogen), maintenance of pregnancy, and inhibition of ovulation (580). In the absence of prolactin, the dominant steroid produced by the corpus luteum of the rat is 20α-hydroxyprogesterone, whose synthesis from progesterone is catalyzed by 20α-hydroxysteroid dehydrogenase (1508). This metabolite of progesterone is "inactive" in most progesterone bioassays. Prolactin enhances progesterone secretion two ways: prolactin potentiates the steroidogenic effects of luteinizing hormone (LH) in granulosa-luteal cells (1471) and inhibits the 20α-hydroxysteroid dehydrogenase enzyme, which inactivates progesterone (580). In other rodents such as hamsters, prolactin is part of a "luteotrophic complex" consisting of LH, follicle stimulating hormone (FSH), and prolactin (672). There is some evidence that prolactin may also be part of a luteotrophic complex in dogs (1322) and primates (1472). In humans, high levels of prolactin inhibit granulosa cell luteinization (10, 1170) and steroidogenesis (1017). Further evidence of luteal dependence on prolactin is found in prolactin receptor knockouts who lack normal luteal function and thus are sterile due to decreased ovulation rate, aberrant oogenesis, and implantation failure (184). Prolactin is essential for progesterone biosynthesis and luteal cell hypertrophy during pregnancy. In addition to luteal function, the prolactin-R mediates numerous functions in granulosa cells and oocytes as well (184).

Aside from its luteotrophic role, there is evidence in the rat that prolactin may be luteolytic as well (1111, 1887) by inducing programmed cell death in the corpora lutea (901, 1156). Prolactin's luteolytic effect seems to be mediated by CD3-positive lymphocytes, which increase the expression of the membrane form of the Fas ligand, known to mediate luteal cell death through the Fas receptor (989). In the rat, as many as three generations of corpora lutea may appear on the ovary. There is evidence that prolactin may perform a "housekeeping function" by inducing the structural regression of the oldest of these. It should be emphasized that the corpora lutea are nonfunctional at the time that prolactin exerts this effect. The mechanism by which prolactin can be both luteotrophic and luteolytic is still uncertain. One suggestion is that at some critical time between periods of exposure to prolactin during the estrous cycle, the corpora lutea of the rat acquire the capacity to express monocyte chemoattractant protein-1, which subsequently interacts with prolactin on proestrus to induce luteal cell death (200, 1773).

Both short and long isoforms of the prolactin-R are present in the ovaries (337, 1621). Transcription of the prolactin-R in the ovaries is controlled by intricate developmental and hormonal regulation (340, 1730). Regulation of transcription of the prolactin-R gene in the ovaries is accomplished by the gonad-specific promoter I and the "generic" promoter III. Essential transcriptional activator of prolactin-R's promoter I is steroidogenic factor-1 (SF-1)-binding consensus element, which is activated by SF-1 (810, 811). SF-1 is a specific zinc finger DNA binding protein, also known as Ad4BP (1089).

Recently, expression of a prolactin-R associated phosphoprotein (PRAP) has been described in luteal cells (468). PRAP binds to the intracellular domain of the long form of the prolactin-R, but not to the short form. Expression of PRAP is upregulated by estrogen and prolactin (469). Structurally, PRAP shows 89% homology with a newly characterized form (type 7) of 17β-hydroxysteroid dehydrogenases/17-ketosteroid reductases (17-HSD), suggesting that PRAP may be an enzyme catalyzing the conversion of estrone to estradiol (1324).

3. Reproductive behavior

A) FEMALE RECEPTIVITY. There are data suggesting that prolactin influences reproductive behavior (476). In humans, high prolactin levels are associated with psychosomatic reactions including pseudopregnancy (1653). There

are prolactin-R in the ventromedial nucleus of the hypothalamus (375), an area which controls female sexual behavior. Coincidentally, iontophoresis of prolactin to this area increases local neuronal electrical activity (743). However, in rats, prolactin's precise action has been confounded by the multiplicity of experimental designs. For example, when given in the third ventricle of estrogen and progesterone-primed ovariectomized rats, prolactin diminishes lordosis frequency, an index of sexual receptivity (470). Though, when given in the midbrain of estradiol-treated ovariectomized rats, prolactin enhances sexual receptivity (738). Enhancement of endogenous prolactin secretion in response to dopamine antagonism has been reported to have no effect on mating behavior in females (1654), whereas elevation of prolactin secretion in response to the nursing stimulus diminishes sexual behavior (1655). In contrast, when the rat is sexually receptive in the afternoon of proestrus, suppression of the spontaneous release of prolactin with a dopamine agonist dramatically attenuates sexual receptivity (1884). Finally, although a null mutation of the prolactin-R gene in the mouse produces most of the defects associated with a deficiency of prolactin, such receptor-deficient females appear to mate normally with heterozygote or wild-type males (1358, 1680). Thus these data, taken together, do not provide a firm basis for assigning a well-defined role for prolactin in female sexual behavior. In contrast, it is clear that prolactin suppresses stereotypical male sexual behavior in rats (451, 896) and sheep (629).

B) PARENTAL BEHAVIOR. Probably the best-characterized prolactin-driven behaviors are the parental behaviors. In mammals, maternal behavior is the most extensively studied (218, 221, 1086, 1530). These include nest building as well as gathering, grouping, cleaning, crouching over, and nursing of the young by the mother. Although most widely described in rats, there is also an extensive literature on the effects of prolactin on the induction and maintenance of these maternal behaviors in mice, rabbit, hamsters, and sheep (219, 1329). It should be emphasized that prolactin, by itself, does not initiate maternal behavior, but merely decreases the latency to the onset of maternal behavior. Intracerebroventricular infusion of prolactin decreases the latency to initiation of maternal behavior in steroid-primed rats (220). The basic observation was made that nulliparous female rats treated with a pregnancy-like regimen of estrogen and progesterone for 10 days showed maternal behaviors with a mean latency of 5–6 days. Superimposition of prolactin treatment on the ovarian steroid regimen reduces the latency of maternal behavior to 1–2 days (217). In addition, hypophysectomized rats failed to display a facilitation of maternal behavior in response to the sequential steroid treatment. On the other hand, prolactin-hypersecreting pituitary transplants placed beneath the kidney capsule of hypophysectomized female rats kept on a maternal ovarian steroid replacement regimen, dramatically advanced the onset of maternal behaviors (218). Suppression of endogenous prolactin release with bromocryptine prevents the onset of maternal behavior, whereas superimposition of prolactin promotes it (222). Prolactin may be exerting this effect by acting within the medial preoptic area of the hypothalamus (220, 1701).

Pup contact has been shown to induce transcription of the long-form prolactin-R mRNA in the brain of female rats. The effect of pup contact on prolactin-R expression is prevented by ovariectomy and hypophysectomy (1701). It seems that the effect of pup contact is not sex specific; the same induction of brain prolactin-R long-form mRNA expression and maternal behavior can be observed in pup-contacted male rats. Administration of prolactin promotes, while female contact suppresses, the effect of pup contact in males (1530). In mice carrying a germ line null mutation of the prolactin receptor gene, homozygous mutant and heterozygous mutant nulliparous females show a deficiency in pup-induced maternal behavior (1086). Moreover, primiparous heterozygous females exhibit a profound deficit in maternal care when challenged with foster pups. Such data suggest that pup contact is required for transcription of the prolactin receptor whose stimulation by prolactin eventuates in maternal behavior (1086).

Although not as widely studied, prolactin may have a role in paternal care as well. The data for this role are most convincing in fish and birds but somewhat less convincing in mammals (1574). Indeed, because prolactin is an "old" hormone, it could be that this role in our most recent ancestors has become somewhat redundant. This is emphasized by the significant stereotypical paternal role of nonmammalian vertebrates (e.g., the male sea horse is the incubator) and the almost nonexistent role in most mammals.

C) PROLACTIN-R IN THE HYPOTHALAMUS. Although the brain contains mainly the long isoform of the prolactin-R, the hypothalamus contains both the long and short forms (323). Within the hypothalamus, prolactin-R mRNA-containing neurons have been found in the anterior as well as the mediobasal hypothalamus (323–325). Also, the mRNA of the long form of prolactin-R is found within the periventricular, paraventricular, supraoptic, arcuate, and ventromedial nuclei of the hypothalamus as well as the medial preoptic area (112). Immunocytochemical data support these observations by showing that these hypothalamic areas contain prolactin-R protein as well (1028, 1415, 1495). Expression of prolactin-R in the brain increases with age (325, 993, 1241), exposure to estrogens (1264, 1598), elevation in serum prolactin levels, and by pup contact (1700).

Few studies have examined the signal transduction pathways specifically activated upon binding of prolactin to its receptor in the CNS. Preliminary data from our

laboratory indicate that systemic administration of prolactin results in nuclear translocation of STAT5 in neurons of the mediobasal hypothalamus. This suggests that the signal transduction pathways coupled to prolactin-R in CNS neurons are similar to those described in peripheral tissues. Prolactin also increases the expression of NGFI-A, NGFI-B, c-*fos*, and c-*jun* in numerous populations of CNS neurons, among them the tuberoinfundibular (TIDA) neurons of the arcuate nucleus (1524).

B. Homeostasis

Aside from its actions on reproductive processes, prolactin plays a role in maintaining the constancy of the internal environment by regulation of the immune system, osmotic balance, and angiogenesis.

1. Immune response

Prolactin is a common mediator of the immunoneuroendocrine network, where nervous, endocrine, and immune systems communicate with each other (631). Prolactin plays a significant role in regulation of the humoral and cellular immune responses in physiological as well as pathological states, such as autoimmune diseases (253, 1295, 1850).

The earliest evidence that prolactin plays a role in the immune response was the demonstration in 1972 that exogenous prolactin enhanced thymic function in prolactin-deficient dwarf mice (314). Shortly thereafter, Nagy and Berczi (1269) found that hypophysectomy or suppression of prolactin secretion with bromocryptine (1273) led to attenuation of humoral or cell-mediated immunity that could be reversed by treatment with exogenous prolactin. A large number of immune perturbations were found to be associated with prolactin deficiency (148, 1269–1273).

As noted in two recent reviews (1145, 1871), prolactin stimulates mitogenesis in both normal T lymphocytes (1828) and the Nb2 lymphoma cell line (1622). It should not be surprising that prolactin affects lymphocytes since prolactin-R has been detected on human peripheral lymphocytes (1517–1519) and their mRNA expression is regulated by prolactin itself (442). Moreover, effects of prolactin on lymphocytes may involve interleukin (IL)-2 since T-lymphocyte activation by IL-2 requires prolactin (344, 712). Interestingly, prolactin's site of action for modifying the effects of IL-2 on lymphocytes appears to be the nucleus (343). Prolactin is also required for mitogen-stimulated proliferation of lymphocytes (741, 757, 758). Nb2 cells, derived from immature T lymphocytes, are dependent on the mitogenic activity of prolactin (1622, 1713). Indeed, this property has served as the basis for a highly sensitive, specific bioassay for prolactin. However, there is not uniform agreement on the role of prolactin in hematopoiesis. Although targeted disruption of the prolactin gene leads to numerous defects in prolactin-dependent events such as lactation, there is no difference between homozygotes and heterozygotes in the frequency of B- and T-cell antigen expression (790). Such results argue that prolactin does not play an indispensable role in primary lymphocyte differentiation or its absence during development can be compensated by other factors.

The role of prolactin in the immune response of the organism is a matter of continuing concern. It appears that immune responses in vivo are enhanced by prolactin. For example, prolactin-secreting pituitary grafts placed beneath the kidney capsule (1270) or administration of prolactin (1272) restores dinitrochlorobenzene-induced contact dermatitis impaired by hypophysectomy. On the other hand, skin allograft transplants elevate serum prolactin (725). During graft rejection, lymphocytic prolactin gene expression is also upregulated (1601). Moreover, elevated serum prolactin levels induced by skin allografts can be suppressed by either bromocryptine or an antilymphocytic serum (1505). However, only antilymphocytic serum prolongs the survival time of the graft (1505). These data suggest that lymphocytic prolactin plays a specific role in skin graft rejection and may play a role in other transplantation responses as well (764).

Immunocytochemical demonstration of prolactin-R on T and B lymphocytes (1769) was followed by detection of mRNA encoding the short and long prolactin-R isoforms in the thymus, spleen, lymph nodes, and bone marrow of both rats and mice (1020). Expression of prolactin-R isoforms was more extensively mapped in rat splenocytes and thymocytes from birth to adulthood (703), as well as during the estrous cycle, pregnancy, and lactation (704). Prolactin's functions are the most extensively described and reviewed in the Nb2 cell line (1920). This cell line also expresses an intermediate (393 amino acid) isoform of prolactin-R (184). In Nb2 lymphocytes, activation of the prolactin-R is associated with (945) *1*) rapid tyrosine phosphorylation of STAT5a, STAT5b, STAT1α, and STAT3; *2*) rapid and selective formation of STAT5a/b heterodimers; *3*) marked Ser, but not Thr phosphorylation of STAT5a and STAT5b; and *4*) the appearance of two qualitatively distinct STAT5 protein complexes that discriminate between oligonucleotides corresponding to the prolactin response elements of the β-casein and interferon regulatory factor-1 gene promoters (945).

2. Osmoregulation

One of the least understood actions of prolactin is regulation of solute and water transport across mammalian cell membranes (1602). Studies in this area were motivated by the finding in lower vertebrates that prolactin stimulates solute transport across cell membranes and thus could be an osmoregulatory hormone (153). Some of

the actions in mammals are easier to envision in a physiological perspective than others. For example, prolactin exerts a host of activities on transport of solute across mammary epithelial cell membranes. In keeping with its lactogenic properties, among the earliest discoveries was the observation that prolactin decreases the transport of sodium and increases the transport of potassium across mammary epithelial cells taken from bromocryptine-treated rabbits (534, 535). Similarly, prolactin stimulates the uptake of amino acids by the rat mammary gland (1825) as well as the uptake of the nonmetabolizable amino acid α-aminoisobutyric acid by mouse mammary explants (1480). The requirement of such prolactin-driven solute movement for lactation has not been described. Prolactin also affects water transport across amniotic membranes. It stimulates water transport across guinea pig and sheep amnion (1114) but inhibits it in human amnion (1026). Prolactin is responsible for fluid (1447), sodium, chloride (1102–1104), and calcium (1365) transport across intestinal epithelial membranes. Correlation between sweat chloride and prolactin concentrations (1492) may implicate prolactin as one of the possible pathogenic factors in cystic fibrosis (968).

Although not examined in a systematic manner, it seems likely that the enhanced solute transport during late pregnancy (205) might be a mechanism whereby prolactin contributes to the preparation by the pregnant mother for subsequent lactation. A similar teleological argument can be made for the observation that prolactin acts on the proximal convoluted tubule of the renal nephron to promote sodium, potassium, and water retention (1685). These data, taken together, argue for the need for systematic studies on the role of prolactin on fluid and solute transport in a physiological context.

3. Angiogenesis

Angiogenesis, the development of blood vessels, is inhibited by proteolytic fragments of native prolactin (333). This antiangiogenic activity is inherent to the 16-kDa fragment (334). In fact, there are specific, high-affinity, saturable binding sites for the 16-kDa fragment of prolactin on capillary endothelial cells (336). The 14-kDa fragment shares the antiangiogenic activity of the 16-kDa fragment (335). In contrast, it has recently been found that intact human prolactin, placental lactogen, and growth hormone have angiogenic activities (1695). Although a physiological significance has not been ascribed to these opposing effects, it seems likely that there may be a therapeutic use for prolactin fragments as local inhibitors of tumorigenesis, or conversely, a role as pathological effector through its antiangiogenic actions.

VI. PATTERNS OF PITUITARY PROLACTIN RELEASE

When the release of prolactin is assessed at the single-cell level, the pattern of prolactin secretion of individual lactotrophs shows sexual dimorphism. In general, slightly more than half the lactotrophs of female rats secrete prolactin in a continuous pattern, whereas those of males secrete in a discontinuous or intermittent pattern (297). In the following sections we summarize the patterns of prolactin secretion at the level of the whole organism under different physiological and experimental conditions.

A. Circadian Rhythm of Prolactin Secretion

Plasma concentrations of prolactin are the highest during sleep and the lowest during the waking hours in humans (1380, 1555). Recent human volunteer experiments prove, however, that this rhythm of prolactin secretion is maintained in a constant environment independent of the rhythm of sleep (1848), although with considerably larger amplitude in women than men. These data indicate that the rhythm of daily prolactin release in humans is a true circadian rhythm that may be generated by the suprachiasmatic nuclei of the hypothalamus (1848).

There is ample chronobiological evidence that the temporal organization of prolactin secretion is controlled by circadian input in rats as well (167, 951). The rhythm of prolactin release is maintained in constant environment and abolished by lesion of the suprachiasmatic nuclei in rats (167, 168). In contrast to humans, there is a tight relationship between sleep patterns and prolactin levels in rats. Experimental data suggest that high prolactin levels may be the cause rather than the result of change in sleep patterns. In rats, using either injection of prolactin (1496) or implantation of anterior pituitary grafts to render the animal hyperprolactinemic (1332), high prolactin levels increase the duration and frequency of rapid-eye-movement sleep (REMS), thus leading to the idea of a functional relationship between nocturnal elevations of prolactin and REMS. There is some evidence that vasoactive intestinal polypeptide (VIP), a potent prolactin-releasing peptide, may also be involved in REMS (863, 1333). Immunoneutralization of circulating prolactin blocks systemically administered VIP-enhanced REMS (981, 1331). However, immunoneutralization of endogenous circulating prolactin only slightly attenuates spontaneous REMS, suggesting that central rather than systemic prolactin may be the physiological effector (981, 1331). Release of prolactin associated with REMS was also described in humans (1556). However, slow-wave sleep (SWS) (1848) also appears to be associated with nocturnal prolactin secretion in humans (1055).

There is ample evidence (see sect. VIIA1A) that dopaminergic tone of hypothalamic origin that exerts inhibitory effect over prolactin secretion (140) also changes throughout the day (420, 1027). It has been shown that dopaminergic activity in the median eminence shows daily changes, strongly suggesting a daily rhythm of dopamine levels in the long portal vessels reaching the anterior lobe of the pituitary gland (1101, 1606, 1903). According to this daily rhythm, the dopaminergic tone of TIDA neurons decreases before the daily elevation in prolactin levels (1101). The presence of this daily rhythm of TIDA neuronal activity in female rats has been verified with various ovarian steroid backgrounds (1606, 1607, 1903). It has been demonstrated that a similar pattern in immediate early gene expression exists in neuroendocrine dopaminergic neurons of female rats in various reproductive states (1027, 1029). These data, as well as experiments conducted in constant environment and manipulations of suprachiasmatic input (1101, 1100, 1606), strongly suggest that the daily rhythm exhibited by neuroendocrine dopaminergic neurons is endogenous in nature and entrained by light.

Hypothalamic oxytocin, which has been identified as a potential PRF, plays an important role in maintaining the endogenous prolactin-stimulatory rhythm (71, 73, 75–77). Indeed, in rats treated with a dopamine antagonist at various times of day to unmask a rhythm of prolactin secretion (71), administration of an oxytocin antagonist abolishes the rhythm (74). Since these initial findings, numerous other candidates of central origin have emerged as possible regulators of circadian release of pituitary prolactin (813, 1858, 1912, 1919).

B. Patterns of Prolactin Secretion in Different Reproductive States

1. Lactation

The best-known physiological stimulus affecting prolactin secretion is the suckling stimulus applied by the nursing young. This has been characterized as a classical neuroendocrine reflex. Just as muscle contraction evoked by an electrochemical stimulus is described as a stimulus-contraction reflex, one can describe the release of prolactin in response to the nursing young as a stimulus-secretion reflex. In rats, blood prolactin concentrations begin to rise within 1–3 min of initiation of nursing, peak within 10 min, are sustained at a constant level as long as nursing continues, and fall when nursing is terminated (684). The expression of prolactin mRNA in the pituitary gland follows the same pattern (1016). Cessation of the suckling stimulus results in termination of prolactin secretion, and the rate of decrease in blood prolactin levels is proportional to the metabolic clearance rate of the hormone (683, 1274). Moreover, the amount of prolactin released is related to the intensity of the stimulus as it is somewhat commensurate with the number of pups nursing (1182). These parameters appear to be similar in all mammals with only subtle exceptions. For example, in the rhesus monkey, nursing induces a biphasic release of prolactin (575). In humans (443, 1683), cattle (1019), and rodents (78, 887), the prolactin-secretory response to nursing is superimposed by the endogenous circadian rhythm of prolactin secretion; that is, the same intensity of suckling stimulus can elevate prolactin levels more effectively at certain times of day when the circadian input enhances the suckling stimulus-evoked secretory response.

The control of suckling-induced prolactin secretion is somewhat enigmatic. It is certain that the suckling stimulus results in a diminution of the amount of dopamine released into portal blood (404) and arriving at the anterior pituitary gland (1281). Thus the suckling stimulus essentially relieves the lactotroph from tonic inhibition. However, the amount of prolactin released in response to suckling is far greater than that resulting from pharmacological or surgical interference with dopamine input to the pituitary gland. This argues for a prolactin-releasing input superimposed on the diminution of the inhibitory input provided by suckling-induced suppression of dopamine. Indeed, there are many candidates for a PRF stimulated by suckling. For example, passive immunization against TRH inhibits suckling-induced prolactin release (405, 1603). However, the supremacy of TRH in regulating suckling-induced prolactin release is not universally accepted (1481). The intriguing observation that posterior pituitary lobectomy abolishes suckling-induced prolactin secretion has led to the suggestion that the posterior lobe transfers a PRF to the anterior lobe through the short portal vessels (827, 827, 1256). The identity of the posterior pituitary PRF has eluded many investigators. Among the obvious candidates for PRF are vasopressin (1283) and its glycopeptide vasopressin-neurophysin precursor (1276, 1277), oxytocin (76, 78) and even dopamine of posterior pituitary origin (1281). However, there is not universal agreement on the candidacy of the vasopressin-neurophysin glycopeptide (829), and there is some indication that the PRF may be a heretofore unidentified posterior pituitary (27, 766, 1059) or intermediate lobe (27) peptide. It is safe to say at this time that, although we have several plausible candidates, none has emerged as the undisputed suckling-induced PRF.

2. Estrous and menstrual cycles

The secretion of prolactin has been most extensively studied during the estrous cycle of the rat. The secretion of prolactin throughout most of the estrous cycle appears low and unchanging from the evening of estrus through the morning of the next proestrus (254, 608, 1296, 1647).

During the afternoon of proestrus, a preovulatory surge of prolactin secretion occurs, which is similar in timing to that of LH (1647). Although the LH surge on proestrus is symmetrical, the surge of prolactin consists of a rapid, sharp peak followed by a prolonged plateau and an extended termination phase (60, 1259). Although most laboratories have reported a single surge of prolactin on proestrus (608, 1296, 1647), others have reported a secondary surge on estrus (254) or continuously elevated prolactin levels on proestrus, estrus, and metestrus (34). Because these latter results may have been caused by the method and frequency of blood collection, it is generally accepted that the afternoon of proestrus is the only time that a major surge of prolactin secretion occurs.

Because the events of the rodent estrous cycle and those of the primate menstrual cycle share some common controls, it would not be illogical to expect a midcycle surge of prolactin during the menstrual cycle that coincides with that of luteinizing hormone. However, only one study finds a small, late follicular phase rise of prolactin secretion culminating in a midcycle peak that is only 50% greater than prolactin levels of the early follicular phase (1812). Such small changes can easily be overshadowed by pulsatile changes, thus leading to a failure to detect significant variations at midcycle in individual samples.

It is clear that the rising blood levels of estradiol signal the hypothalamo-pituitary axis to release this surge of prolactin on proestrus. Administration of an antiserum to estradiol on the morning of diestrus-2 blocks the proestrous surge of prolactin (1302). A single injection of estradiol given to ovariectomized rats results in daily surges of prolactin that are similar in timing to the proestrous surge of prolactin (1297). These data suggest the existence of a circadian hypothalamic timing mechanism that is enhanced by estradiol. This mechanism by which estradiol induces a proestrous surge of prolactin secretion probably involves actions at the preoptic area of the hypothalamus, since caudal transection of preoptic efferents (939) or lesion of the preoptic area (1369) block the estradiol-stimulated surge of prolactin secretion, while implantation of estradiol in the preoptic area stimulates a surge (1370). Indeed, ample evidence suggests that both forms (α and β) of the estrogen receptor are expressed by the neurons of the preoptic area (161, 195, 358, 995, 1039, 1388, 1869, 1925).

Progesterone administered on diestrus-3 of a 5-day cycle will advance the proestrous surge of prolactin by 1 day (1305). Moreover, progesterone enhances the magnitude of an estrogen-induced proestrus-like surge of prolactin in ovariectomized rats (259, 1911). However, the precise role of progesterone in the secretion of prolactin on proestrus has yet to be described.

Hypothalamic control of the preovulatory proestrous surge of prolactin is far from clear. Although it is clear that dopamine inhibits prolactin secretion and that removal of the tonic dopaminergic inhibition results in enhanced prolactin secretion, the role of dopamine as a regulator of the proestrous surge of prolactin is contradictory. Hypothalamo-hypophysial portal blood concentrations of dopamine (140), the activity of tyrosine hydroxylase (287), the turnover of dopamine in the median eminence (411), and the subsequent concentration of dopamine in the anterior lobe of the pituitary gland (420) have been reported to decline on proestrus before the increase in prolactin secretion. On the other hand, others have reported no change in dopamine turnover at the same time (786, 1448). Similarly, dopamine receptors in the anterior pituitary have been reported to both increase (1384) and decrease (748) during the afternoon of proestrus. The source of dopamine controlling prolactin secretion is believed to be TIDA neurons with cell bodies in the arcuate nucleus of the hypothalamus and axons terminating in the median eminence. However, there is ample evidence that some of the dopamine arrives at the anterior lobe of the pituitary gland from the posterior lobe that contains axon terminals of tuberohypophysial dopaminergic (THDA) neurons whose cell bodies are found in the rostral part of the arcuate nucleus (63). In addition, dopamine may arrive from the intermediate lobe that contains axon terminals of periventricular-hypophysial dopaminergic (PHDA) neurons that reside in the hypothalamic periventricular nucleus (655, 656). The short portal vessels connecting the lobes of the pituitary gland may serve as the vascular pathway through which dopamine is transported to the anterior lobe from the neural and intermediate lobes of the pituitary gland. Indeed, the fact that posterior lobectomy results in a chronic elevation of prolactin secretion (1255) suggests a functional role for THDA neurons. However, data are unavailable to suggest a similar role for PHDA neurons.

Further muddying these waters is the fact that a prolactin-releasing hormone of hypothalamic origin must play a role in the surge of prolactin secretion on proestrus. Numerous candidates abound. TRH is one of the earliest proposed candidates. Passive immunoneutralization of endogenous TRH has been reported to partially inhibit (963) or delay the onset (788) of the proestrous surge of prolactin. Indeed, the concentration of TRH in portal blood is slightly elevated during the afternoon of proestrus (553). However, there is no distinct concomitant elevation in TSH secretion during the afternoon of proestrus (178) which, intuitively, should be expected to accompany the increase in prolactin secretion on proestrus. Similar to TRH, the concentration of oxytocin increases in portal blood during the afternoon of proestrus (1551). Hourly injections of an oxytocin antagonist block the proestrous surge of prolactin (867), and administration of an antiserum to oxytocin attenuates the estrogen-induced proestrus-like surge of prolactin (1537).

3. Mating and pregnancy

As noted earlier, prolactin is a luteotrophic hormone in the rat. Indeed, the unmated rat has an extremely short luteal phase due to the lack of sufficient prolactin to maintain the corpus luteum. However, if mating occurs or a copulomimetic stimulus is applied to the uterine cervix, the corpus luteum is rescued. It was assumed that the mating stimulus eventuated in elevated prolactin secretion. With the availability of the first radioimmunoassay for prolactin (1304), it was shown that mating did not induce constantly elevated prolactin secretion but rather twice daily surges of prolactin. If the rats are kept under 12:12-h dark-light cycles, with lights on at 0600 h, the diurnal surge of prolactin secretion begins in the afternoon (1300–1500 h), reaches peak values during the early evening (1700–1800 h), and returns to basal levels by 2400 h. The other surge, called nocturnal, begins by 0100 h, peaks by 0300–0700 h, and approaches baseline by 1100 h. These surges recur for 10 days if the mating is fertile and results in pregnancy (255, 1648), or persist for 12 days in pseudopregnancy when mating is sterile or copulomimetic (584, 1647). There are abundant data which show that the surges of prolactin cease after *day 10* of pregnancy due to the negative-feedback action of placental lactogen acting at both pituitary and hypothalamic levels (64, 649, 1755, 1756, 1760–1763, 1832–1834, 1838), the details of which are described in section VII*C3*.

Prolactin secretion stimulated by copulomimetic stimuli can be initiated and maintained independent of ovarian steroids (585). In contrast, the surges of prolactin secretion of pseudopregnancy end after *day 13* due to the diminishing secretion of progesterone from the waning corpora lutea coupled with the rising titers of estradiol from the newly developing ovarian follicles (645). Moreover, the nonpregnant uterus itself secretes an, as yet, uncharacterized factor, which inhibits prolactin secretion by acting directly on the lactotroph (647, 648, 650).

The areas of the hypothalamus upon which the mating stimulus acts to initiate this unique pattern of prolactin secretion have also been characterized (581, 705–707, 710, 920). The primary transduction pathway involves the pelvic nerve (275, 1509, 1874). Presumably, the mating stimulus is carried over spinal afferent pathways and enters the brain. Although the exact pathways in the entire brain have not been mapped, pharmacological and physiological studies have implicated various areas of the hypothalamus. On the basis of classical lesion and stimulation studies, it appears that the preoptic area of the hypothalamus contains two functional neuronal populations controlling prolactin secretion (581). In the unmated rat, one population is tonically active and inhibits the nocturnal surge of prolactin, whereas the other is inactive (581, 706). It appears that the uterine cervical stimulation of mating inactivates the former and activates the latter, which eventuates in nocturnal and diurnal surges of prolactin secretion. Induction of the surges either by cervical stimulation or manipulation of the preoptic area requires an intact dorsomedial/ventromedial hypothalamic nucleus (707, 710).

The suprachiasmatic nuclei of the hypothalamus are responsible for the faithful timing of the mating-induced surges of prolactin (168), which are under the control of an endogenous circadian rhythm (167). After cervical stimulation, two daily decreases in the activity of neuroendocrine dopaminergic neurons of the hypothalamus occur (1029). It has been suggested that the hypothalamus produces a sex-specific stimulatory rhythm regulating prolactin secretion which is unmasked by the dopamine-lowering actions of the mating stimulus at the uterine cervix (71). It has been proposed that prolactin-releasing quanta of oxytocin are released twice each day into portal blood feeding the sinusoid capillaries of the anterior pituitary gland (73, 76). The timing of these events, the decrease in dopaminergic tone followed by an increase in the concentration of oxytocin in portal blood, corresponds to the release of prolactin in cervically stimulated animals (76). The key neurotransmitters regulating each of these oxytocin-dependent events are different. The early morning (nocturnal) oxytocin-mediated prolactin release is regulated by VIP, whereas the diurnal event seems to be dependent on serotonergic activation (73, 74, 77).

It has been argued that a luteotrophic mechanism, activated by a mating stimulus, is one of the more efficient systems governing reproduction (580). In rodents, it is advantageous for quick turnover of generations to shorten the luteal phase during estrous cycles when an ovulation is not associated with a fertile mating and conception, whereas an active luteal phase, preparing the uterus for implantation of an embryo, is only associated with a mating stimulus.

C. Prolactin Release in Response to Exteroceptive Stimuli

1. Light

A) CIRCADIAN PATTERNS. In photoperiodic mammals such as rats, light is an important regulator of prolactin secretion. Indeed, shifting of the light phase results in a coincidental shift of the proestrous surge (179), the estrogen-induced proestrus-like surge, and the mating-induced surges of prolactin in rats (1418). When placed in constant light, rats become acyclic (772). Complete removal of a photoperiod by placing the animals in constant light or through various means of light deprivation result in free-running proestrus-like surges of prolactin secretion in estrogen-treated ovariectomized rats (1418) and free-running mating-induced surges of prolactin secretion (167,

1418). These effects require an intact suprachiasmatic nucleus (168). These data point to the fact that these events are under the control of an endogenous circadian rhythm and that lighting periodicity entrains that rhythm.

B) SEASONAL PATTERNS. Prolactin secretion is also affected by variations of day length in seasonal mammals. In adult male hamsters, 2 mo of exposure to a short photoperiod (5 h of light, 19 h of darkness) causes testicular regression and a precipitous decline in release of prolactin (98, 170). Although testicular regression is blocked by transections dorsal or ventral to the hypothalamic paraventricular nucleus (845), the fall in prolactin secretion associated with short days is not (99). This may not be unexpected given that the effects of short photoperiod on testicular regression and blunting of prolactin secretion may be dissociated under certain regimens (455), thus suggesting two different levels of control for these two photoperiodic events. Indeed, the effect of shortened photoperiod on prolactin secretion can be reversed by infusion of VIP into the paraventricular nucleus of the hypothalamus (97).

In the ewe, another seasonal mammal, shortened days lead to a diminution of prolactin secretion (927). In rams, the effect presents itself within a week of exposure to the shortened photoperiod (1052). The effect of photoperiod is mediated by melatonin secreted from the pineal gland (385, 1431, 1432), transduced through the suprachiasmatic nucleus (1582), or acting directly on the pituitary gland (1050). Short days also diminish the activity of tyrosine hydroxylase and the content of dopamine in the median eminence (1738, 1816). However, this reduction in dopaminergic activity does not appear to have a direct effect on prolactin secretion (1817). In addition, dopamine does not mediate the suppressing effects of melatonin on prolactin secretion (1051, 1053, 1817).

It has been shown that photoperiodic information regulating postnatal prolactin secretion is transferred from mother to fetus in both sheep (488) and hamsters (1600). Pregnant ewes exposed to short days give birth to lambs that have lower serum prolactin concentrations than those of dams exposed to long days. Prenatal exposure of pregnant hamsters to short days results in male offspring producing higher prolactin concentrations than those from dams exposed to long days. Female hamster neonates are unaffected by altered prenatal photoperiod. These prolactin-secretory responses presumably involve maternal melatonin as affected by the photoperiod (1908, 1909). In fetal sheep, prolactin secretion is also affected by maternal photoperiod or melatonin (124, 1383). However, with increasing gestational age, the fetal hypothalamus appears to mask or suppress these effects (801). The basis for the return of fetal independence from maternal influence is not yet fully appreciated. It is possible that the varying paradigms of photoperiod exposure may have engendered these seemingly paradoxical sequences of events.

2. Audition

Of the many environmental inputs controlling prolactin secretion, the effect of specific sounds is one of the most responsive and robust but the least studied (682, 1733, 1831). Recordings of ultrasounds of hungry pups stimulate prolactin secretion in lactating and virgin female rats (1733). This response is specific to ultrasounds generated by pups as adult ultrasound or background tape noise does not affect prolactin secretion. Although the basis for this response has not been studied, one can easily imagine its utility. Indeed, ultrasound-induced maternal prolactin secretion may be responsible for preparing the mammary gland for a subsequent suckling bout or the released prolactin is transported to the milk to act as a stimulator of the pups' development.

3. Olfaction

Of the chemical senses, olfactory stimuli play a robust role in prolactin secretion. Pheromones secreted by a male unfamiliar to the pregnant female will result in early loss of pregnancy in mice. This phenomenon is referred to as the Bruce effect, in recognition of its discoverer (229–231). The pheromonal signal is conveyed to the accessory olfactory bulb by the vomeronasal nerves, which synapse on the primary dendrites of mitral cells in glomeruli. The mitral cells, in turn, excite cells of the corticomedial amygdala (1038), which excite cells in the medial preoptic area of the hypothalamus and result in excitation of TIDA neurons of the arcuate nucleus (1037). The implication is that the loss of pregnancy occurs due to the dopamine-induced suppression of prolactin secretion (1503) and consequently its luteotrophic support. Indeed, replacement of prolactin reverses the abortive effect of the unfamiliar male's pheromones (453, 454).

In lactating female rats, the odor of the pups placed beneath the mother's cage stimulates prolactin secretion (1183, 1184) but, interestingly, inhibits milk secretion in late lactation (682). On the other hand, when placed next to the mother, pup odors are stimulatory to both prolactin secretion and milk secretion (682). Thus the prolactin secretory mechanism is more sensitive than the galactopoetic mechanism to pup odor in late lactating rats.

4. Stress

It is clear that prolactin secretion is dramatically affected by "stress." A myriad of stresses have been used to characterize such effects on prolactin secretion. These include, but are not limited to, the following: ether stress (116, 667, 866, 876, 893, 1077, 1105, 1200, 1257, 1296, 1913), restraint stress (416, 590, 598, 883, 923, 944, 1446),

thermal stress (1782a), hemorrhage (274, 883), social conflict (817), and even academic stress in humans (1108).

Because, in most cases, the prolactin-secretory response (i.e., stimulation or inhibition) differs depending on the nature of stress, one cannot describe a unitary mechanism but must define the mechanism associated with each specific stress modality.

The prolactin-secretory response to ether stress has been reported to differ during the reproductive state of the rat. During diestrus of the estrous cycle, ether stress increases prolactin secretion (1296). However, there is no universal agreement as to the nature of the responses at proestrus. For example, ether stress has been reported to increase (855), decrease (1231), or have no effect on (1296) prolactin levels during the afternoon of proestrus.

Restraint stress applied before the surge of prolactin secretion on the afternoon of proestrus enhances the surge while application during the surge attenuates it (1649). Similarly, restraint stress suppresses the proestrus-like estrogen-induced afternoon surge of prolactin in ovariectomized rats (598). It has also been reported that restraint stress suppresses the nocturnal surge of prolactin during pseudopregnancy (1221) or pregnancy (1223). Because dopamine is the hypothalamic neurohormone tonically inhibiting prolactin secretion, it is intuitively obvious that dopamine would also be implicated in the stress-mediated effects on prolactin secretion. Indeed, pimozide, a dopamine antagonist, prevents restraint stress-induced decrease in the estrogen-induced afternoon proestrus-like surge of prolactin (598). Moreover, a modest increase in TIDA neuronal activity accompanies restraint stress in estrogen-treated (1224) but not in cycling or lactating (923) rats. Other hypothalamic substances implicated in the prolactin-secretory stress response include serotonin (865, 876), histamine (953, 956), *N*-methyl-D,L-aspartic acid (214), atrial natriuretic peptide (571), β-endorphin and dynorphin (1407), oxytocin (956), and vasopressin (953).

The physiological importance to the organism of the prolactin-secretory response to stress is rather elusive. It is clear that neither the stress-induced attenuation of the proestrous prolactin surge affects the estrous cycle of the rat (1222) nor reduction of the mating-activated nocturnal surge has any effect on the outcome of a pregnancy or pseudopregnancy in the rat (1223). Given the finding of a role for prolactin in humoral or cell-mediated immunity, it can be argued that the prolactin-secretory response to stress has an immunomodulatory function protecting the organism from the consequences of stress (597). Although there are no experimental data to support this hypothesis, it has been suggested that prolactin secretion, particularly during lactation, acts as a protective factor in stress-induced gastric ulcers (464). Teleology would advise that other roles, probably in maintaining homeostatic balance affected by other stress hormones, exist as well.

VII. REGULATION OF PITUITARY PROLACTIN SECRETION

Prolactin secretion is affected by a large variety of stimuli provided by the environment and the internal milieu (Fig. 3). The most important physiological stimuli that elevate pituitary prolactin secretion are suckling (1298, 1732), stress (1296, 1298), and increased levels of ovarian steroids, primarily estrogen (1298, 1301). Such stimuli are transduced by the hypothalamus which elaborates a host of PRF and prolactin-inhibiting factors (PIF) (Fig. 3). In mammals, the control exerted by the hypothalamus over pituitary prolactin secretion is largely inhibitory (140). On the other hand, the hypothalamus is also involved in the acute stimulatory control of prolactin secretion by removal of the inhibition (disinhibition) and/or superimposition of brief stimulatory input. In addition, prolactin secretion is also influenced by numerous factors released by the lactotrophs themselves (autocrine regulation) or by other cells within the pituitary gland (paracrine regulation) (Fig. 3).

A. CNS

The general and well-accepted view is that lactotrophs have spontaneously high secretory activity. Therefore, pituitary prolactin secretion is under a tonic and predominant inhibitory control exerted by the hypothalamus. This view is based on the following observations: *1*) surgical disconnection of the pituitary gland and the medial basal hypothalamus (median eminence lesion or pituitary stalk section) results in gradual increase in plasma prolactin that reaches a plateau within a week after these surgeries (79, 174, 899, 1004), *2*) prolactin secretion occurs at a high spontaneous rate when the anterior lobe is transplanted to a site that has no vascular or neural connection to the hypothalamus (e.g., under the kidney capsule) (523, 524), or *3*) when pituitary cells are cultured in vitro (1298, 1299, 1590). Thus it appears that prolactin secretion is severely restrained in vivo by the action of hypothalamic PIF.

The precise characteristics of the regulation of prolactin secretion are fundamentally determined by the physiological status of the animal. Therefore, for the purpose of this review, we will make reference to the animal model used in the studies involved. To narrow the scope of this review, specific attention will be given to animal models with obvious physiological significance, such as the estrous cycle of female rats (proestrous prolactin-secretory surge), pregnant/pseudopregnant female rats (daily nocturnal and diurnal prolactin surges), lactating female rats (suckling-induced prolactin secretion), and male rats (stress-related prolactin secretion). Different experimental models emphasizing particular stages of the

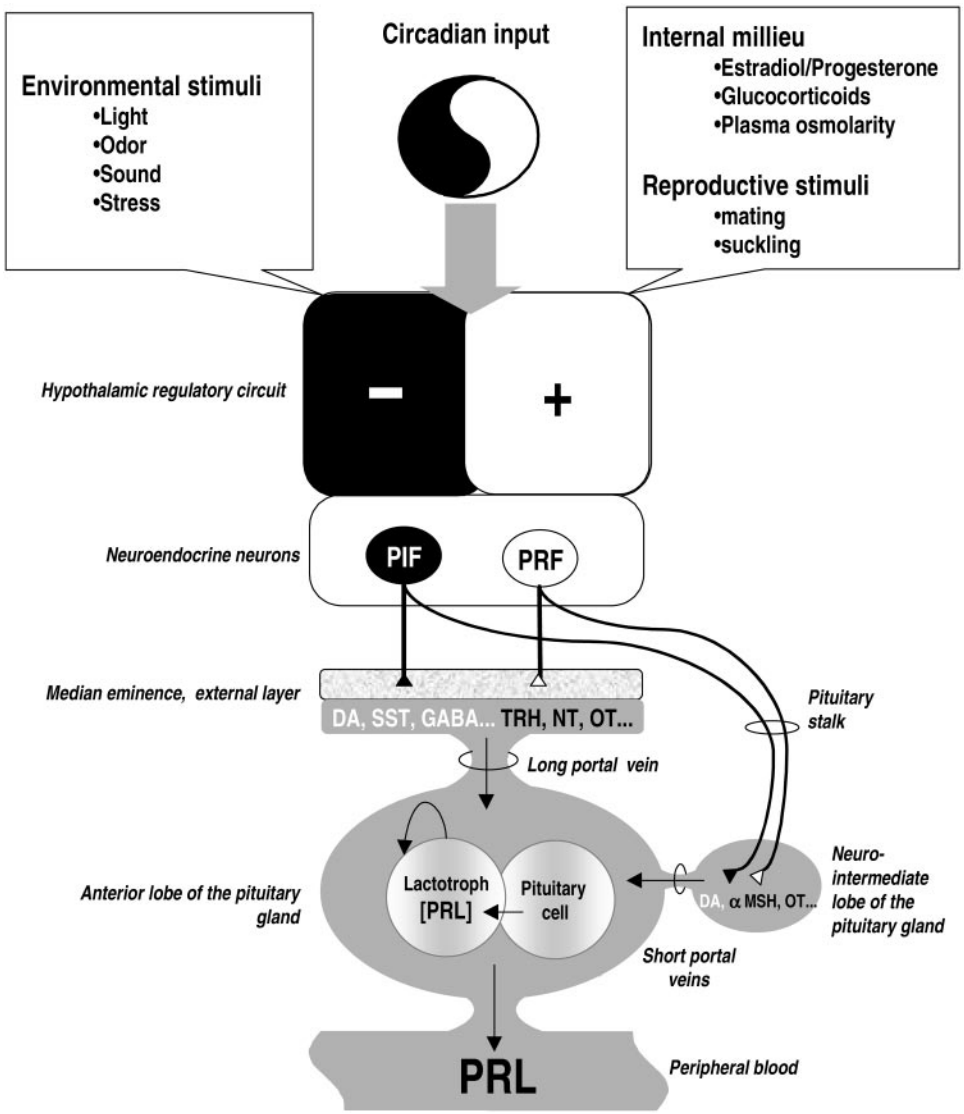

FIG. 3. An overview of the regulation of prolactin secretion. Prolactin secretion is paced by a light-entrained circadian rhythm, which is modified by environmental input, with the internal milieu and reproductive stimuli affecting the inhibitory or stimulatory elements of the hypothalamic regulatory circuit. The final common pathways of the central stimulatory and inhibitory control of prolactin secretion are the neuroendocrine neurons producing prolactin inhibiting factors (PIF), such as dopamine (DA), somatostatin (SST), and γ-aminobutyric acid (GABA), or prolactin releasing factors (PRF), such as thyrotropin releasing hormone (TRH), oxytocin (OT), and neurotensin (NT). PIF and PRF from the neuroendocrine neurons can be released either at the median eminence into the long portal veins or at the neurointermediate lobe, which is connected to the anterior lobe of the pituitary gland by the short portal vessels. Thus lactotrophs are regulated by blood-borne agents of central nervous system or pituitary origin (α-melanocyte stimulating hormone) delivered to the anterior lobe by the long or short portal veins. Lactotrophs are also influenced by PRF and PIF released from neighboring cells (paracrine regulation) or from the lactotrophs themselves (autocrine regulation).

estrous cycle (e.g., ovariectomized females with various ovarian steroid replacement) are also considered.

1. Biogenic amines

A) DOPAMINE. *I) Dopamine is the major PIF.* Observations that drugs affecting catecholamine metabolism also alter prolactin secretion (79, 361) and the fact that dopamine is present in high concentration in both the median eminence (593) and the hypophysial stalk blood (140, 142, 621, 1422) led several investigators to conclude that dopamine is the major physiological hypothalamic PIF. Ample experimental evidence shows that dopamine inhibits prolactin release from pituitary lactotrophs both in vivo and in vitro (1096–1098). Subsequently, dopamine receptors have been detected on pituitary membranes (226, 369, 373, 639). Dopamine receptors located on lactotroph membranes belong to the D_2 subclass of the dopamine receptor family (279, 280, 1171). Recent evidence emphasizes the physiological importance of hypothalamic dopamine in regulating lactotroph function. Mice with a disrupted D_2 receptor gene have anterior lobe lactotroph hyperplasia and hyperprolactinemia (925, 1526). The hyperplasia ultimately leads to lactotroph adenoma in both male and female D_2 knockout mice (92).

II) Anatomy of the neuroendocrine dopaminergic neurons. Using the Falk and Hillarp amine-fluorescence method (533), Dahlström and Fuxe (379) mapped the catecholaminergic neuron populations and classified them as A1 to A15 according to their rostrocaudal distribution in the CNS (379). The dopaminergic neurons of the periventricular and arcuate nuclei of the medial-basal hypothalamus (termed A14 and A12, respectively) provide dopamine to the pituitary gland (655, 656, 783, 922).

The A14 and A12 dopaminergic neuron populations

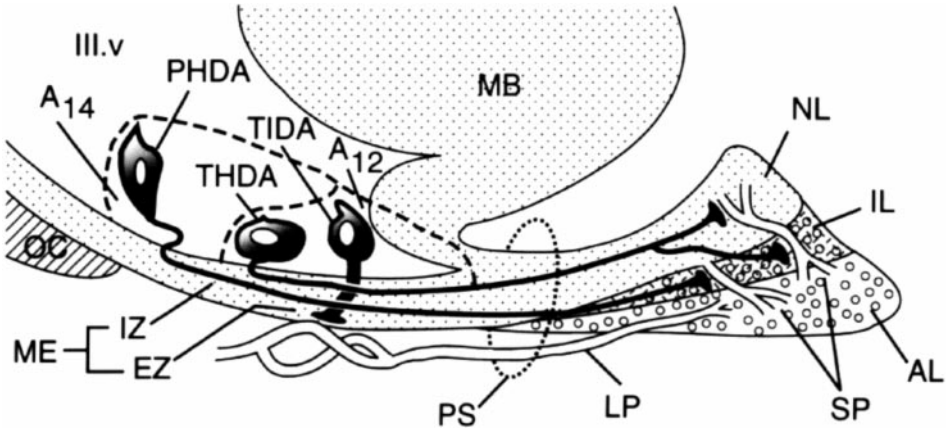

FIG. 4. Neuroendocrine dopaminergic neuron populations in the rat hypothalamus. Perikarya of the periventricular hypothalamic dopaminergic (PHDA) neurons (A14 cell group) are located in the periventricular nucleus, and their axons terminate in the intermediate lobe of the pituitary gland (IL). The arcuate nucleus (A12 cell group) contains the perikarya of two distinct neuroendocrine dopaminergic neuron populations. The tuberohypophysial dopaminergic (THDA) neurons project from the rostral arcuate nucleus both to the neural (NL) and intermediate (IL) lobes of the pituitary gland. From the dorsomedial part of the arcuate nucleus the tuberoinfundibular (TIDA) neurons project to the external zone (EZ) of the median eminence (ME). TIDA terminals release dopamine into the perivascular spaces of the fenestrated capillary loops of the EZ, giving rise to the long portal veins (LP). The long portal veins empty into the sinusoids of the anterior lobe (AL) of pituitary gland. Small short portal (SP) veins connect the fenestrated capillaries of the neural and intermediate lobes with the anterior lobe sinusoids. Thus dopamine of TIDA, THDA, and PHDA origin can reach lactotrophs, located in the anterior lobe of the pituitary gland. III.v, 3rd ventricle; OC, optic chiasma; MB, mammillary body; IZ, internal zone of the median eminence; PS, pituitary stalk. [From Lerant et al. (1029). Copyright The Endocrine Society.]

can be divided into three anatomically and functionally different systems based on the rostrocaudal distribution of the dopaminergic perikarya and their terminal fields in the distinct lobes of the pituitary gland (Fig. 4). TIDA neurons are located mostly in the dorsomedial part of the arcuate nucleus (A12) and project to the external zone of the median eminence (922) where dopamine is released into the perivascular space surrounding the capillary loops of the pituitary portal system. The intermediate and neural lobes of the pituitary gland are innervated by two virtually independent groups of hypothalamic dopaminergic neurons (130, 656). The periventricular hypophysial dopaminergic (PHDA) neurons (A14) are located in the hypothalamic periventricular nucleus and terminate in the intermediate lobe (655). On the other hand, THDA neurons are found in the rostral arcuate nucleus (A12) between the previous two cell groups and project to both the intermediate and the neural lobe of the pituitary gland (783, 784). The microanatomy and biochemistry, as well as the distinct physiological functions of the TIDA and THDA neurons, were first described by Holzbauer and Racke (783). Subsequent studies provided more detailed morphological and functional characterization of the three neuroendocrine dopaminergic systems of the hypothalamus (419, 657, 759, 922, 1076, 1279, 1281, 1373, 1414).

III) TIDA neurons and their regulatory properties. Dopamine of TIDA origin, delivered though long portal vessels into the sinusoid capillaries of the anterior lobe, is considered the major physiological regulator of prolactin secretion (1024).

TIDA neurons have unique regulatory properties compared with other dopaminergic neurons of the CNS, like the nigrostriatal (NSDA) and mesolimbic (MLDA) dopaminergic neurons (1368). Moreover, there are significant differences between the regulatory properties of TIDA neurons in males and females (1368). In females, basal TIDA activity (412, 414) and responsiveness to prolactin are higher than in males (414). This may be explained by tonic inhibition of the activity of TIDA neurons in male rats by endogenous opioids, which is not present in female rats (1123). TIDA neuronal activity is decreased by ovariectomy and increased by orchidectomy (708). These effects were reversed by appropriate steroid treatment (709). There are sexual differences in the response to stress, which decreases TIDA activity in females, but not in male rats (415). Because all of the above experiments were performed in vivo, it cannot be firmly concluded that the sexual specificity was directly at the dopaminergic neuron.

Due to the preponderant influence of dopamine on prolactin secretion at the pituitary level and the well-established feedback action of prolactin on these neurons, it is difficult to separate/isolate the central effects of dopamine from its direct influence on prolactin secretion. Therefore, until recently, the role of dopamine as neurotransmitter in regulation of prolactin secretion was poorly documented. Nevertheless, dopamine can affect prolactin secretion by acting centrally, in addition to its direct action on the lactotroph (155, 156, 474, 475, 486, 487). In male rats, specific D_1 antagonists elevate, whereas D_1 agonists (88) decrease dihydroxyphenylacetic acid (DOPAC) content in the median eminence (155, 475),

indicating D_1 receptor-mediated inactivation of TIDA neurons. Because D_1 receptors have been shown to be coupled to G_o or G_s proteins (1401) that stimulate adenylate cyclase activity, these data suggest D_1-mediated decrease in TIDA activity is mediated by activation of an inhibitory neuron innervating TIDA neurons.

Other pharmacological experiments suggest that TIDA neurons receive stimulatory input through D_2 receptors (156, 474, 486). The latter influence is thought to be mediated by inhibiting inhibitory (possibly dynorphinergic) interneurons (1124). In earlier pharmacological experiments, acute administration of less selective dopamine agonists (e.g., apomorphine) or antagonists (e.g., haloperidol) failed to alter the activity of TIDA neurons (413, 539). On the basis of recent observations made by using pharmacological probes more selective at different dopamine receptor subtypes, it has been concluded that a simultaneous activation or inhibition of D_1 and D_2 receptors cancels the actions mediated by these receptors on TIDA neurons (475).

IV) THDA and PHDA neurons. The role of dopamine released from PHDA and THDA axon terminals at the neurointermediate lobe has attracted more attention during the past few years. For example, it has been reported that the activity of both PHDA and THDA neurons, unlike the TIDA system, is independent of circulating gonadal steroids (1279). Moreover, there are no marked differences between male and female rats in the activity of THDA neurons (759). In addition, it has recently been found that TIDA and THDA neurons, but not PHDA neurons, regulate the control of the secretion of prolactin in response to the suckling stimulus (1281). Surgical removal of the neurointermediate lobe results in a three- to fourfold increase in basal plasma prolactin levels in male, as well as cycling and lactating female rats (143, 1406). Consistent with this finding is the report that electrochemically detectable dopamine in the anterior pituitary gland is reduced after surgical removal of the posterior lobe (1248). Moreover, in lactating rats, basal- and suckling-induced pituitary prolactin secretion is suppressed after water deprivation (1279). Because the THDA system is selectively activated by dehydration (30, 785, 1443, 1764), it is conceivable that dopamine, released by nerve terminals in the neurointermediate lobe of the pituitary gland, may travel to the anterior lobe through the short portal vessels to affect prolactin secretion. Indeed, haloperidol (a D_2 dopamine receptor antagonist) pretreatment can block dehydration-induced plasma prolactin depletion (1279). Thus a reduction or an elevation of dopamine level in blood carried by the short portal vessels may provide a mean by which prolactin secretion of lactotrophs can be affected during lactation.

It is well known that dopamine, released from terminals of PHDA neurons in the intermediate lobe (19, 19, 493, 1711), tonically inhibits the secretion of α-melanocyte stimulating hormone (α-MSH) from melanotrophs of the intermediate lobe (201, 1054, 1747). Therefore, assuming that PHDA neurons participate in the regulation of prolactin secretion, one can expect parallel changes in plasma levels of prolactin and α-MSH during an acute stimulus like suckling (1811). However, it has been clearly shown that there is no change in plasma α-MSH in response to nursing (933). Therefore, an acute diminution in the activity of PHDA-regulated α-MSH secretion does not occur during the suckling stimulus. However, the observations that the dopamine concentration in the neurointermediate lobe is lower and the basal level of plasma α-MSH is higher in lactating than in cycling female rats (1811) indicate some supporting role for PHDA neurons in the regulation of prolactin secretion during lactation.

V) Is dopamine the sole PIF? The question whether dopamine is the sole PIF mediating tonic hypothalamic inhibition is still unsettled. In early studies of this issue, investigators reported that the amount of dopamine in stalk blood is sufficient to account for only about two-thirds of the prolactin inhibition normally observed (403, 1299). This conclusion was based on quantitative studies in which dopamine was replaced in rats depleted of endogenous dopamine with the tyrosine hydroxylase (TH, the rate-limiting enzyme of dopamine synthesis) inhibitor α-methyl-*para*-tyrosine (α-MpT), and the rate of dopamine infusion was set to mimic the levels measured in stalk blood of intact animals (621, 1024). Although the inhibitory influence of dopamine on pituitary prolactin secretion is established beyond a reasonable doubt, an inverse relationship between hypothalamic secretion of dopamine and pituitary secretion of prolactin does not always exist. For instance, the dopamine level in hypophysial stalk plasma is five to seven times lower in males than in females (140, 142, 696), but plasma levels of prolactin are not much different. Moreover, a mirror-image relationship between dopamine concentrations of the median eminence or the portal blood and plasma prolactin has also not been demonstrated in lactation (404, 1421, 1423). The apparent inconsistency between dopaminergic activity and prolactin secretion could easily be resolved by assuming that additional PIF (e.g., GABA and somatostatin) may also contribute to the negative control of prolactin secretion. These alternative PIF candidates (listed in Table 2) are discussed later in this section.

VI) Prolactin secretion due to dopamine withdrawal. The most plausible mechanism for an increase in prolactin release is disinhibition, i.e., that a given stimulus reduces the tonic inhibitory effect of the hypothalamus thus freeing the pituitary gland to express its inherent capacity to secrete prolactin spontaneously at a very high rate (1024, 1299, 1301). Indeed, treatment of rats with sufficient amounts of α-MpT to completely suppress dopamine secretion into hypophysial stalk blood results in

an increase in prolactin secretion (621, 694) quantitatively similar to those observed after suckling or stress. Similar results can be obtained in vitro when removal of dopamine infusion results in a rapid increase of prolactin release (530). Thus disinhibition is a potential mechanism by which neurogenic stimuli induce release of prolactin. However, conflicting results have been reported about the change in dopaminergic neuronal activity in response to the suckling stimulus. Dopaminergic neuronal activity has been described to increase (595), remain unchanged (1240, 1835), or slightly decrease (322, 1181, 1219, 1585) during a single bout of suckling. Most direct studies have been those in which the mammary nerve was stimulated electrically to simulate suckling and dopamine release was detected in hypophysial stalk blood (404, 1423) or in the median eminence with an electrochemical probe (1421). Using this experimental paradigm, only a brief (3–5 min) 60–70% decline in dopamine release was observed (404, 1421, 1423). This decline was followed by a series of rapid pulses of dopamine above the baseline which lasted for the duration of mammary nerve stimulation (1423). These results have led to the conclusion that a decrease in dopamine outflow from the hypothalamus itself is insufficient to account for the suckling-induced prolactin release. However, recent experiments have clearly demonstrated that dopamine content of the inner zone of the anterior lobe obtained from lactating rats is reduced after a 10-min suckling stimulus (1281). This finding seems to explain the previous controversial results, since the inner zone of the anterior lobe has been shown to be the most responsive to the inhibitory action of dopamine (188, 1280). Moreover, increased responsiveness to prolactin secretagogues (like TRH, ANG II, or forskolin) have been observed in lactotrophs of the inner zone, but not the outer zone of the anterior lobe of the pituitary gland after a 10 min suckling stimulus (1280).

VII) Dopamine as a stimulator of prolactin secretion. Several observations on pituitary cells in vitro indicate that dopamine is also capable of stimulating prolactin secretion, especially at low (pM) concentration (252, 427, 979, 1614). It appears that the in vivo status of the donor animals determines the lactotrophs' responsiveness to dopamine in vitro. For example, lactotrophs obtained from suckled lactating rats (761), or estradiol- and progesterone-treated ovariectomized female rats (346), have a propensity to respond by stimulation when challenged with dopamine in vitro. More than a decade ago, Denef et al. (427) then Shin (1614) first reported that a very low concentration of dopamine (1,000-fold lower than those required for maximal inhibition) could actually stimulate prolactin secretion from male rat pituitary cells in vitro. Kramer and Hopkins (979) and more recently Burris and co-workers (251, 252) have extended these studies using both static and dynamic cultures of pituitary cells from cycling female rats. This latter group has found that a rapid reduction in dopamine concentration from 10^{-7} M (a dose that maximally inhibits prolactin secretion) to 10^{-10} or 10^{-12} M caused a greater stimulation of prolactin release than that evoked by complete removal of dopamine (251). Arey et al. (72) and Nagy and co-workers (1280, 1282) have published the first reports, which have clearly suggested a possible physiological relevance of these in vitro data. Arey et al. (72) have demonstrated that infusion of 10 $ng \cdot kg^{-1} \cdot min^{-1}$ dopamine to freely moving rats results in a further increase in the already elevated plasma prolactin when synthesis of endogenous dopamine is blocked by the TH inhibitor α-MpT. The other group has used anterior pituitary cells obtained from nonsuckled (separated from their litters for 4 h) or suckled (for 10 min) lactating rats that were exposed to various concentrations of dopamine in vitro. Prolactin release was measured by reverse hemolytic plaque assay. Surprisingly, pituitary cells from nonsuckled rats exhibited only the prolactin-inhibitory response to dopamine but never actually stimulated prolactin above basal values as has been found for pituitary cells derived from males or cycling females (761, 1282). In striking contrast, a brief suckling stimulus applied immediately before death rendered the prolactin cells responsive to stimulation by 10^{-12} M concentration of dopamine (761).

The case for dopamine enhancement of prolactin secretion both in vitro and in vivo raises the question of the physiological relevance of this phenomenon. Have lactotrophs in situ ever been exposed to dopamine levels low enough to be stimulatory? The suckling stimulus results in a brief and transient reduction in the level of dopamine in long hypophysial portal vessels (404, 1423, 1499). Dopamine concentration in the portal circulation of cycling rats is the lowest during the day of proestrus (140). However, it is doubtful that a 50–70% decrease in portal blood dopamine (140, 404) is sufficient to achieve concentrations capable of stimulating prolactin release. On the other hand, dopamine concentration in stalk blood (140, 142, 621) is in the low nanomolar range (10^{-8} M), which is either ineffective or has only a weak inhibitory effect in vitro (1097), but 100- to 1,000-fold lower doses are required to stimulate prolactin release. One possible explanation is that the diminution in dopamine arriving at the anterior pituitary through the long portal vessels may not accurately reflect the total amount of dopamine the gland "sees." Indeed, a significant portion of the dopamine arriving at the anterior lobe originates from axon terminals in the neurointermediate lobe (1248) and is delivered through short portal vessels (420, 422).

It has been argued that dynamic release of prolactin is partially the consequence of complete withdrawal of dopamine (1133, 1135, 1138). Indeed, many of the transduction events mediating dopaminergic inhibition of prolactin secretion are completely reversed when dopamine is acutely withdrawn (674, 675, 767). Though there is no

doubt that these data support this contention, it is difficult to conceive that the dopaminergic neuron becomes completely quiescent to facilitate prolactin secretion. Indeed, it has been shown that a diminution of dopamine stimulates a far greater amount of prolactin secreted than that in response to complete withdrawal (252).

Another possible explanation for these apparent controversies is the assumption that dopamine may require supplementary agent(s) to effectively inhibit prolactin release and thus properly function as the PIF (1617, 1620). Shin et al. (1617) proposed ascorbic acid, routinely used to protect dopamine from oxidation, as a major candidate for the supplementary factor of dopamine. It is quite clear that ascorbic acid is not a simple antioxidant and can truly potentiate the inhibitory effect of dopamine in vitro by 100 times. Therefore, ascorbic acid may serve as a "responsiveness" agent for potentiating dopamine inhibition of prolactin release. Frawley and co-workers (761) have provided evidence that α-MSH from the intermediate lobe can also function as a responsiveness factor in vitro. In contrast to ascorbic acid, α-MSH decreases the responsiveness of lactotrophs to the inhibitory effect of a high dose of dopamine and enhances their responsiveness to the stimulatory effect of a low dose (761). Ascorbic acid, α-MSH, and possibly other substances as well, produced either in the hypothalamus or in the pituitary gland, may function as a lactotroph responsiveness factor (LRF). These responsiveness factors can be defined as substances with little or no direct influence on prolactin release themselves while they can exert profound effects on prolactin secretion by altering lactotrophs' responsiveness to the classical hypothalamic releasing and/or inhibiting factors.

VIII) Signal transduction pathways in lactotrophs coupled to the dopamine receptor. A number of transduction mechanisms have been described that mediate dopaminergic control of prolactin secretion. Inhibition of prolactin secretion by activation of D_2 receptors has been linked to inhibition of adenylyl cyclase (508, 565) and inositol phosphate metabolism (272, 510, 513, 1635). Moreover, activation of the D_2 receptor modifies at least five different ion channels. Dopamine activates a potassium current that induces plasma membrane hyperpolarization (847) and increases two voltage-activated potassium currents while decreasing two voltage-activated calcium currents (492, 1067–1069, 1070, 1110). It has been shown that the nonhydrolyzable GTP analog guanosine 5′-*O*-(3-thiotriphosphate) (GTPγS) potentiates dopaminergic inhibition of voltage-sensitive calcium channels (1066). With the use of varying antibodies raised against specific G proteins (1065) or antisense oligonucleotide technology (100), it has been shown that the excitation of voltage-sensitive potassium channels through D_2 dopamine receptors is a function of $G_{i\text{-}3}\alpha$, whereas the inhibition of voltage-activated calcium channels is mediated by $G_o\alpha$ proteins (1065). Thus inhibition of prolactin secretion in response to dopamine is a function of coupling of D_2 receptors to a $G_{i\text{-}3}\alpha$ which inhibits adenylyl cyclase activity and concomitantly excites voltage-sensitive potassium channels while coupled to $G_o\alpha$ and inhibiting voltage-sensitive calcium channels. Although the inhibition of cyclase activity may be unrelated to the inhibition of exocytosis (1002), the net effect on prolactin secretion appears to be mediated by inhibition of the calcium channels and excitation of potassium channels.

In contrast, stimulation of prolactin secretion by dopamine involves binding to a D_2 receptor (252) which is functionally coupled to a G_s (251) and in turn activates voltage-sensitive calcium channels (582) that subsequently increase intracellular calcium (248) to facilitate exocytosis (327, 1740).

IX) Prolactin feedback on neuroendocrine dopaminergic neurons. It is well established that prolactin affects its secretion by regulating its own hypothalamic control through a short-loop feedback mechanism (1194). Elevation of serum levels of prolactin increases hypothalamic dopamine synthesis (412) and the concentration of dopamine in hypothalamo-hypophysial portal blood (695). The rate of dopamine synthesis is reduced by hypophysectomy or lowering blood levels of prolactin with bromocryptine (418). Recently, the presence of prolactin-R has been described in all subpopulations (TIDA, THDA, PHDA) of the neuroendocrine dopaminergic neurons (69, 1028), providing the anatomical basis for short prolactin feedback. All of these subpopulations are activated by prolactin (419). With the use of an interesting animal model, the prolactin-deficient dwarf mouse, it has been shown that TIDA neurons do not develop in sufficient number in the absence of prolactin (1413, 1414). Prolactin replacement during development (1498), but not when an adult (1414), reverses this deficit.

X) The dopamine transporter as regulator of prolactin secretion. Termination of dopamine action is primarily achieved by its reuptake by the dopamine transporter located on the terminals of dopaminergic neurons. Mice lacking the dopamine transporter gene are incapable of nursing their young and are significantly growth retarded (626). These animals have a marked reduction in the size of the anterior and intermediate lobes but not the posterior lobe of the pituitary gland (193). Accompanying the anterior pituitary hypoplasia is a diminution of prolactin and growth hormone message and an increased amount of extracellular dopamine in the anterior lobe (193, 421). It is not only the dopamine transporter of TIDA neurons that is effective in regulating prolactin secretion, but the transporter in THDA and PHDA neurons as well (421). Activity of the transporter on TIDA, THDA, and PHDA neurons is required to clear dopamine from the respective perivascular spaces and thus allow prolactin secretion.

B) NOREPINEPHRINE AND EPINEPHRINE. Early pharmacolog-

ical data indicated a tonic inhibitory influence of central noradrenergic systems on basal or estradiol-induced prolactin secretion (1012). The tonic inhibitory effect of norepinephrine is likely mediated by α_1-adrenergic receptors (400). On the other hand, the proestrous surge of prolactin secretion and stress-induced prolactin release is suppressed by surgical or chemical (6-hydroxydopamine) impairment of central noradrenergic pathways (1003). Blockade of central norepinephrine biosynthesis does not alter suckling-induced prolactin release in lactating rats (286).

Data concerning the role of epinephrine in regulating anterior pituitary hormone secretion are scarce. Although the selective blockade of epinephrine biosynthesis in the CNS blocks the estradiol/progesterone-induced LH surge, the secretion of prolactin is not altered by an inhibitor of phenylethanolamine-*N*-methyltransferase (PNMT) (1734). On the basis of these observations, epinephrine does not appear to have a major function in regulation of prolactin secretion (1734). However, other pharmacological (911, 1012, 1818) and morphological data (775) suggest that central adrenergic mechanisms are involved in the regulation of prolactin secretion. More recently, by using light and electron microscopic immunocytochemical techniques, PNMT-immunoreactive axon terminals have been detected terminating on the cell bodies and dendrites of dopaminergic neurons in the arcuate nucleus (805), thus providing a morphological basis for the modulation of TIDA neuronal activity by epinephrine. Taken together, it seems quite conceivable that adrenergic modulation, mediated by either norepinephrine or epinephrine, plays an important role in stress-induced prolactin secretion; the functional context of the immunocytochemical findings (775, 805) is still undefined.

C) SEROTONIN. Although receptors for serotonin are present in the anterior lobe of the pituitary gland (262, 263), serotonin does not stimulate prolactin release in vitro (999, 1000), suggesting that it functions as a neurotransmitter rather than a neurohormone. It seems that the dorsal raphe nucleus is the main source of the ascending serotonergic pathways involved in the regulation of prolactin secretion (Fig. 6) (551, 1788).

Intracerebroventricular or intravenous infusion of serotonin (5-hydroxytrypamine) or its precursor 5-hydroxytryptophan results in an increase of plasma prolactin levels in rats (999, 1085), as well as in humans (919). Moreover, inhibition of serotonin synthesis, while not affecting prolactin secretion in intact rats (972), reduces prolactin release in estrogen-primed rats (260, 313) as well as completely blocks suckling-induced release of prolactin (972). After a block of serotonin synthesis, administration of 5-hydroxytryptophan, the immediate precursor of serotonin, restores the prolactin response to nursing (972). A low dose of the serotonin-receptor blocker methysergide has also been shown to abolish the prolactin response to suckling (600). Suckling results in a rapid (within 5 min) decrease in the hypothalamic concentration of serotonin and an elevation of its metabolite 5-hydroxyindoleacetic acid, simultaneously with the release of prolactin (1181). Although the studies with serotonin receptor antagonists are not always conclusive (986), it can be safely assumed that serotonin facilitates suckling-induced prolactin release. 5-Hydroxytryptophan-induced prolactin release requires an intact neurointermediate lobe (1200) and is blunted by hypothalamic ablation in rats (1341). An essential role of the hypothalamic paraventricular nucleus (PVN) in the 5-hydroxytryptophan- or serotonin agonist-induced increase of prolactin secretion has also been demonstrated (104, 105, 107, 1200). These data suggest hypothalamic target(s) for the ascending serotonergic pathways. However, the hypothalamic dopaminergic neurons do not seem to be the major site where serotonin exerts its prolactin-releasing activity because serotonin elevates prolactin more or less independently of the concentration of dopamine in the portal circulation (1420). Dopamine infusion cannot prevent serotonin-induced prolactin release, and 5-hydroxytryptophan can further increase plasma prolactin in rats pretreated with either α-MpT, the inhibitor of the biosynthesis of dopamine or reserpine, a dopamine-depleting agent (1152).

Serotonin afferents terminating in the suprachiasmatic region are important in the regulation of prolactin secretion, especially in generating the estrogen-induced prolactin surge of ovariectomized rats (921). However, pharmacological lesion of the serotonin neurons with 5,7-dihydroxytryptamine (5,7-DHT), either at the dorsal raphe or suprachiasmatic regions, does not affect suckling-induced or the high afternoon episodic prolactin bursts in lactating rats (1284).

Within the last decade, several serotonin receptor types have been identified in the CNS, but the specific role of one or the other in the mediation of the prolactin response to serotonin is still superficially understood. $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ serotonin receptor agonists increase plasma prolactin in vivo (108, 1040). More recently, the pivotal role of the paraventricular hypothalamic nucleus in the mediation of serotonin-induced prolactin release has been confirmed (104, 105). It has been shown that after a selective lesion of the PVN, prolactin release induced by a $5HT_{2C}$ receptor agonist is completely prevented, and the stimulatory effect of the $5HT_{2A}$ agonist is significantly reduced, whereas there is no change in prolactin response induced by the $5HT_{1A}$ receptor agonist (106, 107). The latter observation suggests that other structures may also have a role in the mediation of the serotonin-induced prolactin response.

D) HISTAMINE. Early pharmacological experiments indicated clearly that endogenous histamine has a stimulatory influence on prolactin secretion (1780). For instance,

intracerebroventricular injection of histamine increases prolactin secretion from male or ovariectomized estradiol-primed rats (59, 456, 458, 460, 1044, 1484), whereas H1 histamine receptor antagonists block suckling- or stress-induced prolactin release (59, 644, 1044). On the other hand, H2 histamine antagonists rather than H1 block exogenous histamine-induced prolactin secretion (58, 457, 460, 1468). Although the precise pharmacological profile of the receptor(s) mediating histamine effects on prolactin secretion is not clear, it seems that histamine may affect prolactin secretion predominantly through H2 receptor activation (58) and that the effects of H1 antagonists on prolactin secretion observed earlier are likely due to a heretofore uncharacterized nonspecific effect of these compounds (1780).

There is little doubt that the effect of histamine on prolactin secretion is mediated through the CNS (960, 962, 1580). Indeed, a wide variety of histaminergic compounds show little direct effect on the pituitary gland (58, 1780, 1879). Because the histamine-induced rise in prolactin secretion coincides with a decrease in dopamine concentration in portal blood (622), it seems likely that the neuroendocrine dopaminergic neurons in the hypothalamus, especially the TIDA system, are the primary targets for a central histaminergic influence. On the other hand, histamine-stimulated prolactin secretion may not be mediated by an inhibition of TIDA systems after all, since intracerebroventricular injection of histamine, while producing a dose-dependent increase of prolactin secretion, does not affect the biochemical indexes of dopaminergic neuronal activity (DOPAC concentration or L-DOPA accumulation) in the median eminence (557). Although the latter results cast some doubt on the direct histaminergic influence on TIDA neurons, it still seems likely that a histamine-dopamine interaction at the hypothalamic level is part of the neural mechanism by which histamine modulates prolactin secretion (558). In addition, histamine, through a presynaptic H3 histamine receptor (1571), is capable of modulating the release of vasopressin (953, 955), norepinephrine (554), serotonin (555, 875), endogenous opioids (958), and dopamine (1571), all of which are involved in the regulation of prolactin secretion.

The role of the central histaminergic system in regulating prolactin secretion was corroborated by the finding that bilateral lesion of the posterior hypothalamus (1317), which destroys histaminergic neurons exclusively localized in the mammillary nuclei (16, 838, 1376), inhibits stress-induced prolactin secretion in male rats (961). In addition, inhibition of histamine synthesis and release by activation of central presynaptic H3 receptors (90, 603) diminishes stress-induced prolactin secretion (961, 1656).

2. Acetylcholine

In GH_3 cells, muscarinic acetylcholine receptor activation decreases prolactin secretion (1885). With the consideration of the rapid deactivation of acetylcholine by the omnipresent cholinesterases, it seems unlikely that acetylcholine of hypothalamic origin subserves a neuroendocrine role as a regulator of prolactin secretion (276).

Cholinergic stimulation by systemic or intracerebroventricular administration of cholinergic agonists causes a decrease in serum prolactin concentration (662, 665, 1043). Moreover, cholinergic agonists (nicotinic and, to a lesser extent, muscarinic) prevent suckling- or estradiol-induced prolactin secretion (58, 180, 1696). It is generally assumed that the inhibitory effect of acetylcholine and its agonist is mediated through the stimulation of TIDA neurons (504, 665, 1696, 1885). This assumption is further supported by the finding that acetylcholine agonists prevent the morphine-induced increase of prolactin secretion (1261), since morphine is known to affect prolactin secretion by decreasing TIDA activity (472, 742, 1836). Acetylcholine administered intracerebroventricularly decreases the concentration of dopamine in portal blood (622), which is obviously inconsistent with the acetylcholine-induced decrease of prolactin secretion (662, 665, 1043). The latter observation indicates that in addition to the hypothalamic neuroendocrine dopaminergic systems, there are other targets of cholinergic modulation of prolactin secretion.

3. Neuropeptides

A) TRH. TRH was originally isolated as a hypophysiotrophic factor that stimulates thyroid-stimulating hormone (TSH) secretion from pituitary cells (1566). Subsequently, TRH has been shown to stimulate prolactin release from lactotrophs in a dose-dependent manner both in vitro and in vivo (178, 202, 1723).

TRH-like immunoreactivity is widely distributed in the CNS (774, 1186). Most of the TRH-immunopositive perikarya projecting to the median eminence are in the parvicellular subdivision of the paraventricular nucleus of the hypothalamus (227, 724, 774, 1015, 1186). TRH is secreted into hypophysial stalk blood (520, 553), and its receptor is present on pituitary cells (1129), specifically on lactotrophs (763). These data would suggest that almost all of the requirements for considering TRH as a PRF in a physiological context are satisfied.

TRH can efficiently stimulate pituitary prolactin secretion in vivo in estrogen-primed male rats (1419) but not in normal male or lactating female rats (681, 1419, 1481). However, the release of prolactin and TSH is dissociated. TSH secretion is found to be only modestly affected (1481) or unaffected (1615) by stress or suckling, whereas

prolactin responses to the same stimuli are quite significant (1481, 1615).

Injection of specific antibodies to immunoneutralize hypophysiotrophic factors (passive immunization) is widely used to confirm the physiological relevance of a given factor. TRH antiserum can suppress the proestrous prolactin surge (963) and attenuate the suckling-induced prolactin response (405). However, TRH antiserum only weakly reduces prolactin-releasing activity of the hypothalamic extract (203, 1704), suggesting that TRH is not the only authentic PRF.

In addition to its well-established role as a prolactin-releasing hormone, TRH may also affect prolactin secretion by acting within the CNS. It has been reported that central administration of TRH inhibits prolactin secretion (1342), most likely through stimulation of TIDA neurons (836, 1342). Because TRH-immunopositive neural projections from the paraventricular nucleus to the arcuate nucleus have been detected (227), there is a morphological basis for a direct TRH/dopamine interaction at the hypothalamic level.

Many studies at the cellular level argue for a role for TRH in the control of prolactin secretion. TRH receptors in lactotrophs have been detected by Hinkle and Tashjian (763). With the use of modern immunocytochemical approaches, TRH receptors have been found on the plasma membrane as well as intracellularly in rat lactotrophs (1917). Primary cultures of rat pituitary cells were stained with an antibody to the native TRH receptor and with a bioactive, fluorescent analog of TRH, rhodamine-TRH. Rhodamine-TRH specifically stained 86% of lactotrophs and 21% of nonlactotrophs from primary pituitary cell cultures. Lactotrophs and thyrotrophs accounted for 90% of cells that were labeled with rhodamine-conjugated TRH, but there were occasional lactotrophs and thyrotrophs that did not show detectable staining with antireceptor antibodies or with rhodamine-TRH (1917). These data imply that some of the functional heterogeneity among lactotrophs (190, 298, 773, 830, 1625, 1708, 1814, 1921) may result from a differential expression of the TRH receptor. With the use of TRH receptor immunocytochemistry and rhodamine-labeled TRH, it has been demonstrated convincingly that the TRH receptor undergoes ligand-directed endocytosis in normal cells (1917). TRH receptors were localized on the surface of cells before TRH exposure, and rhodamine-TRH fluorescence was confined to the plasma membrane when TRH binding was performed at 0°C, where endocytosis is blocked. When cells were incubated with TRH at 37°C, receptors were found in intracellular vesicles in both lactotrophs and thyrotrophs, and rhodamine-TRH was rapidly internalized into endosomes at elevated temperatures (1917).

Once bound to the receptor, TRH activates GTP-binding proteins (1002), which have been characterized as either G_s (943), G_q or G_{ll} (807). Activation of G_q or G_{ll}, in turn, activates membrane-bound phospholipase C that catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate to yield inositol trisphosphate and diacylglycerol (57, 529, 807, 1684). Inositol trisphosphate mediates the mobilization of nonmitochondrial calcium in lactotrophs (617). Diacylglycerol, in turn, activates calcium-dependent protein kinase C (467) which phosphorylates voltage-sensitive calcium channels resulting in increased Ca^{2+} influx, and thus enhances prolactin exocytosis (563, 564, 747).

TRH was originally depicted as rapidly stimulating a biphasic pattern of prolactin secretion characterized by a first phase fast elevation within 30 s followed by a lower amplitude sustained secondary phase (17, 924). On the basis of studies in tumorous cell lines, it has been suggested that this pattern of prolactin secretion parallels and is the result of similar changes in intracellular calcium. More specifically, it has been suggested that inositol trisphosphate induces an initial rapid release of calcium from intracellular stores that mediates the first phase of prolactin secretion while the second phase is the consequence of diacylglycerol-induced activation of protein kinase C, phosphorylation of a voltage-gated calcium channel, and ultimately entrance of calcium from extracellular sources (215, 614–616, 722, 971). However, using selective pharmacological depletion of intracellular calcium stores or blockade of voltage-sensitive calcium channels, it was suggested that in normal pituitary cells, calcium influx and/or transduction pathways linked to calcium influx are more important to prolactin secretion in response to TRH than is liberation of Ca^{2+} from cytoplasmic stores (1558).

Newer data have revealed more of the spatiotemporal complexity of the cytoplasmic Ca^{2+} changes. For instance, using membrane capacitance measurements to study TRH-induced modulation of exocytosis by metabolically intact perforated patch-clamped rat lactotrophs, it was found that TRH promotes exocytosis through three distinct stages (563). First, within 30 s, TRH transiently evokes exocytosis that is independent of membrane depolarization and extracellular calcium influx, but is likely driven by Ca^{2+} released from inositol trisphosphate-sensitive intracellular pools. Second, within 3 min of exposure, TRH facilitates depolarization-evoked exocytosis while inhibiting the voltage-gated calcium current. Finally, after 8 min, TRH further enhances depolarization-evoked exocytosis by increasing high voltage-activated calcium channel current through a protein kinase C-dependent mechanism (564).

Finally, there is a large amount of literature showing that transient dopamine antagonism (716–721) or transient dopamine withdrawal (1132–1134, 1136–1138) magnifies the stimulatory effect of TRH on prolactin secretion. Although the data are convincing, the interpretation must be approached with caution, since it is unlikely that,

under physiological conditions, dopaminergic neurons become totally quiescent. It seems more likely that the lactotroph is exposed to diminishing concentrations of dopamine rather than a complete absence of dopamine. The effect of a reduction of dopamine exposure on TRH-stimulated prolactin secretion has yet to be determined.

B) OXYTOCIN. Oxytocin is synthesized in the PVN and supraoptic nucleus (SON) and axonally transported to the neural lobe where it is briefly stored until release from terminals. Axons of the oxytocin neurons passing through the median eminence already form synaptic boutons, which contact the capillary loops of the median eminence. Indeed, oxytocin release into the long portal vessels has been well-established (620, 1320). Moreover, short portal vessels connecting neural lobe and the inner zone of the anterior lobe also provide a potential route for delivering oxytocin to the adenohypophysis.

The stimulatory effect of neurointermediate lobe extracts on prolactin release has been thought to be partially due to the influence of oxytocin in the extracts (1537). Oxytocin is secreted into the hypophysial portal blood in 10–15 times higher concentrations than found in the peripheral circulation (620), and high-affinity receptors resembling the uterine oxytocin receptors are present in the anterior lobe. However, the prolactin-releasing potency and efficacy of oxytocin in vitro are rather low (827, 1537), and the definitive role of oxytocin as a neurohypophysial PRF requires further attention.

Several studies have previously indicated that, at least in certain experimental situations, oxytocin may be involved in the stimulatory regulation of prolactin secretion (1372, 1542). Although a large dose of oxytocin induces a rise in plasma prolactin in male or ovariectomized female rats (1087), it fails to affect prolactin secretion in lactating rats. In contrast, subcutaneous administration of a low dose of oxytocin induces a reduction in basal as well as stress-induced secretion of prolactin in male rats (1087, 1235, 1243). Attempts to antagonize the action of endogenous oxytocin in vivo have also resulted in conflicting data. Passive immunization with oxytocin antisera delays and reduces prolactin surges induced by suckling or by estrogen (1537). On the other hand, injection of a specific oxytocin antagonist, which blocks suckling-induced milk ejection, does not alter concomitant prolactin release (867). However, treatment with an oxytocin antagonist prevents the proestrous surge of prolactin (867). Moreover, oxytocin antagonism blocks the endogenous stimulatory rhythm (73, 74, 76) that governs prolactin secretion in female rats (71). Similarly, oxytocin antagonism blocks mating-induced prolactin secretion (74). Therefore, it seems likely that oxytocin may act as a PRF under some (but not all) physiological states.

In addition to its role as neurohormone, the possibility of central effects of oxytocin should also be taken into consideration (1309, 1310). For instance, oxytocin as neurotransmitter may play a stimulatory role in regulating TIDA neurons (1919), which, in turn, would convey an inhibitory influence on prolactin secretion.

C) VASOPRESSIN. Similar to oxytocin, vasopressin is synthesized by the magnocellular neurons located mainly in the posterior division of the paraventricular and the supraoptic nuclei (1657). In addition, vasopressin immunoreactivity is also found in the parvicellular neurons of the medial division of the paraventricular neurons (1657). The axons of the magnocellular neurons pass through the median eminence en route to the posterior lobe of the pituitary gland (782), whereas the parvicellular neurons project directly to the external zone of the median eminence to terminate on the primary capillary bed from which the long portal vessels arise (1657). Therefore, vasopressin can reach the anterior lobe of the pituitary gland from both sources, through the long or the short portal systems (673).

Previous studies have clearly indicated that disturbances in the water and electrolyte regulation at the level of the neural lobe severely alters adenohypophysial prolactin secretion (450, 829, 1283). Bilateral anterior hypothalamic deafferentation behind the optic chiasm or lesion of the PVN interrupting the paraventriculo-, and supraoptico-hypophysial tract (948), or denervation of the neural lobe (1811) result in diabetes insipidus (145) and prevent suckling-induced prolactin release in oxytocin-substituted lactating animals. In addition, there is no suckling-induced hormone response in homozygous Brattleboro mothers suffering diabetes insipidus due to the genetic failure of the biosynthesis of arginine vasopressin (829, 1283, 1283). Moreover, passive immunizations against arginine vasopressin (1283), or the glycopeptide moiety of the vasopressin-neurophysin-glycopeptide precursor, with a highly specific antiserum attenuates the suckling-induced rise of plasma prolactin (1276). Taken together, these data suggest that vasopressin and related peptides play a significant role in regulating prolactin secretion.

Although arginine vasopressin induces prolactin release in vivo (1372, 1785, 1809), it does not effectively release prolactin in vitro (734, 1616). There are arginine vasopressin receptors in the rat anterior pituitary (47, 957), and arginine vasopressin is present in high concentration in portal blood (1926). In addition, neurophysin II, the midportion of the prepro-vasopressin molecule, can stimulate prolactin release from the anterior lobe but not through a direct effect on the pituitary gland (1618). The 39-amino acid glycopeptide comprising the COOH terminus of the vasopressin precursor has been reported to stimulate (1276), inhibit (1567), or have no effect (829) on prolactin release from cultured pituitary cells. Passive immunization studies support the stimulatory role of this peptide in the control of prolactin secretion (1276). Despite some controversial and inexplicable results, vaso-

pressin, its precursor, its specific neurophysin, or other factors associated with diabetes insipidus may affect pituitary prolactin secretion (50, 952).

Vasopressin exerts its physiological effects by activating at least two different receptors: the V_1 ("vascular") vasopressin receptor is most abundant in vascular smooth muscle cells and hepatocytes, whereas the V_2 receptors were originally found in the renal tubular epithelial cells (857). The V_1 couples to the phosphoinositide signaling pathway, whereas the V_2 receptors activate adenylate cyclase (857). The arginine vasopressin-induced increase in prolactin secretion is mediated mainly through V_1 (50, 952), although other vasopressin receptor(s) may also play a role (954, 955).

D) THE SECRETIN/VIP FAMILY. Several biologically active peptides of the secretin/VIP family, such as VIP, peptide histidine-isoleucine (PHI) and the recently discovered pituitary adenylyl cyclase-activating polypeptide (PACAP) have been shown to significantly affect pituitary prolactin secretion.

VIP was originally isolated from porcine small intestine (1527). Its presence was then demonstrated in the hypothalamic paraventricular nuclei and the median eminence (162, 380, 1010, 1191, 1399, 1638). PHI and VIP are synthesized from a common precursor (848) and are homologous to each other (1709, 1727). Both peptides are secreted in equimolar amounts into hypophysial portal blood (1608). The new relative in this family is PACAP (1208). PACAP is a VIP-like hypothalamic peptide occurring in two forms, PACAP-27 and the COOH-terminally extended PACAP-38. These peptides share strong sequence homology (68%) with the NH_2-terminal portion of VIP and can induce a very strong accumulation of cAMP in cultured anterior pituitary cells (1208) by binding to high-affinity receptor sites (1623).

VIP can stimulate prolactin release both in vivo and in vitro (917, 1512, 1591, 1823) through a direct action on VIP receptors found in anterior pituitary cells (125). VIP stimulates prolactin release in vitro between 10^{-7} and 10^{-10} M concentrations in a dose-related manner (1608–1610). Moreover, it is detected in the portal blood in a concentration ~10 times higher than that found in the general circulation (1528), which is sufficient to stimulate prolactin release from pituitary cells in vitro. These findings suggest that VIP may be an important mediator of prolactin release in different physiological situations. Moreover, when passive immunization is performed to neutralize VIP in the plasma (891, 1611), stimulation of prolactin release by ether stress is completely blocked (1611), whereas suckling-induced prolactin response is only partially inhibited (4). Simultaneous administration of VIP and PHI antisera completely blocks 5-hydroxytryptophan-induced prolactin release (891), while passive immunization with antisera to either VIP or PHI results in only a minimal effect (891). Taken together, these data suggest that endogenous VIP-like peptides likely play a role as hypothalamic neurohormones (i.e., PRF) by transducing central stimulatory influences on the pituitary lactotrophs (1313, 1506), particularly those which are conveyed by serotonergic mechanisms (891). VIP also plays a role as an autocrine regulator of prolactin secretion (715, 1275), and as such, can be released by the lactotrophs themselves. Therefore, the source of VIP affected by in vivo immunoneutralization is not clear. As to what proportion of the reduction of prolactin release by VIP antiserum is due to the neutralization of VIP of hypothalamic origin remains to be established.

Similar to VIP, PHI can stimulate prolactin release in the freely moving rat (892, 1343, 1873) as well as from dispersed pituitary cells (1538). The relative contribution of PHI and VIP to the control of prolactin secretion requires further investigation.

Systemic injection of PACAP-38 significantly and dose-dependently stimulates pituitary prolactin in both male (1025) and nonsuckled lactating female rats (67). This effect of PACAP on prolactin secretion is likely related to its stimulation of prolactin gene expression (212, 352, 1815) through a protein kinase A-mediated pathway (353). Surprisingly, PACAP-38 dose-dependently inhibits prolactin release in both monolayer cultures (858) and reverse hemolytic plaque assay (858) of rat pituitary cells. Thus in vitro and in vivo experiments provide contrasting effects of PACAP-38 on pituitary prolactin release.

Early observations already indicated that, in addition to their direct action on lactotrophs, there is a hypothalamic site of action for some of these peptides (849, 917, 1823). However, there is no consensus as yet concerning the central effects of the secretin/VIP peptide family on prolactin secretion. For instance, preoptic injection of VIP, but not of secretin or PHI, stimulates prolactin secretion (123), suggesting specific actions of VIP on the preoptic mechanisms governing prolactin secretion in ovariectomized rats (123).

Both PACAP and VIP, when administered intracerebroventricularly to conscious ovariectomized estradiol-implanted female rats, stimulate TIDA activity (813). However, the effects of these peptides on prolactin secretion are opposite: whereas PACAP inhibits, VIP stimulates prolactin secretion (813). The inhibitory effect of PACAP on prolactin secretion is consistent with its stimulation of hypothalamic dopaminergic activity. It seems, however, that in the case of VIP, an additional unknown mechanism comes into play [perhaps an increase of PRF from hypothalamic sources (74, 1547)] that would override the consequence of TIDA activation. Interestingly, in sheep, PACAP also inhibits prolactin secretion (1560) by acting within the medial basal hypothalamus (40). However, in anesthetized male rats, central administration of

PACAP-27 or PACAP-38 elicits a dose-related increase in plasma prolactin level (1900).

E) OPIOIDS. The discovery of opiate receptors in the CNS in the early 1970s (1405, 1636, 1731) initiated the search for endogenous ligands for these receptors. The first two endogenous opioid peptides (EOP) were soon discovered (815, 816) and termed enkephalins (Met-enkephalin, H-Tyr-Gly-Gly-Phe-Met-OH; and Leu-enkephalin, H-Tyr-Gly-Gly-Phe-Leu-OH). Later studies revealed that endogenous opioids consist of three separate peptide families, enkephalins, dynorphins, and endorphins, encoded by three separate genes (19). Based on pharmacological characteristics and the biological response they initiate, three major types of opiate receptors have been identified (1130), and later cloned (μ, δ, and κ) (245, 935, 1119, 1196). They all belong to the seven transmembrane G protein-coupled receptor superfamily (934, 1119).

The enkephalin immunopositive neurons are the most widely distributed among the EOP expressing neurons (931). In the hypothalamus the paraventricular and supraoptic nuclei are abundant in enkephalin-immunopositive neurons that project to the posterior lobe of the pituitary gland. The endorphin/ACTH immunopositive neurons are distributed almost exclusively in the medial basal hypothalamus (arcuate nucleus, extended rostrally into the retrochiasmatic area, caudally into the submammilary region, and dorsally into the zone between the ventricular surface and the ventromedial hypothalamic nucleus) and in the brain stem (nucleus intercomissuralis of the tractus solitarius) (1316).

Distribution of the opiate receptors in the hypothalamus was studied extensively, first by receptor autoradiography (1034) and, following the molecular cloning of various types of opiate receptors (522, 935, 1041), by in situ hybridization (1119). These studies revealed an abundant expression of κ-receptors in the magnocellular neurons (PVN, SON), arcuate nucleus, and medial preoptic area (1119). However, with the exception of the medial preoptic area, expression of the μ-receptor is modest in these areas (1119), which seems somewhat discordant with the previous pharmacological characterization of the opiate receptors affecting TIDA neurons and/or prolactin secretion (965). It is important to add, however, that by immunohistochemical methods, strong staining for a μ-receptor-like protein is found in the external zone of the median eminence (1119). Because little μ-opiate receptor mRNA was found in the median eminence, it is assumed that the μ-receptor protein is synthesized elsewhere and transported to the median eminence along the axons of the phenotypically uncharacterized neurons. The latter findings strongly indicate a presynaptic inhibitory function of μ-receptors at the median eminence level. It has been reported that endogenous opioids can antagonize the effect of dopamine at the pituitary level (1511), although this conclusion was later contested by others (448).

A considerable amount of data obtained with a wide variety of opiate agonists indicate that endogenous opioids indeed play an important role in regulating prolactin secretion (1346). The opiate receptor subtypes mediating the effect of opiate agonists on prolactin secretion are predominantly μ and κ (984, 985). Opioid receptor blockade by a single intravenous injection of naloxone completely suppresses the proestrous prolactin surge (833), indicating that some endogenous opioid activity is required to generate the prolactin secretory surge during proestrus in the rat. In addition, endogenous opioid peptides play an important role in the hypothalamic control of the menstrual cycle (545, 546).

Recent investigations reinforced the notion that endogenous opioids contribute to suckling-induced prolactin secretion by inhibiting neuroendocrine dopaminergic neurons in the hypothalamus (70). Sustained naloxone infusion (12 h) decreases prolactin concentration in the serum of nursing lactating dams. In the absence of suckling stimuli, the infusion of naloxone does not influence the already low prolactin concentration. However, it robustly diminishes suckling-induced prolactin secretion following pup deprivation. Consistent with the effects on prolactin secretion, TH activity in the median eminence is elevated, and TH mRNA level is increased in the arcuate nucleus by sustained naloxone infusion (70). In addition, endogenous opioids also mediate the nocturnal surge of prolactin secretion in pseudopregnant rats (1525).

Most stressful stimuli activate inhibitory neuronal pathways that decrease the activity of TIDA neurons resulting in an increase of prolactin secretion (415, 415, 866, 868, 1076). Endogenous opioids (83, 440, 547, 693, 1806) and opiate agonists (31, 86, 440, 693, 908, 1121, 1123, 1467, 1806) suppress the activity of TIDA neurons, presumably by activation of μ and/or κ type of opiate receptors (261), while increasing prolactin secretion (742, 1804, 1805). Because specific opiate antagonists suppress stress-induced prolactin secretion in most cases (473, 866, 1504, 1540, 1634, 1789, 1891), it seems likely that endogenous opioids contribute to the stress-induced increase of prolactin secretion via inhibition of the TIDA system. The responsiveness of TIDA neurons to stress is not influenced by the stage of the estrous cycle, indicating that the level of ovarian steroids in the circulation may not be the primary feedback signal affecting the responsiveness of TIDA neurons to endogenous opioids (415). However, sustained elevation of adrenal glucocorticoids, resulting from chronic activation of the hypothalamo-pituitary-adrenal axis, decreases the efficacy of opioid agonists to affect TIDA activity and/or prolactin secretion (540, 541, 908, 937). These latter observations indicate that the regulation of prolactin secretion by endogenous opioids is

well integrated into the overall neurohumoral mechanisms of adaptation (homeostasis).

Hyperprolactinemia, brought about by pregnancy, pseudopregnancy, lactation, or experimental manipulations (e.g., pituitary grafts under the kidney capsule, chronic D_2 dopamine antagonist administration), invariably results in elevated enkephalin gene expression in TIDA neurons (1185, 1187). The latter effect of heightened prolactin secretion is augmented by progesterone, whereas estradiol has little or no effect (1187). Although enkephalins might serve as a negative-feedback signal that regulates TIDA activity during pregnancy in an autocrine manner (1187), the physiological significance of these intriguing observations is still uncertain.

It is well established that certain elements of the neural circuitry regulating prolactin secretion are especially sensitive to ovarian and/or adrenal steroids. The actual hormonal milieu and the previous history of the animal seems equally important to determine the characteristics of the regulation of prolactin secretion by endogenous opioids. For instance, long-term application of estradiol to the arcuate nucleus reverses the role of endogenous opioids and serotonin in the regulation of prolactin secretion, whereas opioid antagonism with naloxone or serotonin synthesis inhibition by *para*-chlorophenylalanine both elevate prolactin secretion (281, 282). Moreover, the prolactin response to an enkephalin analog is dependent on the presence or absence of the suckling stimulus (1278).

Although extrahypothalamic site(s) whereby endogenous opioids alter prolactin secretion cannot be excluded, the prevailing view of the locus of endogenous opioids' action asserts that it takes place at the hypothalamic level (1485, 1836, 1880). Indeed, chemical lesions within the arcuate nucleus by neonatal administration of monosodium glutamate impairs the ability of morphine to induce prolactin secretion (49) while the opiate antagonist naloxone diminishes the release of prolactin evoked by electrical stimulation of the medial basal hypothalamus (48). A number of functional studies indicate that opioids directly affect the activity of the TIDA neurons (472, 742, 1836). Recently described neuroanatomical studies support this assertion (1119).

Prolactin at a concentration of 100 nM stimulates the release of β-endorphin from hypothalamic organ culture while decreasing the secretion of gonadotrophic hormone-releasing hormone (GnRH) (265). The latter effect of prolactin is blocked by naloxone, indicating that hyperprolactinemia-induced depression of gonadotropin secretion is mediated by endogenous opioids (265). The connection between hyperprolactinemia and the suppression of GnRH secretion by persistent activation of an endogenous opioid system is supported by several other observations. For instance, the polycystic ovarian condition induced by estradiol valerate (which induces hyperprolactinemia) can be relieved by chronic treatment with an opiate antagonist (290).

F) ANG II. The octapeptide angiotensin II is the main effector of the renin-angiotensin system (194, 1521). The final steps of its biosynthesis involve consecutive proteolytic cleavages of its inactive precursors, angiotensinogen and angiotensin I, by renin and angiotensin converting enzyme (ACE), respectively (194, 544). Angiotensin II is produced both systemically and locally in various tissues, such as the vascular endothelium, heart, brain, pituitary, ovary, and adrenal gland (194, 544, 1521). It is important in regulation of blood pressure, vascular tone, and salt and water homeostasis, and it can influence cell growth, migration, differentiation, and apoptosis in many different target tissues (194, 544, 1521).

Pharmacologically, angiotensin receptors have been classified into two subtypes: AT_1 and AT_2 receptors (194, 243, 1751). Although both AT_1 and AT_2 receptors have been detected in the brain (869, 870, 1021, 1023, 1778), it appears that AT_1 is the dominant receptor subtype in adults (1022, 1364, 1778). In addition to the AT_2 receptor (832), two isoforms of the AT_1 receptor, AT_{1A} and AT_{1B}, have been isolated in rodents by molecular cloning (711, 850, 894, 1710). The AT_{1B} is the predominant ANG II receptor expressed in the pituitary gland (1022) while AT_{1A} is present in areas of the hypothalamus pertinent to the regulation of pituitary function (869, 871, 871a, 1022, 1777).

Numerous observations indicate clearly that ANG II could contribute to the physiological regulation of prolactin secretion, both at hypothalamic (1265, 1266, 1521, 1673, 1675, 1678, 1777) and pituitary (14, 14, 36, 409, 746, 1575) levels. When applied directly to pituitary cells in vitro, ANG II seems more specific than TRH, the leading contender among the PRF candidates, as it releases prolactin while it has little or no effects on other pituitary hormones (14). Moreover, the in vitro efficacy of ANG II on prolactin secretion is greater than TRH (14).

Centrally administered ANG II appears to be inhibitory to prolactin secretion in male (1266) as well as female (1265, 1521, 1675, 1678) rats, regardless of the endocrine status of the animal. On the other hand, the endogenous angiotensin system in the hypothalamus does not seem to be involved in maintaining the low level of basal prolactin secretion, since centrally administered angiotensin receptor antagonist or angiotensin convertase inhibitor do not increase prolactin secretion of ovariectomized female (1265) or male (1266) rats. However, the blockade of the central angiotensin system by these compounds greatly facilitates stress- or estradiol-induced prolactin secretion (1265, 1266, 1521). On the basis of these data, it has been proposed that a possible function of the endogenous angiotensin system in the hypothalamus is to limit the magnitude of prolactin secretion in response to environmental or endogenous stimuli (1521, 1673).

Several studies support the hypothesis that hypothalamic AT_1 receptors participate in the ovarian steroid feedback on prolactin secretion (1521, 1673). The number of AT_1 receptors in the arcuate nucleus is inversely related to prolactin secretion: low during proestrus and highest at estrus and confined to the dorsomedial portion of the arcuate nucleus (1586) where the cell bodies of the TIDA system are located (527). In subsequent studies, it has been demonstrated that a combined treatment of estradiol and progesterone induces ANG II AT_{1A} receptor mRNA expression specifically in dopaminergic neurons in the dorsomedial arcuate nucleus (871a). As demonstrated earlier, these dopaminergic neurons also express estradiol and/or progesterone receptors (967, 1548, 1549, 1626, 1861). It appears, therefore, that the ovarian steroid-induced regulation of ANG II receptors in TIDA neurons exemplifies the generally accepted concept that a wide array of central peptidergic and peripheral hormonal signals converge on and are integrated by the TIDA neurons (Fig. 5).

Signaling events coupled to AT_1 receptors include elevation of phosphatidylinositol hydrolysis through phospholipase C activation and intracellular Ca^{2+} mobilization, increase of cAMP formation, activation of multiple protein kinases (protein kinase C, several protein tyrosine kinases, mitogen-activated protein kinases), and protooncogene expression (506, 513, 610, 1075, 1572, 1902). There is ample evidence that an increase in phosphatidylinositol hydrolysis through phospholipase C activation is the major initial signaling event elicited by ANG II receptor activation in lactotrophs (269, 270). In addition, ANG II causes an elevation in cAMP formation in lactotroph-enriched pituitary cell preparations in parallel with its stimulatory effect on prolactin secretion (93). The effect of ANG II on adenylyl cyclase seems to be phospholipase C-mediated since it is sensitive to inhibition of the phospholipase C/protein kinase C pathway (93). Dopamine inhibits angiotensin-induced phosphatidylinositol turnover and cAMP formation in a pertussis toxin-sensitive manner (513). Peripheral hormones such as ovarian steroids or glucocorticoids seem to modulate the sensitivity of adenohypophysial cells to the dopaminergic inhibition of ANG II effects (513, 1265, 1675).

G) SUBSTANCE P. Substance P and related peptides (neurokinin A and neurokinin B) are members of the mammalian tachykinin peptide family, currently referred to as neurokinins (1456). These peptides result from processing two preprotachykinin (PPT) gene products. Substance P and neurokinin A originate from PPT-A, whereas neurokinin B originates from PPT-B. The physiology and pharmacology of these peptides and their receptors have been reviewed (1359, 1456). Although these peptides have been found in many different tissues, they are mainly expressed in neurons (932, 1359). It appears that their main physiological function is related to neurotransmission (932, 1359).

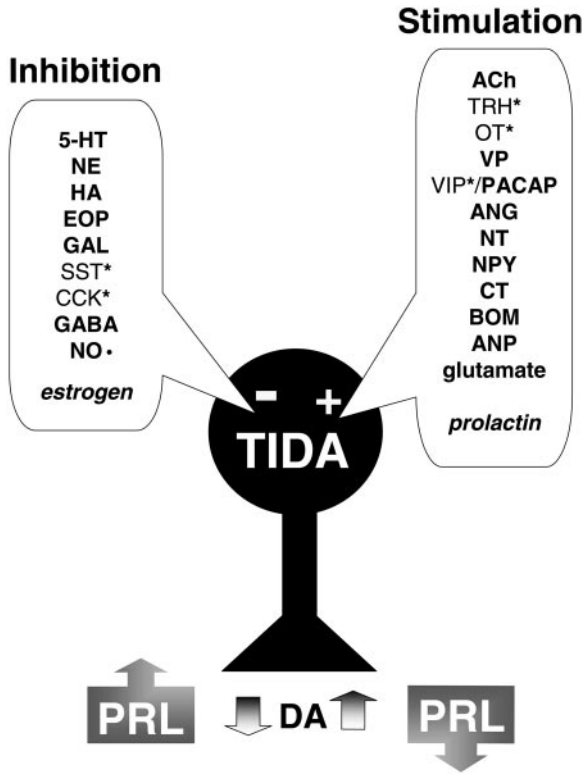

FIG. 5. Direct effects of neurotransmitters, neuromodulators, and peripheral hormones on the activity of tuberoinfundibular dopaminergic system (TIDA). The inhibitory agents (*left*) will promote an increase of prolactin secretion as a result of diminishing TIDA activity. On the other hand, the stimulatory neurotransmitters and progesterone (*right*) will tend to decrease prolactin secretion as a result of increasing output of TIDA neurons. It should be noted, however, that many of these agents have multiple levels of action, often with opposing biological effect. Therefore, in some cases (*), effects on PRF and/or directly at the lactotrophs will prevail over the influence on TIDA activity. See text for references and further details. 5-HT, serotonin; NE, norepinephrine; HA, histamine; EOP, endogenous opioid peptides (endorphin, enkephalin, dynorphin, nociceptin/orphanin); GAL, galanin; SST, somatostatin; CCK_8, cholecystokinin-8; GABA, γ-aminobutyric acid; NO, nitric oxide; ACh, acetylcholine; TRH, thyrotropin releasing hormone; OT, oxytocin; VP, vasopressin; VIP, vasoactive intestinal polypeptide; PACAP, pituitary adenylate cyclase-activating peptide; ANG II, angiotensin II; NT, neurotensin; NPY, neuropeptide Y; CT, calcitonin; BOM, bombesin-like peptides (gastrin-releasing peptide, neuromedin B, neuromedin C); ANP, atrial natriuretic peptides.

High immunoreactive substance P concentration is found in the median eminence-arcuate region in primates (777, 1005, 1500), while it is less abundant in rodents (228, 376, 1062). However, in rats receiving colchicine intraventricularly, numerous substance P immunoreactive cell bodies and fibers are found in the arcuate nucleus, the ventral portion of the ventromedial nucleus, the dorsomedial nucleus, and the periventricular area (1776). Abundant immunoreactive fibers are also found in the median eminence surrounding capillaries in the subependymal layer, as well as in the palisade structure in the external

layer of the median eminence (1776). In the arcuate nucleus, synapses of substance P fibers are readily detectable by immunoelectron microscopy. In the median eminence, substance P immunoreactive fibers are frequently seen in the subependymal, internal, and external zones (1776). In the median eminence, immunoreactive substance P fibers do not form synapses but appear terminate on the basal lamina covering the pericapillary space (1776). In some cases, extrusions of substance P immunoreactive fibers into the perivascular space are also observed. Moreover, a high level of expression of substance P receptors has been detected in all of these areas of the hypothalamus (1120). Taken together, these neuroanatomical attributes indicate strongly that substance P acts as a neurotransmitter in the arcuate nucleus and other parts of the hypothalamus and, as such, is likely involved in the regulation of prolactin secretion. In addition, substance P may modulate the release of PRF/PIF neurohormones presynaptically in the median eminence. Finally, the rather conspicuous presence of immunoreactive substance P fibers in the external zone of the median eminence indicates that substance P could have a role as a neurohormone and might reach the lactotrophs in the pituitary gland through the long portal vessels (1776).

Specific substance P binding sites have been detected in the pituitary (930, 1006, 1007), and by the combined application of receptor autoradiography and immunocytochemistry, specifically in lactotrophs (1008). Prolactin secretion is enhanced when pituitaries are incubated in the presence of substance P (1819, 1820). Moreover, prolactin secretion increases following intravenous administration of substance P (1482), indicating that substance P probably has a direct action on lactotrophs.

Substance P injected intraventricularly induces an increase in prolactin secretion in primates (489) as well as rats (1820). Microinjection of substance P into the medial preoptic area of conscious, freely moving animals increases prolactin secretion both in normal and orchidectomized rats (1416). Conversely, substance P antagonist or substance P antiserum injection in the same area decreases prolactin secretion, indicating that endogenous substance P in the medial preoptic area exerts a stimulatory influence over prolactin secretion (1416). However, negative results with centrally injected substance P antiserum or substance P antagonist have also been reported. For instance, in castrated male rats, substance P antagonists or substance P antiserum failed to influence prolactin secretion (402). It appears that the actual effect of substance P on prolactin secretion depends on the dose and route of administration: intracerebroventricularly injected substance P stimulates prolactin secretion, whereas at lower doses it is inhibitory (80, 81, 701). Similar paradoxical effects of substance P have been observed with intravenous administration (1482, 1739, 1820).

On the basis of pharmacological and neuroanatomical evidence, there is little doubt that substance P is an important factor in the regulation of prolactin secretion (861). However, the neural mechanism by which substance P or other members of the tachykinin/neurokinin family exert their action on prolactin secretion is not yet understood. The fact that these peptides have multiple sites of action, together with the possibility that biologically opposing effects can be elicited by these peptides at different loci, makes it difficult to explore their physiological role in regulating pituitary hormone secretions. Local administration of recently developed specific neurokinin receptor agonists and antagonists (932) would help to elucidate the precise physiological role of substance P and other tachykinins/neurokinins in regulating prolactin secretion.

There are some observations suggesting that tachykinins in the CNS and the pituitary are involved in prolactin feedback regulation. For instance, antiserum to substance P reduces the increase of GABA content in the hypothalamus induced by hyperprolactinemia (11). More information is available on substance P concerning the gonadal steroid-mediated feedback on prolactin secretion. Estradiol increases substance P content in medial basal hypothalamus, dorsomedial hypothalamus, and mammillary bodies in guinea pig (166). In female rats, pituitary content of substance P and substance P mRNA levels decrease dramatically after estradiol treatment (1338). Because the hypothalamic level of substance P mRNA was unchanged in these experiments, the regulation of substance P gene expression by estradiol in female rats seems to be confined to the pituitary (1338).

Three receptors subtypes of the mammalian neurokinins have been identified (NK-1, NK-2, and NK-3) and sequenced by molecular cloning. All belong to the G protein-coupled receptor superfamily (for references, see Refs. 932, 1456). Neurokinin receptor activation leads to an increase of intracellular free Ca^{2+}, an effect mediated through G_q-activated phospholipase C (932). In lactotroph-enriched anterior pituitary cell cultures, substance P caused a translocation of certain protein kinase C isozymes (1158).

H) GALANIN. The peptide galanin consists of 29 amino acids, originally isolated from porcine intestine and named after its NH_2- and COOH-terminal residues, glycine and alanine (1728). The rat galanin amino acid sequence was first deduced from an estrogen-induced prolactinoma cDNA library (1839).

Galanin has a widespread distribution throughout the CNS and peripheral nervous system. The patterns of galanin-containing neurons in the CNS and their possible physiological functions have been reviewed (136, 1188). The heavy presence and specific distribution of galanin-positive neurons in the hypothalamus suggested an important function for this peptide in the neuroendocrine

regulation of anterior pituitary hormone secretion. Indeed, the incidence of galanin-immunoreactive cells is the highest in the hypothalamus, and the galanin immunopositive fibers are most abundant in the external zone of the median eminence. Most of the fibers in the median eminence originate from the ventrolateral portion of the arcuate nucleus (for references see Ref. 1188). The concentration of galanin in the portal blood is 4- to 10-fold higher than in the peripheral blood (1078). It appears that galanin meets all criteria to be considered as a hypothalamic-hypophysiotrophic hormone (1080). However, galanin is also abundantly expressed in the anterior lobe of the pituitary gland (909). A sex difference in galanin expression is detectable in the median eminence, neurointermediate lobe, and the anterior pituitary where the concentration of immunoreactive galanin is significantly higher in females (596). Interestingly, a few galanin-positive nerve fibers have been also detected in the anterior lobe of the rat (1061).

It appears that the anterior pituitary expresses a unique high-affinity galanin receptor that differs in its ligand structure-affinity requirements from galanin receptors previously characterized in the brain (1890). Only the hypothalamus has the capacity to express both types of galanin receptors (1890). It is clear that the galanin receptors belong to the G protein-coupled receptor superfamily (136, 914, 1188, 1842); however, the intracellular signaling mechanism coupled to these receptors in lactotrophs has not yet been elucidated. Information provided by nonpituitary cell types offers little clue to the mechanism of galanin's action in lactotrophs (914). For example, it has been reported that galanin is inhibitory on muscarinic acetylcholine receptor-mediated stimulation of phosphoinositide turnover in the hippocampus (1366) and activates ATP-dependent K^+ channels in pancreatic tumor cells (471) as well as insulinoma (996) and pheochromocytoma (439) cell lines in a pertussis toxin-sensitive manner. All these signaling events would be inconsistent with a direct prolactin-releasing effect of galanin in lactotrophs. Investigations on a clonal pituitary cell line implicate phospholipase C activation as a key event leading to sustained elevation of prolactin secretion by galanin (727).

Galanin is capable of stimulating prolactin secretion in a pituitary cell line, GH_3/B6, predicting the possibility of a direct pituitary action (697). Indeed, it has been shown that galanin is capable of stimulating prolactin secretion in a cultured pituitary cell preparation (465, 1890, 1890) and that specific galanin antiserum inhibits basal prolactin secretion (1890). The latter observation strongly suggests a paracrine and/or autocrine regulation by galanin (discussed in sect. VII*B1*A*II*). Moreover, galanin also has been shown to directly regulate lactotroph proliferation (1889). On the basis of the fact that galanin is secreted into peripheral blood (909, 1078), and its secretion is regulated by hypothalamic factors such as dopamine and somatostatin (inhibition), as well as by TRH (stimulation) (824), it has been suggested that galanin might be a novel anterior pituitary hormone (1188, 1842).

Centrally administered galanin increases prolactin secretion, whereas it has a weak or no effect when given peripherally (973, 1177, 1360). These observations indicate that the prolactin-releasing effect of galanin likely results from its hypothalamic action, possibly by altering the balance between stimulatory and inhibitory outputs of the prolactin release-regulating circuitry. This latter hypothesis is supported by observations that galanin-containing axons synapse on dopaminergic neurons in the arcuate nucleus (806) and that galanin reduces [^{3}H]dopamine release from the median eminence (1327) and stimulates VIP release from the hypothalamus (844, 844). Moreover, the central action of galanin on prolactin secretion requires serotonin (975), α_2-noradrenergic, and opioid elements (793, 976). Passive immunization experiments with specific galanin antiserum indicate that endogenous galanin may not play a significant role regulating prolactin secretion in male rats (1360). On the other hand, galanin presumably plays an important role in regulating prolactin secretion during proestrus in female rats (1079, 1188). Because passive immunization against galanin blunts the preovulatory prolactin surge, it is assumed that the contribution of endogenous galanin to neural events leading to the proestrous prolactin surge is stimulatory (1079, 1188).

Hyperprolactinemia, induced by implanting anterior pituitaries under the renal capsule, reduces galanin content in the pituitary (726). Chronically high prolactin concentration in the blood also suppresses estradiol-induced galanin expression in the pituitary (726). How hyperprolactinemia affects galanin in the CNS is not yet known.

It has been shown that the gene encoding rat galanin contains a functional estrogen response element in its regulatory region (1842). The galanin mRNA-inducing effect of estradiol is most impressive in the pituitary (see sect. VII*B1*A*II*). Although less robust than in the pituitary, estrogens clearly have a positive effect on galanin gene expression in the hypothalamus (910, 1033).

I) NEUROTENSIN. Neurotensin, a peptide of 13 amino acids, was originally isolated from bovine hypothalamus (288). The potential role of neurotensin in neuroendocrine regulation has been reviewed by Aronin et al. (89) and more recently by Rostene and Alexander (1507).

It is intriguing that there is extensive coexistence of neurotensin and dopamine in hypothalamic arcuate and periventricular neurons (831). Neurotensin is present in the median eminence (946) and in the anterior lobe of the pituitary gland (630). The major, but not exclusive, source of neurotensin immunoreactivity in the external layer of the median eminence is the neuronal somata located in the hypothalamic arcuate nuclei (946).

Several observations indicate that neurotensin is capable of affecting lactotrophs in vitro (505). For example, neurotensin dose-dependently increases prolactin secretion (ED_{50} = 0.6 nM), an action additive with TRH and VIP (505). Because neurotensin is present in a high concentration in the median eminence (946), it seems reasonable to assume that neurotensin is a potential PRF distinct from TRH or VIP (505).

Neurotensin has opposite effects on prolactin secretion, depending on the site of administration. Intracerebroventricular administration of neurotensin decreases, whereas peripheral administration of neurotensin increases prolactin secretion (964, 1166, 1167, 1482), indicating that neurotensin can affect the neuroendocrine regulation of prolactin secretion at multiple levels (1166). It seems likely that neurotensin causes stimulation of prolactin secretion by acting at a site(s) which is outside of the blood-brain barrier (1166). As for the locus of central inhibition of prolactin secretion, the stimulation of TIDA neurons by neurotensin offers a plausible mechanism (964, 1167). Indeed, several observations indicate that neurotensin enhances the activity of TIDA neurons (692, 964, 1167, 1373). In addition, centrally administered neurotensin can prevent prolactin secretion elicited by stress or serotonergic or opioid agonists (1166, 1167, 1753). The effect of neurotensin on the TIDA system likely results from a direct action on these neurons (964).

Data provided by passive immunization with a highly specific neurotensin antiserum conversely reflect the effects of exogenous peptide administration and further emphasize the physiological importance of neurotensin in regulating prolactin secretion (1166). For instance, intraventricular injection of a neurotensin antiserum results in an increase in prolactin secretion, whereas intravenous injection of the same antiserum leads to a decrease in prolactin secretion (1166). These experiments reveal a central (possibly hypothalamic) inhibitory and a peripheral (possibly pituitary) stimulatory influence of endogenous neurotensin on prolactin secretion. The changes in neurotensin concentration in the median eminence (followed over time by push-pull perfusion technique) correlate well with the surge of prolactin secretion induced by estradiol priming (1866).

Lactation increases neurotensin immunoreactivity in the hypothalamus, particularly in the TIDA neurons (1126). That a physiological hyperprolactinemia coincides with an enhancement of neurotensin expression, especially in neurons which are responsible for hypothalamic inhibition of prolactin secretion, indicate, albeit indirectly, that neurotensin might play a role in mediating prolactin feedback signaling. Indeed, recent pharmacological experiments using a specific neurotensin antagonist, SR-48692, provide direct evidence that neurotensin mediates the hyperprolactinemia-induced activation of TIDA neurons in both male and female rats (751).

The expression of the neurotensin gene is intricately regulated by steroid hormones as well as second messenger signals at the promoter level. A synergistic regulation of neurotensin gene expression by cAMP and glucocorticoids has been reported (1315). Sexually dimorphic neurotensin neurons in the preoptic area possess estradiol receptors (752), and female rats have a larger number of neurons bearing both neurotensin and estradiol receptors (752). Interestingly, neonatal masculinization with testosterone propionate selectively increases neurotensin content in the medial basal hypothalamus but not in the medial preoptic area (444).

It appears that neurotensin does not affect adenylyl cyclase in lactotrophs (1179), and its stimulatory influence on prolactin secretion results from activation of the intracellular Ca^{2+}-mobilizing cascade as well as by increasing Ca^{2+} influx through voltage-dependent calcium channels (1179). In addition, arachidonic acid release and activation of the lipoxygenase pathways may also contribute to the prolactin-releasing effect of neurotensin (271, 1179). In the CNS, neurotensin activates dopaminergic neurons via a non-pertussis toxin-sensitive G protein, likely $G\alpha_{q/11}$ (1856).

j) NEUROPEPTIDE Y. Neuropeptide Y is a member of the pancreatic polypeptide family isolated by Tatemoto et al. in 1982 (1725, 1726). Neuropeptide Y has a multifaceted role in a wide variety of physiological functions (897), and its physiological role in modulating LH secretion is especially well established (579, 897).

With the use of specific neuropeptide Y antisera, detailed maps of the neuropeptide Y systems in the CNS have been provided (for references, see Ref. 897). High-density neuropeptide Y-positive terminals are found throughout the medial preoptic and anterior hypothalamic areas, as well as the periventricular, suprachiasmatic, paraventricular, and supraoptic nuclei (328, 430, 1286, 1336). The medial basal hypothalamus is particularly rich in neuropeptide Y-positive nerve endings, especially the arcuate nucleus and the median eminence. The majority of the neuropeptide Y terminals have been found in the internal and the subependymal zone, although fibers in the external zone in close proximity to the portal capillaries are detected (1169, 1172). Many neuropeptide Y-positive fibers lie in close proximity to the cell bodies and dendrites of luteinizing hormone releasing hormone (LHRH), CRH, oxytocin, vasopressin, and TRH neurons (1800). Neuropeptide Y and norepinephrine are frequently found colocalized in many areas in the CNS and in the peripheral sympathetic system (525, 526, 776, 781, 1561). It appears that, in many cases, neuropeptide Y and norepinephrine act in concert to modulate target cell function (897). However, neuropeptide Y is not confined to the norepinephrinergic system in the CNS because several neuropeptide Y-positive perikarya have been detected in

the hypothalamus, especially in the ventromedial portion of the arcuate nucleus (28, 328, 430, 1286).

Expression of neuropeptide Y in the mediobasal hypothalamus is increased during lactation (330, 331, 1107, 1400, 1646). The appearance of immunoreactive neuropeptide Y in TIDA neurons is especially striking since these neurons do not normally express detectable levels of neuropeptide Y in other physiological situations. The appearance of neuropeptide Y positive terminals around the loops of the hypothalamo-hypophysial portal capillaries shows a remarkable plasticity since these terminals largely disappear within 24 h followed by the cessation of nursing (330, 331, 1857).

Neuropeptide Y stimulates prolactin secretion in cultured pituitary cells obtained from random cycling female rats (302). On the other hand, in primary cultures of anterior pituitary cells obtained from lactating or ovariectomized estradiol-treated animals, neuropeptide Y causes a concentration-dependent decrease in prolactin secretion (1857). The inhibitory effect of the peptide is additive to the inhibition of prolactin secretion caused by dopamine (1857). Withdrawal of the peptide from the culture medium results in a quick rebound of prolactin secretion, similar to that of dopamine withdrawal (1857). In addition, neuropeptide Y, alone or in combination with dopamine, decreases TRH-induced prolactin release (1857); the presence of neuropeptide Y markedly augments the inhibitory effect of dopamine (1857).

The presence of neuropeptide Y in TIDA neurons and in periportal nerve terminals in the median eminence indicates that the peptide can affect prolactin secretion either by modulating dopamine release presynaptically and/or by affecting dopamine's action in the pituitary (1857). It has been hypothesized that a possible function of the neuropeptide Y expressed in TIDA neurons during lactation is to amplify the inhibitory action of dopamine on prolactin secretion (1857).

In the male rat, intracerebroventricular administration of neuropeptide Y decreases prolactin secretion (592, 1466). The central inhibitory effect of neuropeptide Y on prolactin secretion is probably mediated by stimulating TIDA neurons, since the activity of these dopaminergic neurons increases upon neuropeptide Y administration (592). Moreover, neuroanatomical observations at the electron microscopic level reveal synaptic connections between TH-positive cells and neuropeptide Y-positive fibers (714). These observations undoubtedly reveal the potential of neuropeptide Y as a regulator of prolactin secretion and suggest a central site of action. It is still uncertain, however, whether endogenous neuropeptide Y significantly contributes to the tonic inhibition of prolactin secretion in male rats since previous reports on the effects of centrally administered neuropeptide Y antiserum on prolactin secretion are conflicting (618, 1465, 1466). Neuropeptide Y antiserum increases plasma prolactin level only in intact males, suggesting that the central inhibitory action of neuropeptide Y probably depends on sex steroids (618).

It has been noted that stimulation of central neuropeptide Y Y2 receptors by injection of neuropeptide Y or a Y2 agonist in the lateral ventricle increases prolactin gene expression in the pituitary (604). The mechanism by which central neuropeptide Y affects prolactin mRNA levels in the anterior pituitary gland and its physiological significance is unclear.

Expression of neuropeptide Y in the mediobasal hypothalamus increases dramatically during lactation (330, 331, 1107, 1646). However, although the elevated neuropeptide Y expression is a lactation-dependent phenomenon, it does not require high plasma prolactin levels (1400). Therefore, it appears that neuropeptide Y in the hypothalamus does not mediate prolactin feedback per se. The increased expression of neuropeptide Y gene in the arcuate nucleus is likely related to feeding behavior and/or adaptive changes in energy balance necessary to sustain lactation (1107, 1379).

In the medial basal hypothalamus, neuropeptide Y Y2 receptors are upregulated by estradiol and decreased by progesterone cotreatment in ovariectomized rats (1381). However, the functional significance of these changes in regulating prolactin secretion during the estrous cycle is unclear.

On the basis of ligand binding and pharmacological studies, at least two neuropeptide Y receptors might exist in the CNS (897). The Y1 receptor is coupled to phospholipase C and inositol phosphate metabolism and enhances intracellular Ca^{2+} mobilization upon activation, while the Y2 receptor decreases Ca^{2+} influx resulting in an inhibition of the target cell's secretory activity (528, 1849). Both Y1 and Y2 couple negatively to adenylyl cyclase (897). All of the effects of neuropeptide Y on these signaling events can be prevented by pertussis toxin, which indicates G_o/G_i mediation (528, 897). Moreover, it seems that neuropeptide Y, similar to the effects of dopamine, reduces Ca^{2+} entry through voltage-dependent Ca^{2+} channels in lactotrophs (1857). In cultured lactotrophs obtained from lactating animals, neuropeptide Y reduces the intracellular Ca^{2+} elevation caused by TRH (1857). The latter effect of neuropeptide Y is more robust on the sustained phase of TRH-induced intracellular Ca^{2+} concentration elevation, which is consistent with the notion that neuropeptide Y mainly affects Ca^{2+} influx (1857). It is interesting to note that a similar cooperativity between LHRH and neuropeptide Y on gonadotrophs has been reported earlier (374). In the latter case, however, neuropeptide Y augments stimulatory signaling elicited by LHRH, and it was suggested that neuropeptide Y facilitates Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (374). Although the precise mechanisms for these actions of neuropeptide Y have not been elucidated, it is intriguing that the same

peptide receptor might be coupled to different intracellular signaling pathways exerting biologically opposing cellular events.

K) SOMATOSTATIN. The presence of growth hormone release-inhibiting factor in the hypothalamus was first discovered in 1968 (982), and the active tetradecapeptide, named somatostatin, was later purified by Guillemin et al. (211). It became apparent from the beginning that somatostatin not only inhibits GH, but the secretion of prolactin, TSH, and ACTH as well (1394, 1460, 1783). Two biologically active forms of somatostatin (somatostatin-14 and somatostatin-28) have been identified as the product of the same gene (519, 1434, 1568). The molecular biology and physiology of somatostatin have been reviewed (1251, 1390, 1863).

Somatostatin immunoreactive neurons are widespread throughout the CNS and peripheral nervous system (556). In the hypothalamus, somatostatin neurons that project to the external zone of the median eminence are mainly concentrated in the medial preoptic and the anterior periventricular area, as well as in the paraventricular nucleus (724). These "neuroendocrine" somatostatin neurons receive abundant afferent connections from galanin, neurotensin, neuropeptide Y, GABA, serotonin, enkephalin, substance P, TRH, and catecholaminergic systems (3, 157, 318, 724, 895).

Somatostatin inhibits basal as well as TRH- or VIP-induced prolactin secretion in vitro in prolactin-producing cell lines or hemipituitaries (461, 462, 466, 509, 733, 941). Although somatostatin and its analogs are capable of inhibiting prolactin secretion in vivo, somatostatin inhibits prolactin secretion with lower efficacy compared with its effect on growth hormone secretion (1394). However, the concentration of immunoreactive somatostatin in the portal blood is high enough to be biologically relevant to the regulation of prolactin secretion (3, 319). Injection of somatostatin antisera intravenously causes a marked increase in plasma prolactin concentration, indicating that endogenous somatostatin may indeed exert an inhibitory influence over prolactin secretion in vivo (507).

Similar to many other prolactin secretagogues, estradiol can profoundly alter the responsiveness of lactotrophs to somatostatin (942, 994). Indeed, although somatostatin causes a robust inhibition of prolactin secretion in male or ovariectomized female estradiol-primed rats, its effect in normal or pimozide-treated animals is much less robust (359, 651, 913, 1018). Interestingly, although long-term exposure to estradiol gradually diminishes the dopaminergic control of prolactin secretion (1001) and eventually leads to an uncoupling of inhibitory signaling to D_2 dopamine receptors (1454), the sensitivity of lactotrophs to somatostatin increases with estradiol treatment (1001). The significance of these observations as related to the mechanism of estradiol-induced tumorigenesis of lactotrophs is not yet clear. In anterior pituitary cells and tumorous MtTW-10 cells of pituitary origin, somatostatin inhibits estradiol-induced prolactin, galanin, and growth hormone secretion and synthesis (824, 826). Galanin is characterized as a potent auto- and paracrine PRF (258, 825, 1888). Thus somatostatin might affect prolactin secretion, in part, by inhibiting galanin release/synthesis from lactotrophs. Because the synthesis and release of galanin in the lactotroph is strongly estradiol dependent (258, 803), the suggested galanin-mediated mechanism for somatostatin's action on prolactin secretion would be consistent with its sensitivity to estradiol (359, 651, 1018).

The pharmacological characterization of somatostatin receptors in lactotrophs, somatotrophs, and thyrotrophs indicates a single class of somatostatin binding sites in these cell types (515). Interestingly, in prolactin-producing tumorous cells, specific somatostatin binding is always found, although usually in lower density than in growth hormone-producing cells, whereas nonprolactin producing chromophobe adenomas are devoid of ^{125}I-somatostatin binding sites (507). The fact that normal lactotrophs as well as tumorous cells of "mammosomatotroph" origin are capable of expressing somatostatin receptors emphasizes the potential of somatostatin and its analogs in regulating lactotroph function under varying physiological or pathological conditions.

The advances made in the molecular biology and pharmacology of the somatostatin receptor family have been reviewed recently (1251, 1393, 1463). Molecular cloning has revealed six somatostatin receptors (SST1–5, two splice-variants for SST2) encoded by five separate genes, all belonging to the G protein-coupled receptor superfamily (1391, 1392, 1463). All somatostatin receptor subtypes (proteins and/or mRNA) have been detected in the hypothalamus and the pituitary (390, 463, 671, 1190, 1195, 1334, 1375, 1744). The SST2A and SST5 receptors are rather abundant in the anterior lobe of the pituitary gland (390, 1190, 1334). Lactotrophs as well as tumorous cells in the mammosomatotroph lineage preferentially (but not exclusively) express the SST5 receptor subtype (671, 1190, 1195, 1613). Although previous pharmacological studies indicate that more than one somatostatin receptor exists (1394, 1462), such multiplicity of SST receptors revealed by molecular cloning is somewhat unexpected (625, 1391, 1462, 1463). With respect to anterior pituitary hormone secretion, the functional significance of the molecular diversity of somatostatin receptors has not been clarified as yet. Recent developments in the synthesis of potent subtype-selective peptidomimetics (both agonists and antagonists) will undoubtedly help the functional characterization of the different somatostatin receptor subtypes (1494, 1904).

Somatostatin receptor expression in the pituitary gland is sensitive to ovarian and adrenal steroid hormones. For instance, estradiol upregulates SST2 receptor

gene expression in rat prolactinoma cells (1829, 1830). Short-term exposure to glucocorticoids upregulates, whereas a prolonged exposure downregulates the expression of somatostatin receptors in pituitary cells (1573), as well as in a rat prolactinoma-derived cell line (1829, 1892). These observations indicate that responsiveness of lactotrophs and somatotrophs to somatostatin is regulated through the expression of somatostatin receptors, and such regulation by these steroids is consistent with their effects in vivo on somatostatin-induced modulation of prolactin and growth hormone secretion.

The widespread distribution of somatostatin and somatostatin receptors throughout the entire CNS indicates clearly that somatostatin subserves a role as neurotransmitter as well (556, 1462). The possibility that somatostatin might affect prolactin secretion through affecting the TIDA system has been suggested earlier (898). With respect to prolactin secretion, it is noteworthy that estradiol-induced regulation of somatostatin receptors in the brain is restricted to the arcuate nucleus of the hypothalamus. In ovariectomized rats, estradiol treatment significantly increases the number of ^{125}I-somatostatin binding sites in the ventrolateral part of the arcuate nucleus (1645). In the same region, somatostatin binding is higher in proestrus compared with other stages of the estrous cycle (1645). The expression of somatostatin receptors, SST2 receptor subtype in particular, is upregulated by estradiol (135, 1588). However, to what extent these changes in the expression of somatostatin receptors within the arcuate nucleus reflect on the regulation of prolactin secretion is not clear.

The affinity of ^{125}I-somatostatin binding and the in vitro potency of different somatostatin analogs on adenylyl cyclase and intracellular free Ca^{2+} are well correlated, suggesting a possible causal relationship between biological effects of somatostatin and the inhibition of adenylyl cyclase and/or intracellular free Ca^{2+} (941, 1715). However, the inhibition of hormone secretion by somatostatin cannot be explained solely through adenylyl cyclase and/or Ca^{2+} entry inhibition. Thus it has been suggested that another mechanism of transduction may be involved in the inhibitory actions of somatostatin on prolactin, growth hormone, and TSH secretion (941, 1715).

L) CALCITONIN. Calcitonin, a polypeptide originally described as a plasma Ca^{2+}-lowering hormone (360) secreted by the parafollicular cells (C cells) in the thyroid gland (570), has been shown to inhibit prolactin secretion (reviewed in Ref. 1631). Calcitonin and calcitonin gene-related peptide (CGRP) are apparently encoded by the same gene (853), but the processing pathway is tissue specific; whereas the parathyroid gland is the major source of calcitonin, in the CNS the CGRP is the dominant form (33, 570, 1502).

Calcitonin-like immunoreactivity is present in the CNS and in lactotrophs of the anterior lobe of the pituitary gland (1225). Calcitonin is most abundant in the inner portion of the anterior lobe (1595). In accordance with the latter observation, salmon calcitonin antiserum causes more robust prolactin secretion when applied to lactotrophs obtained from the inner region of the anterior lobe (1595).

Calcitonin peptides are capable of inhibiting basal as well as TRH-stimulated prolactin secretion by acting directly on dispersed pituitary cells in culture (514, 880, 1225, 1593–1595, 1597, 1631, 1894). The effects of calcitonin-like peptides on prolactin secretion seem specific since these peptides do not influence GH, LH, FSH, and TSH secretion (880, 1593, 1597, 1894). The inhibitory effect of calcitonin on prolactin secretion is dependent on the thyroid status of the animal, since in pituitaries obtained from thyroidectomized animals, calcitonin stimulates prolactin secretion (1905). Endogenous calcitonin release by pituitary cells in culture is sufficient to inhibit prolactin secretion since anti-salmon calcitonin antiserum increases prolactin secretion (1595, 1660) even in the presence of dopamine (1595). Cell immunoblot assay and RIA reveal that anterior pituitary cells are capable of releasing calcitonin-like peptides (1660), indicating a paracrine regulation of prolactin secretion by these peptides (discussed further in sect. VII*B1*A*VII*). These data suggest that calcitonin is a physiologically important inhibitor of prolactin secretion and likely acts in concert with dopamine and other PIF to provide a tonic inhibition of prolactin secretion (1595).

Several investigations have concluded that calcitonin-like peptides are effective in inhibiting prolactin secretion when administered in vivo (495, 531). That calcitonin is a physiological regulator of prolactin secretion has gained further support by recent evidence showing that passive immunization with salmon calcitonin antiserum increases plasma prolactin concentration within 30 min of antiserum administration (1595). Calcitonin-like peptides lower prolactin secretion induced by stress in prepubertal female rats or by the suckling stimulus in lactating animals (495, 1348). Intracerebroventricular administration of a calcitonin analog lowers basal as well as stress- or morphine-induced prolactin secretion (1633). These data suggest that, in addition to its direct effects in the pituitary, calcitonin has central inhibitory activity on prolactin secretion as well, probably through enhancement of hypothalamic inhibitory pathways controlling prolactin secretion (1308, 1633). It has been suggested that calcitonin has a potential role as neuromodulator in the CNS (1679) and it may decrease prolactin secretion by activating the TIDA system (341). Taken together, it seems very likely that endogenous calcitonin plays a role in tonic inhibition of prolactin secretion (1595). However, in spite of the numerous observations concerning the effects of calcitonin on prolactin secretion in a wide

variety of in vivo situations (119, 370–372, 495, 531, 1347, 1348, 1633, 1905), the precise physiological role of calcitonin in the regulation of prolactin secretion is not yet understood.

The signaling mechanism coupled to calcitonin receptors in lactotrophs is not clear. However, interactions of calcitonin with well-known prolactin secretagogues provide some clue (880, 1593, 1597, 1894). The inhibition of TRH-induced prolactin secretion by calcitonin seems rather selective, since prolactin release induced by other Ca^{2+}-mobilizing secretagogues such as ANG II or neurotensin, or by a Ca^{2+} ionophore A23187 or maitotoxin (an activator of voltage-dependent Ca^{2+} channels), is unaffected by calcitonin (880, 1593, 1597, 1894). Likewise, prolactin secretion elicited by adenylyl cyclase-activating secretagogue VIP or forskolin (a direct activator of adenylyl cyclase) was unaffected by the presence of calcitonin (880, 1593, 1597, 1894). It seems likely that calcitonin receptor activation on lactotrophs interferes with the phospholipase C-related signaling cascade, including Ca^{2+} mobilization from intracellular stores, decrease in inositol phosphate production, as well as a subsequent reduction in cytosolic free Ca^{2+} concentration and arachidonate liberation (514, 880, 1661). Extended exposure to calcitonin inhibits phosphatidylinositol turnover (1660), although in some cases the effect of calcitonin on phosphatidylinositol hydrolysis seems bimodal, consisting of a quick increase followed by a sustained inhibition (1660, 1661).

M) BOMBESIN-LIKE PEPTIDES (GASTRIN-RELEASING PEPTIDE, NEUROMEDINS B AND C). The first representatives of this peptide family, bombesin and ranatensin, were isolated from amphibian skin (516, 517), followed by their mammalian counterparts, gastrin-releasing peptide (GRP), and neuromedins B and C (1199, 1852). These peptides are localized to hypothalamic neurons (928, 1377, 1671, 1792). Given intracerebroventricularly, they are potent inhibitors of basal as well as stimulated prolactin secretion in rats (929).

GRP-positive perikarya are found in the parvicellular part of the paraventricular nucleus and in the periventricular nucleus in close proximity of the third ventricle (928, 1377, 1792). Beaded terminals and fibers are found in the suprachiasmatic nucleus as well as the area dorsal and lateral to the suprachiasmatic nucleus in the region of the periventricular nucleus, while the median eminence displays no immunoreactivity for GRP (928, 1377, 1792). The differential and region specific expression of the two bombesin-like peptides neuromedin B and GRP (1288, 1377, 1844) and their corresponding receptor subtypes (126, 1217, 1671, 1845) suggests that these structurally closely related peptides may have distinct physiological functions in the CNS.

Bombesin and its analogs are capable of stimulating prolactin secretion from GH_4C_1 cells in vitro (1876). Moreover, the bombesin-like peptide neuromedin C stimulates prolactin secretion from anterior pituitary cell aggregates cultured in serum-free medium supplemented with thyroxine and dexamethasone (797, 799). The presence of estradiol in the culture medium augments this effect of neuromedin C that can be blocked by specific bombesin receptor antagonists (798, 799). These observations clearly suggest that bombesin-like peptides can exert a direct stimulatory influence on prolactin secretion at the pituitary level. The influence of these peptides on pituitary hormone secretion seems to be specific for lactotrophs since the effectiveness of these peptides on the rest of the anterior pituitary hormones is rather unremarkable (797, 799, 1876).

The lactotroph has the intrinsic capacity to synthesize GRP/bombesin-like peptides (798). However, the participation of GRP-like peptides in local control of hormone release is suspect since a potent receptor antagonist of GRP does not affect basal, stimulated (by VIP, TRH, or ANG II), or suppressed (by dopamine) prolactin secretion from perifused microaggregates of pituitary cells (798).

When given intravenously, bombesin-like peptides increase prolactin secretion in anesthetized steroid-primed rats (700, 1483). However, contrary to the effects of systemic administration, centrally administered bombesin has a very potent and long-lasting inhibitory effect on prolactin release induced by acute stress in conscious male rats (1705). Similarly, synthetic porcine GRP, given intracerebroventricularly, suppresses basal as well as opiate-stimulated prolactin secretion, whereas it does not suppress domperidone-induced elevation of prolactin secretion (1153). Bombesin injected into the third ventricle of ovariectomized conscious rats suppresses prolactin levels in the plasma, concomitant with an increase in tyrosine hydroxylase activity in the hypothalamus (95). In addition, bombesin suppresses basal as well as PGE_2-induced prolactin secretion when given intracerebroventricularly to rats under urethane anesthesia (912). Moreover, intracerebroventricular bombesin lowers basal prolactin levels in conscious male rats and prevents morphine-, bremazocine-, and stress-induced prolactin secretion. The same dose of bombesin has no effect on prolactin secretion following α-MpT or haloperidol treatment. These results indicate that bombesin acts as an inhibitor of prolactin release, not on the lactotroph itself, but rather by an increase of inhibitory dopaminergic tone (257, 929). Indeed, GRP stimulates spontaneous release of dopamine from perifused rat hypothalamic fragments in vitro (886).

It seems that bombesin/GRP peptides exert an overall inhibitory influence over prolactin secretion since central administration of bombesin also prevents the estradiol-induced afternoon prolactin surge. Applied in a smaller dose, bombesin delays the surge but does not prevent it from occurring (1099). The effect of bombesin

seems specific since it can be prevented by administering bombesin together with a specific bombesin antagonist. Interestingly, temporarily lowering endogenous dopaminergic tone dominating the lactotrophs by a single injection of sulpiride at 1400 h reinstates the prolactin surge (1099). The latter observation indicates that bombesin suppresses the estradiol-induced prolactin surge through activating the hypothalamic neuroendocrine dopaminergic systems.

Bombesin not only blocks the prolactin surge but also the circadian changes in TIDA activity (1100). In suprachiasmatic nuclei-lesioned animals, these rhythms are absent and bombesin treatment is without effect. Microinjection of bombesin into the suprachiasmatic nuclei blocks the diurnal changes in TIDA activity and prolactin secretion, whereas injection into the arcuate nucleus does not disturb the rhythmic changes in TIDA and prolactin secretion. It has been suggested that bombesin may act on the rhythm generation center, the suprachiasmatic nucleus, to disrupt TIDA neuron activity associated with the prolactin surge (1100).

Bombesin given intraventricularly decreases prolactin secretion both in male and female rats, but only in males was this effect of bombesin associated with an increase of TIDA activity (1757). The loss of gonadal hormones after ovariectomy renders TIDA neurons responsive to the stimulatory effects of bombesin, whereas immunoneutralization of prolactin does not affect the ability of bombesin to alter the activity of TIDA neurons (1757). Intracerebroventricular injection of bombesin causes a dose- and time-related increase in the activity of TIDA and PHDA neurons and a corresponding decrease in prolactin and α-MSH concentrations in the plasma (1122). Bombesin fails to alter the activity of dopaminergic neurons terminating in the striatum, nucleus accumbens, or in the neural lobe of the pituitary gland (THDA). Because equimolar doses of bombesin and GRP cause similar activation of the TIDA and PHDA systems (1122), it seems likely that a "GRP-preferring" receptor subtype (126, 1671) mediates these effects. A highly specific antiserum against GRP injected into the third ventricle to immunoneutralize endogenous GRP-like peptides in the hypothalamic area increases prolactin secretion (928), underlining the physiological significance of the endogenous GRP-related peptides in regulating prolactin secretion.

The effects of these peptides on prolactin secretion in humans seem less impressive. For instance, bombesin given intravenously (5 ng·kg^{-1}·min^{-1} for 2.5 h) does not alter basal but attenuates TRH-induced prolactin secretion in healthy male volunteers (1426). One group (1234) found no effect of bombesin infusion (200–600 pmol·kg^{-1}·h^{-1}) on pituitary hormone secretion, while the biological activity of the bombesin used in this study was confirmed by observing a brisk increase in serum gastrin concentrations and in gastric acid secretion (1234). On the other hand, it has been reported that bombesin (10 ng·kg^{-1}·min^{-1} for 60 min) elicited prolactin release in six of eight subjects (1425). One study found GRP (0.12 pmol·kg^{-1}·min^{-1} for 30 min and 1.5 pmol·kg^{-1}·min^{-1} for an additional 30 min) ineffective on prolactin secretion while it increased ACTH and cortisol in the serum (959).

Application of microaggregate culture in combination with GRP/bombesin receptor autoradiography and immunocytochemistry for pituitary hormones reveals that the bombesin receptor is expressed mainly in lactotrophs (796). Without estradiol supplement, the proportion of bombesin receptor expressing cells are very low, usually <1%. The presence of 1 nM estradiol in the tissue culture medium robustly increases the number of cells expressing bombesin receptors while dexamethasone has an opposite effect. It seems, therefore, that bombesin receptor expression in the pituitary is estradiol inducible, whereas glucocorticoids have a suppressive effect (796). These data are in good agreement with the effects of estradiol and dexamethasone on the responsiveness of the lactotroph to GRP/bombesin-like peptides observed in a similar experimental settings (798, 799).

Specific, high-affinity bombesin binding sites have been characterized in a pituitary cell line (GH_4C_1) using [^{125}I-Tyr^4]bombesin (1877). Scatchard analysis reveals one class of bombesin binding sites, and the estimated value of the equilibrium dissociation constant [(K_d) ~1.2 nM] agrees closely with the half-maximal concentration (ED_{50} ~0.5 nM) for bombesin stimulation of prolactin release. Subsequent studies have shown that mammalian bombesin-like peptides exert their effects via different receptors (126, 1671, 1845).

Both bombesin and TRH stimulate prolactin secretion from GH_4C_1 cells (ED_{50} ~2 nM, E_{max} ~100 nM). No additional stimulation of prolactin secretion can be seen when bombesin is combined with TRH, while the effects of bombesin and VIP are additive (177). The additive nature of the interaction with VIP confirms a previous suggestion that bombesin-like peptides do not act through adenylyl cyclase stimulation (461). Both bombesin and TRH elicit rapid inositol trisphosphate formation (within 2–4 s). Bombesin causes the same biphasic changes in membrane potential as TRH, and both peptides cause a rapid and sustained increase in intracellular free Ca^{2+} (177, 461, 462, 1766). These results suggest that bombesin stimulates prolactin secretion via an immediate formation of inositol trisphosphate similar to the action of TRH (177, 467, 1703).

Taken together, although a great many pharmacological studies suggest that the GRP/bombesin family of peptides exert effects on prolactin secretion, various uncertainties/inconsistencies among the data cited above postpone their assignment as physiologically relevant controllers of prolactin secretion.

N) CHOLECYSTOKININ. The cholecystokinin (CCK) and

gastrin family of peptides, originally described as gastrointestinal hormones (368), share a common COOH-terminal pentapeptide amide sequence (1691). The COOH-terminal tetrapeptide represents the bioactive core of these molecules (1860). Although gastrin is present in very small concentrations, CCK (in its tyrosine-sulfated form) is predominant in the CNS (1457, 1796, 1797), where it likely functions as a neurotransmitter (366, 1795).

Immunoreactive CCK and its COOH-terminal octapeptide (CCK-8) are found in the CNS of various mammalian species (449, 1252, 1692, 1693, 1797). The observation that CCK and dopamine colocalize in the mesencephalic dopaminergic system spurred further interest in this peptide family (13, 367, 778–780, 1402). CCK-like peptides have been found in hypothalamic regions relevant to the regulation of pituitary function (43, 137, 138, 204, 300, 431, 879, 947, 949, 1128, 1193, 1367). The pharmacology and molecular structure of the CCK receptor family have been reviewed (1860). In the hypothalamus and in most areas in the CNS, the vast majority of the receptors are CCK_B type, although CCK_A is also present and the two receptors often colocalize (1860). A large body of pharmacological and physiological studies support the notion that gastrin/CCK-like peptides play a role in the regulation of anterior pituitary function, including prolactin secretion.

Early experiments did not suggest a significant biological effect for CCK-like peptides at the pituitary level, since no effect on prolactin secretion was detected following an incubation of various concentrations of CCK-8 in vitro with hemipituitaries obtained from ovariectomized rats (1822). It was later found that CCK-8 and to a lesser extent CCK-33 can stimulate pituitary prolactin secretion in vitro (1109). Because the effective concentration range of CCK-8 in these experiments was rather high (10^{-6} to 10^{-5} M), it seems unlikely that CCK is present in the portal blood in a biologically effective concentration (1109). It has been reported that CCK-8 elicits a dose-dependent stimulation of prolactin secretion from dispersed rat anterior pituitary cells (1150). The effective concentration range of CCK-8 in these experiments seems physiologically more relevant (10^{-11} to 10^{-7} M) (1150). With the assumption that the sensitivities of lactotrophs in culture and in vivo are comparable, the latter observation indicates that CCK-8 may, after all, act directly on anterior pituitary cells to stimulate prolactin release.

The less than dramatic effects observed in vitro (1109, 1822) correlate well with the relative ineffectiveness of CCK-like peptides to alter prolactin secretion after peripheral administration. For instance, intravenous injection of CCK-8 does not affect basal prolactin secretion of freely moving male rats, even in a dose as high as 5 μg/rat (1714). In addition, systemic injection of the nonselective agonists of CCK-8 (caerulein), CCK_B selective agonists (CCK-4 and pentagastrin), CCK_A antagonist (devazepide), or CCK_B antagonist (L-365,260) does not affect prolactin secretion in male rats (1116). In one early experiment, however, intravenous injection of CCK-8 to female rats causes a short-lived dose-dependent increase in prolactin secretion (1822).

The remarkable difference in terms of efficiency when a CCK-like peptide is given intracerebroventricularly (912, 1822) instead of intravenously indicates clearly that these peptides likely affect prolactin secretion at hypothalamic sites, presumably by altering the activity of prolactin-releasing and/or inhibiting hormone-producing neurons. Indeed, central administration of CCK-8 increases prolactin secretion in freely moving male rats, an effect prevented by the specific CCK antagonists proglumide or benzotript (1714). The enhancement of prolactin secretion by dopamine D_2 antagonists (haloperidol, sulpiride, domperidone) is not altered by central CCK administration. However, when endogenous dopamine is depleted by α-MpT or reserpine, CCK-8 increases plasma prolactin levels. In addition, the decrease of prolactin secretion induced by the dopamine agonist apomorphine can be antagonized by centrally administered CCK. These data indicate that the central effect of CCK-8 is mediated, at least in part, by modulating the output of the neuroendocrine dopaminergic neurons of the hypothalamus (1714). In addition, the elevation in prolactin secretion by CCK-8 can be prevented by intracerebroventricularly administered VIP antiserum (1714). Therefore, one possible route through which CCK-8 increases prolactin secretion in male rats is by stimulating VIP through a central CCK receptor (1714).

Interestingly, when injected into the third ventricle of the brain of conscious ovariectomized rats, 4 or 400 ng CCK-8 does not change prolactin secretion, whereas an intermediate dose (40 ng) of CCK-8 increases plasma prolactin levels within 15 min (1822). Injection of a specific CCK antagonist, proglumide, into the third ventricle of intact male rats causes a robust decrease of prolactin secretion, indicating a tonic central action of CCK on prolactin secretion (1821). On the other hand, ovariectomized female rats respond to central CCK antagonism with stimulation of prolactin secretion (1821). Taken together, the fact that CCK antagonism alters prolactin concentrations in both sexes underlines the physiological importance of endogenous CCK-like peptides in the regulation of prolactin secretion. However, an explanation for the observed sexual differences is not yet available (1821). It is noteworthy that both CCK_A and CCK_B receptors are present in the hypothalamus and are likely involved in the regulation of anterior pituitary hormone secretion in vivo (1410). Because opposite biological effects can be mediated by CCK_A and CCK_B receptors (1115), some of the ambiguity surrounding the effects of CCK on prolactin secretion in female rats may be related to the fact that the sulfated CCK-8 applied in these exper-

iments is not a subtype selective agonist on these receptors.

Anesthesia, not surprisingly, interferes with the central effects of CCK-like peptides. For instance, intraventricularly administered CCK-8 to urethane-anesthetized rats suppresses prolactin secretion (912), whereas in conscious animals CCK-8 is stimulatory (see above).

Electrophysiological data strongly support the view that CCK is an important neurotransmitter in regulating neuroendocrine function of the hypothalamus. For instance, when extracellular single-unit activity is recorded in vitro using brain tissue slice preparation, CCK-8 elicits a robust activation in the majority of neurons within the area of the arcuate nucleus (1049, 1371). CCK-8 is found even more effective in stimulating neuronal activity than glutamate, a well-recognized stimulatory neurotransmitter in the CNS. Estrogen replacement to ovariectomized animals significantly increases the proportion of cells which respond to CCK by excitation (1371). The dorsomedial portion of the arcuate nucleus, where most of the TIDA neurons reside, was included, although not specifically targeted in these experiments. Nevertheless, it is difficult to reconcile the overall excitatory effect of CCK on arcuate neurons (1049, 1371) with its stimulatory effect on prolactin secretion in vivo (1822).

Taken together, CCK-like peptides, acting as neurotransmitters or neuromodulators in the hypothalamus, play an important role in the regulation of prolactin secretion. The most likely locus of the action of these peptides is the arcuate nucleus-median eminence region. The latter conclusion is supported by the observation that local injections of gastrin or CCK-8 in the preoptic region do not change prolactin concentration in the serum (940), while these peptides stimulate prolactin secretion when injected into the third ventricle (see above).

Human pituitary tumors often contain CCK-like immunoreactivities, although the role of CCK peptides and/or their receptors in pituitary tumorigenesis is not known (1459). In healthy males and females, continuous intravenous injection of pentagastrin does not affect prolactin secretion (32). Caerulein (an amphibian peptide, which mimics the biological actions of CCK) does not change basal prolactin secretion but accentuates TRH-induced prolactin release in normal men (1563). Similarly, CCK-8 administered to normal men has no effect on basal prolactin secretion (1285). Intravenous infusion of CCK-8 (140 ng/kg) stimulates prolactin secretion in a dose-dependent fashion (264).

The intracellular signaling pathways coupled to CCK receptors have not yet been fully elucidated (182). All CCK receptors cloned to date apparently belong to the G protein-coupled receptor superfamily (1860). However, the G protein(s) mediating the ionic effects of CCK are not pertussis toxin sensitive (182), indicating that the response to CCK does not involve a G_i or a G_o. The direct prolactin-releasing effect of CCK is dependent on extracellular Ca^{2+} (1150). In the CNS, the predominant action of CCK is excitatory because it causes depolarization of the neuronal membrane that leads to an increased firing rate. These effects of CCK result from an inhibition of K^+ conductance and increasing Ca^{2+} influx through a calcium-dependent nonselective monovalent cation channel (182).

o) ATRIAL NATRIURETIC PEPTIDES. Atrial natriuretic peptide was first isolated from mammalian heart tissue (900). Three members of the atrial natriuretic peptide family have been isolated and designated A-type (ANP), B-type (BNP), and C-type (CNP) natriuretic peptide (1697, 1698). The biologically active forms consist of 28, 32, and 22 amino acids, and all contain a 17-amino acid ring structure formed by a disulfide bond between two cysteine residues. The ring structure seems essential for their biological activities (1151).

Atrial natriuretic peptide positive cell bodies are detected in the rostral hypothalamus (mostly in the preoptic and periventricular nuclei, median preoptic nucleus, anterior wall of the third ventricle, organum vasculosum laminae terminalis) that project to the median eminence and the neural lobe of the pituitary (713). Atrial natriuretic peptide is detected in the hypophysial portal blood of both male and female rats in a concentration higher than that of the peripheral plasma (1604). The distribution of atrial natriuretic peptide throughout the hypothalamus and the pituitary suggests that both neuromodulator and neuroendocrine effects of these peptides should be considered.

Although most of the data suggest hypothalamic targets for atrial natriuretic peptides in regulating prolactin secretion (see below), a direct hypophysial component of atrial natriuretic peptide's action cannot be excluded, since in some experiments atrial natriuretic peptide is capable of inhibiting prolactin secretion in vitro (482).

Atrial natriuretic peptide administered into the third ventricle decreases basal as well as stress-induced prolactin secretion in male rats, indicating that atrial natriuretic peptide can act centrally to alter neuronal activities responsible for the hypothalamic control of prolactin secretion (1531, 1533). These effects of atrial natriuretic peptide are sensitive to dopamine antagonism; therefore, it seems conceivable that atrial natriuretic peptide exerts its effects through stimulation of hypothalamic dopaminergic neurons (566, 1534). The influence of endogenous atrial natriuretic peptides on prolactin secretion is less well understood because the results obtained by passive immunization with an antiserum to atrial natriuretic peptides are somewhat equivocal (571). Much of the ambiguity could result from the fact that the two major forms of atrial natriuretic peptide in the CNS have opposing neuroendocrine effects by affecting different subsets of neurons (1536). Selective lesions of CNP and atrial natriuretic

peptide targets in the hypothalamus reveal that the two peptides do not act directly on TIDA neurons (1536).

Estradiol injection to ovariectomized animals 24 h before the blood collection resulted in a significant decrease of atrial natriuretic peptide concentrations in the portal plasma (1604). Because the direct pituitary effect of atrial natriuretic peptide is inhibitory to prolactin secretion, the latter finding is consistent with the overall stimulatory influence of estradiol on prolactin secretion. However, this finding is contradicted by the fact that the concentration of atrial natriuretic peptide in the portal plasma remains unchanged throughout the day of proestrus, indicating that atrial natriuretic peptide may not play a role in the spontaneous prolactin surge (1604).

It seems likely that the major role of the hypothalamic atrial natriuretic peptides is the modulation of stress-induced hormone secretion from the anterior pituitary (571). A complementary function of prolactin and atrial natriuretic peptide in maintaining water and ion (especially sodium) homeostasis has been suggested (713, 1685). However, the physiological relevance of atrial natriuretic peptide-mediated regulation of prolactin secretion is not yet clear.

The signal transduction mechanism for atrial natriuretic peptide in the brain and the pituitary has recently been reviewed (713). Although the field is still controversial, it seems that activation of guanylyl cyclase is the major signaling event elicited by atrial natriuretic peptide-like peptides (305, 321, 1345). The increased cGMP was utilized to detect atrial natriuretic peptide-responsive cells within the brain. Cells within the paraventricular nuclei of the hypothalamus are among the responsive cellular elements in the brain (for references, see Ref. 713).

P) ENDOTHELINS. Vasoactive peptides produced by the endothelial cells were discovered based on their strong and long-lasting vasoconstrictor activity (591, 624, 756, 1510). Three peptides were later identified as products of three different genes and named endothelin (ET)-1, ET-2, and ET-3 (843, 1901). It has been thought that the physiological role of these peptides is to serve as paracrine regulatory signals emanating from the endothelium to affect vascular smooth muscle tone (839, 1141, 1142). It is now quite apparent that these peptides have a wide array of physiological functions (814, 1291, 1790) and can modulate secretory functions in many endocrine tissues (1140, 1291, 1689).

The distribution of ET receptors in the CNS has been investigated, first with in situ hybridization (787) and more recently with immunocytochemical methods (990). In the hypothalamus and especially in the pituitary, ET_A is the predominant receptor subtype, while the ET_B receptors are most abundant in the cerebellum (787). Recent studies with an ET_A receptor specific antibody revealed a strikingly matching topography of ET_A receptor immunoreactivity with catecholaminergic neurons throughout the brain (990, 1895). For instance, in the hypothalamus, the arcuate and the periventricular nuclei, the parvicellular regions of the paraventricular nucleus, and the zona incerta contain strongly immunopositive cell bodies for ET_A receptors (990, 1895). Although this finding is suggestive of a specific functional relationship between endothelin and catecholaminergic systems in the brain, it needs to be reinvestigated with double-label techniques to establish the proposed synaptic connections and demonstrate colocalization of ET_A receptor and tyrosine hydroxylase in the same neuron unequivocally.

There is ample evidence that endothelin-like peptides are involved in the regulation of prolactin secretion (485, 902–905, 1544). Endothelins act directly on the lactotroph to decrease (902, 903, 1544) or increase (485, 906) prolactin secretion dependent on the physiological environment. These data suggest an important role for endothelins in the intrinsic regulatory mechanisms of the pituitary gland (905, 1577), which are discussed in section VII*B1*A*IV*.

Recent observations, however, indicate that endothelin-like peptides may also subserve a role as neuromodulators or neurotransmitters. For instance, immunocytochemical studies indicate that ET-1-containing axon collaterals of the hypothalamic magnocellular neurons can reach the area of dopaminergic cell bodies in the periventricular and arcuate nuclei (1895). Because high levels of ET_A receptor immunoreactivity have been detected in these dopaminergic neurons (990), it seems conceivable that endothelins affect prolactin secretion by influencing the activity of the hypothalamic neuroendocrine dopaminergic neurons.

The hypothalamic magnocellular neurons in the supraoptic and paraventricular nuclei were the first neural system where endothelin-like immunoreactivity was detected in the brain (1915). The physiological role of endothelins in the hypothalamo-posterior pituitary system is not well understood. It is interesting to note, however, that physiological conditions exacting profound demand on magnocellular neurons (e.g., water deprivation, lactation) robustly decrease the endothelin-like immunoreactivity in these neurons (1915). On the other hand, expression of ET-1 increases significantly in the supraoptic and paraventricular nuclei from early to late gestation (794). These, admittedly scarce, observations suggest an inhibitory function for endothelins in regulating oxytocin and/or vasopressin secretion and, perhaps indirectly, prolactin secretion.

The hypothalamic magnocellular system has been considered as a potential source of endothelin-like peptides for the anterior lobe of the pituitary gland (1690, 1915). It is conceivable that these neurons provide endothelins to the anterior lobe through their axon collaterals to the median eminence, in a way similar to oxytocin and vasopressin (50, 620, 782). Alternatively, endothelins re-

leased at the posterior lobe of the pituitary gland can reach the anterior lobe through the short portal system. Because endothelins likely influence the blood flow through the portal vascularizations in both cases, until recently, there was limited enthusiasm to consider endothelins as target cell-specific neurohumoral signaling molecules (905). However, recent observations of the magnocellular neurons reveal that part of the ET-1 precursor is not converted to the biologically active mature peptide but is packed in vesicles, transported to the axon terminals, and presumably released by regulated exocytosis (1520) as big ET-1 (1895). Because big ET-1 is practically inactive, it can theoretically reach the anterior lobe through the long portal vessels without affecting the blood flow of the portal vasculature. Assuming that the target cells express endothelin convertase enzyme and endothelin receptors, the big ET-1 will be converted to bioactive ET-1 on the cell surface. The locally generated mature ET-1 will then affect the cell and possibly its neighbors as well (1895). It is noteworthy that, in vitro, a non-cell-permeable endothelin convertase enzyme inhibitory peptide (1233) increases prolactin secretion (905), thus indicating that signaling through big ET-1 might be feasible for lactotrophs.

Taken together, the anatomical distribution of ET-like peptides and precursors, as well as endothelin receptors in the hypothalamus and the pituitary, indicate that endothelins of hypothalamic origin may act as neurotransmitter/neuromodulator or neurohormone to regulate prolactin secretion. However, none of these modes of action for endothelin has yet been proven experimentally.

Q) "NEW" PROLACTIN-RELEASING PEPTIDES. Although many of the peptides described above are all "candidates" for the physiological prolactin-releasing hormone of hypothalamic origin, none has definitively been assigned that role. A novel approach has recently been taken to describe another prolactin-releasing peptide of neural origin. With the use of the PCR, a seven-transmembrane-domain receptor, designated hGR3, was isolated from the human pituitary gland and identified as an "orphan receptor" on the basis that an endogenous ligand had not been identified (765). Chinese hamster ovary cells transfected with hGR3 receptor were used to isolate the endogenous ligand from crude bovine hypothalamic extract. The detection of the endogenous ligand relied on the fact that in these cells, activation of hGR3 receptors evokes the release of arachidonic acid, one of the signal transduction cascades known to control pituitary prolactin secretion from pituitary cells. Three bioactive peptides were subsequently isolated from the extract and purified by standard HPLC methodology (765). The cDNA encoding two of the peptide sequences of 20 and 31 amino acids were isolated from bovine, human, and rat brain and found to be highly conserved. The prolactin-releasing peptide mRNA for each is most abundant in the medulla oblongata (589, 1197), whereas only moderate amounts are found in the hypothalamus and the anterior lobe of the pituitary gland (589, 1147).

The synthetic peptides (1319) stimulate release of prolactin from a rat pituitary cell line as well as normal pituitary cells from lactating rats but does not affect the secretion of any other pituitary hormones (765). However, compared with equimolar quantities of some of the other well-described prolactin-releasing peptides, the 31-amino acid peptide is the only substance that potently stimulates prolactin secretion from cells obtained from lactating rats (765). Unfortunately, the claims of bioactivity as an authentic prolactin-releasing peptide have not been fully confirmed. When anterior pituitary cells obtained from male rats are exposed to the peptides, neither the 20- or 31-amino acid peptide stimulates prolactin secretion, whereas only the highest doses of either peptide stimulate prolactin secretion from pituitary cells obtained from random cycling female rats (1541). On the other hand, when administered intravenously to male rats or female rats during proestrus, estrus, or metestrus, the 31-amino acid peptide stimulates prolactin secretion in a dose-dependent manner during each stage of the estrous cycle (most effective during proestrus) as well as in male rats (1148). However, the effective dose is 10-fold greater in male than female rats. Such data suggest that the steroid milieu may determine the response of the lactotroph to these newly discovered peptides.

Immunocytochemical approaches reveal prolactin-releasing peptide-positive fibers in the paraventricular and supraoptic nuclei of the hypothalamus and in the neural lobe of the pituitary gland, whereas cell bodies are found in the dorsomedial and ventromedial nuclei of the hypothalamus (835, 1139). Within the paraventricular nucleus, double-label immunocytochemistry reveals synaptic contact with oxytocin-positive neurons. However, no prolactin-releasing peptide-positive cells or fibers are found in the external layer of the median eminence (835, 1139, 1897), the site at which one would expect to find neurohumoral terminals. On the other hand, immunoreactive processes in the hypothalamus often make contact with ependymal cells lining the third ventricle (835). In other parts of the brain, prolactin-releasing peptide-positive neurons (310, 835) and its message (1197) are noted mainly in two areas of the caudal medulla: ventrolateral reticular formation and commissural organ of the nucleus of the solitary tract, corresponding to the A1 and A2 noradrenergic areas. The distribution of the peptides in the CNS and intestine as well as the receptor throughout the CNS, anterior pituitary gland, and adrenal medulla has suggested an additional role for prolactin-releasing peptides in the central feedback control of neuroendocrine and autonomic homeostasis (1497)

The identification of immunopositive fibers in the neural lobe suggests that the peptide may arrive from the

neural lobe to the anterior lobe through short portal vessels connecting the two lobes. However, establishment of the physiological significance of these prolactin-releasing peptides awaits their identification in hypothalamo-hypophysial portal blood to be considered a neurohormone or in the anterior pituitary gland to be considered a paracrine or autocrine factor.

4. Amino acids

The group of amino acids that includes glutamate, aspartate, glycine, and GABA, and perhaps homocysteic acid and taurine, constitute the most widespread neurotransmitter family in the mammalian CNS (446). Because the vast majority of the excitatory neurotransmission is glutamatergic, and likewise, most of the inhibitory neurotransmission is GABA mediated, the focus is on these two amino acid neurotransmitters in this review.

A) AMINO ACID RECEPTORS. Most of the amino acid receptors belong to the ligand-gated ion channel superfamily of proteins (so-called ionotropic receptors), whereas others are members of the G protein-coupled receptor superfamily (metabotropic receptors). Although the cloned subunits of the ligand-gated ion channels are usually capable of forming a functional homomeric channel, these channels usually lack several features of the native channel complexes. Indeed, the native amino acid receptors are heteromeric structures, made up of several different subunits and auxiliary subunits. The differences in receptor composition likely confer varying modulatory capacity on the channel (446).

Ionotropic glutamate receptors consist of three subclasses: α-amino-3-hydroxy-5-methyl-4-isoxasolepropionate (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. These receptors respond to glutamate or glutamate analogs by activating a cation channel that is part of the receptor complex (for references, see Ref. 1409). Through different combinations of subunits and/or by alternative splicing of their mRNA, a large variety of these channels can exist. The glutamate receptor subunits are large (~100,000 Da) compared with other ligand-gated ion channels such as $GABA_A$, glycine, or ACh_N receptors. The functional AMPA and kainate receptors are permeable to monovalent cations (Na^+ and K^+) only, and they usually mediate rapid excitatory events. The NMDA receptor comprises a glutamate binding site, a strychnine-insensitive glycine binding site, a polyamine binding site, and a phencyclidine (MK-801) binding site. It seems that glycine is a necessary coagonist for NMDA receptors. Unlike the AMPA and kainate receptors, the ion channel of NMDA receptors is also permeable to calcium, and this permeability has been linked to many of the long-term effects of NMDA receptors (1409).

Metabotropic glutamate receptors are members of the G protein-coupled receptor superfamily with a characteristic seven transmembrane topology. Several metabotropic glutamate receptors have been identified with differing amino acid homologies, agonist preferences, and signal transduction pathways. The mGluR1 and mGluR5 receptors are linked to the phosphoinositol signal transduction pathway (sensitive to quisqualate), while mGluR2 and mGluR3 receptors are linked to the inhibition of cAMP cascade (the best agonist is glutamate); mGluR4, mGluR6, and mGluR7 are also linked to the inhibition of the cAMP cascade, but prefer L-(+)-2-amino-4-phosphonobutyrate (L-AP4) as an agonist (reviewed by Petralia and Wenthold, Ref. 1409).

As predicted (446), the surprisingly large variety of molecular forms of GABA, glutamate, and other amino acid receptors revealed by molecular cloning approaches present a daunting challenge for physiologists to establish the functional implications of these amino acid receptors.

B) EXCITATORY AMINO ACIDS. The excitatory amino acid (EAA) neurotransmission in the neuroendocrine hypothalamus has recently been reviewed (1793). On the basis of a great many morphological and electrophysiological (1791) studies, glutamate mediates most if not all fast excitatory inputs to the neurons in the arcuate nucleus (1793). Application of receptor autoradiography, in situ hybridization, and immunocytochemistry have provided detailed information concerning the distribution of binding sites, mRNA, and channel proteins for the large variety of glutamate receptors (for references, see Ref. 1409). Compared with the rest of the CNS, excitatory amino acid receptors in the hypothalamus are present in light to moderate density (1409). Most of the kainate receptors are in the arcuate nucleus-median eminence (1160, 1782), while NMDA binding sites were found in the preoptic area (1125). It is important to this review that several subtypes of AMPA, kainate, and NMDA receptors are detectable in all three lobes of the pituitary gland (1409). The latter observation indicates that, in addition to the CNS, glutamate receptors may play a direct role at the pituitary level (1409).

It is generally assumed that EAA exert their effects on prolactin secretion by acting at hypothalamic targets (208, 209). It has been reported, however, that glutamate increases prolactin secretion when applied in monolayer culture of dispersed pituitary cells of adult female rats (1074). Pharmacological characterization indicates that the receptor involved in the direct effect of glutamate on lactotrophs likely belongs to the NMDA subclass of the glutamate receptors (1074).

In neonatal rats, many neurons in the medial basal hypothalamus and the retina are vulnerable to systemically administered monosodium glutamate (MSG). Consequently, neonatally administered MSG causes severe disturbances in the regulation of anterior pituitary functions of the adult animal (21, 144, 350, 652, 1408, 1461, 1493, 1735, 1774). It is interesting to note that acute systemic

administration of MSG to the adult animal elicits a rapid and transient release of prolactin (1735). The latter result indicates that components of the regulatory circuitry of prolactin secretion not protected by the blood-brain barrier are sensitive to a glutamatergic stimulus (1735). Excitatory amino acids acting at the NMDA receptor likely play a role in modulating the activity of neuronal systems that regulate the release of both PRF and PIF (91). The effects of excitatory amino acids on prolactin secretion are largely determined by the relative activity of these two regulatory systems. Indeed, in a physiological situation with PRF dominance over PIF (lactation), EAA or EAA agonist administration decreases prolactin secretion (91) through activation of PIF (TIDA). In the case of male rats, where inhibition is the predominant central influence on prolactin secretion, EAA increase prolactin secretion presumably through activating PRF secretion into hypophysial portal blood (91).

The effects of excitatory amino acids on prolactin secretion change with the reproductive state of the animal and the site of administration (208, 209). As with CNS administration, the predominant effects of these agonists are through stimulation of PRF and/or inhibitory interneurons affecting TIDA/PHDA. On the other hand, in the case of systemic administration, these agonists can reach only the arcuate nucleus-median eminence region, which includes the TIDA/PHDA neurons (208, 209). Central administration of agonists to kainate or NMDA receptors stimulates prolactin release in both cycling and lactating animals (1). Peripheral administration of NMDA agonists stimulates prolactin secretion, whereas kainate has no effect (1). In contrast, systemic injection of either agonist to lactating animals inhibits prolactin secretion, indicating that lactation qualitatively alters the responsiveness of the neural circuitry involved in the regulation of prolactin secretion (1). Interestingly, changes in responsiveness to EAA of those neuronal circuits regulating either prolactin or LH secretion are opposite in nature (1). Nevertheless, the effects of lactation (and the suckling stimulus per se) at the level of the pituitary gland should also be considered, since lactation fundamentally alters the responsiveness of the lactotroph to both releasing and inhibiting factors, possibly by remodeling signaling mechanisms coupled to the receptors of these factors (1048).

Hyperprolactinemia (induced by pituitary grafts under the kidney capsule) significantly reduces glutamate concentration in the mediocortical amygdala (1117). It seems likely, however, that this effect of chronically elevated prolactin concentration in the plasma is related to the behavioral changes associated with hyperprolactinemia rather than the regulation of pituitary prolactin secretion per se (1117).

c) INHIBITORY AMINO ACIDS (GABA). It has been reported that GABA is partially responsible for the nondopaminergic PIF activity within hypothalamic extracts (1569). GABA neurons have been visualized by immunohistochemistry using an antibody against glutamate decarboxylase (GAD), an enzyme of GABA biosynthesis (1718, 1827). Cells of the anterior lobe contain specific receptors for GABA (664). Therefore, it is not surprising that GABA directly inhibits the release of prolactin (511, 1441, 1569). However, the effective molar concentration of GABA is ~100 times higher than that of dopamine tested in an in vitro superfusion system (1155). GABA concentrations in hypophysial stalk blood have been equivocally reported to be either higher than (1206) or lower than (1247) that of peripheral plasma.

Initial observations concerning the effects of GABA on prolactin secretion detected both stimulatory and inhibitory influences (1357, 1386). Although in the mid 1970s evidence in favor of dopamine as the major PIF had already been strong (1299), efforts to isolate a nondopaminergic (potentially peptidergic) PIF from the hypothalamus continued. One of these endeavors pointed toward GABA as a potential hypothalamic PIF (1569) and provided impetus for further studies on the role of GABA in regulating pituitary function (292, 511, 1441).

The early results concerning the involvement of GABA in the regulation of prolactin secretion were reviewed by Cocchi et al. (347), Racagni et al. (1440), Muller et al. (1250), and later by Apud et al. (52). On the basis of biochemical and immunocytochemical studies, it has been concluded that there are two different GABAergic systems affecting pituitary function: one is intrinsic to the mediobasal hypothalamus (tuberoinfundibular GABAergic system), whereas the other is extrinsic with cell bodies located outside the hypothalamus that project to the mediobasal hypothalamus and establish synaptic contacts with aminergic and peptidergic neurons involved in endocrine functions (52, 1173, 1546, 1570, 1716, 1718, 1719). On the basis of numerous biochemical and immunocytochemical studies (52, 54, 56, 1442), it seems that GABA is not synthesized in the anterior pituitary but rather originates from the CNS and is transported to the anterior lobe of the pituitary gland via the hypophysial portal system. Indeed, immunochemical and electron microscopic studies detect an abundant GAD-positive (GABAergic) nerve plexus in the external zone of the median eminence (1716, 1827) and nerve endings adjacent to the perivascular space of the fenestrated portal capillaries (1719). In addition, morphological evidence suggests a strong GABAergic innervation of the paraventricular and supraoptic hypothalamic nuclei (1174, 1737), areas thought to be important in PRF-mediated effects on prolactin secretion (1303).

The GABAergic neurons in the medial basal hypothalamus receive multiple intrahypothalamic and extrahypothalamic inputs. A direct stimulation of hypothalamic GABAergic neurons by serotonin (12) and substance P (11) has been demonstrated. Because these latter trans-

mitters have a stimulatory influence on prolactin secretion, it seems reasonable to assume that the GABAergic neurons stimulated by serotonin and substance P function as inhibitory interneurons affecting TIDA activity (1049, 1173, 1717).

The turnover of dopamine in the medial preoptic/anterior hypothalamic area, nucleus accumbens, anterior mediobasal hypothalamus is decreased, whereas dopamine turnover in the mediocortical amygdala is increased by the $GABA_A$ agonist muscimol (588). The effect of muscimol on the mediobasal hypothalamic dopaminergic neurons could be related to the elevated prolactin level caused by the same treatment (588).

In dispersed anterior pituitary cells in a cell-perifusion apparatus, GABA and the GABA agonist muscimol dose-dependently inhibit the release of prolactin (679). GABA antagonists (bicuculline and picrotoxin) block the action of GABA or muscimol, indicating the presence of specific $GABA_A$ receptors on pituitary lactotrophs (679).

The relatively low potency and efficacy of GABA and GABA mimetics on prolactin secretion in vitro makes it difficult to assess the true regulatory and/or clinical potential of GABA at the pituitary level (54, 55, 1168). Although both the brain and anterior pituitary GABA receptors have similar affinity for GABA in Scatchard analysis, in displacement studies pituitary GABA receptors show significantly less affinity for the $GABA_A$ agonist muscimol or the antagonist bicuculline (54). In addition, in male rat anterior pituitary slices, 10^{-6} M GABA is effective in decreasing prolactin release only in the presence of ethanolamine-*O*-sulfate, a potent GABA-transaminase (GABA-T) inhibitor (54). The low affinity of GABA mimetics and the rapid degradation of GABA in vitro could, at least in part, explain the relatively weak direct effects of these compounds on lactotrophs. It is also conceivable that there are two distinct GABA receptors and/or signaling pathways that elicit opposing biological effects on lactotrophs. Indeed, the $GABA_A$ receptor agonist muscimol has a biphasic effect on prolactin secretion in vitro, since at low concentrations it stimulates whereas at high concentrations it inhibits prolactin secretion (38, 39). In addition to its effects on secretion, GABA (through $GABA_A$ receptors) inhibits prolactin gene expression by acting directly on lactotrophs (1072, 1073).

The GABA receptors in the anterior pituitary have been thoroughly characterized (for references, see Ref. 52). From functional studies, it seems likely that the predominant receptor in lactotrophs is $GABA_A$. Indeed, the ability of $GABA_A$ agonists to displace [^{3}H]GABA binding from anterior pituitary membranes correlates well with their potency to inhibit prolactin secretion under stimulated conditions (e.g., hyperprolactinemia induced by dopamine antagonists). It has been recognized that $GABA_A$ receptors in the CNS are part of a multimolecular complex consisting of a chloride ionophore and its associated regulatory protein, a bicuculline-sensitive GABA binding site, a benzodiazepine recognition site, and a membrane-bound protein that can alter GABA and benzodiazepine sensitivity (363). $GABA_A$ receptor in the anterior pituitary and the CNS present similar affinity constants when evaluated by Scatchard analysis (54). However, in displacement studies, muscimol (a $GABA_A$ agonist) and bicuculline (a $GABA_A$ antagonist) show 10–100 times less affinity in the anterior pituitary (54). Interestingly, benzodiazepines and barbiturates potentiate the stimulatory effect of muscimol on prolactin secretion, whereas the inhibitory phase is not affected by these drugs (39). These results indicate that the effect of GABA on lactotrophs is complex and that at least one component of the $GABA_A$ receptor-mediated effects is modulated by benzodiazepines and barbiturates, similar to that described in the CNS (39, 661, 1826).

Although the majority of the studies have described $GABA_A$ receptor-mediated regulation of prolactin secretion at the pituitary level, several observations indicate that prolactin secretion can also be modulated through $GABA_B$ receptors. The $GABA_B$ agonist baclofen (*β-p*-chlorophenyl-γ-aminobutyric acid) decreases basal and TRH-stimulated prolactin secretion in a concentration-dependent manner when applied in monolayer culture of dispersed anterior pituitary cells (1091).

In many cases, the effects of systematically administered GABA agonists on basal prolactin secretion in vivo are less than impressive (55, 394–396, 459, 1168). It should be considered, however, that under basal condition, prolactin secretion is tonically suppressed by dopamine of hypothalamic origin; therefore, a further decrease in prolactin secretion by any putative PIF is likely to be modest. However, after relieving the dopaminergic inhibition of prolactin secretion by haloperidol (D_2 dopamine antagonist), $GABA_A$ agonists are capable of significantly decreasing prolactin secretion (55, 397). In addition, the stimulation of prolactin release by histamine is prevented, and the proestrous prolactin surge is significantly blunted by systemic treatment with GABA mimetics or GABA-T inhibitors (459, 1632). It has been reported that in male rats, the $GABA_B$ agonist baclofen blocks prolactin secretion induced by a variety of stressful conditions (430a, 1092). In addition, the same agonist also decreases the elevation of prolactin elicited by serotonin or a suckling stimulus. On the other hand, baclofen is ineffective in changing prolactin secretion following the blockade of dopaminergic neurotransmission by haloperidol or α-MpT (1092). It has therefore been suggested that baclofen inhibits prolactin secretion through a PRF component of the neuroendocrine responses evoked by stress or suckling (1092, 1881).

Centrally administered GABA or the $GABA_A$ agonist muscimol (5 nmol) in most cases reduces hypothalamic dopamine turnover while resulting in increased prolactin

concentration in the plasma (588, 998, 1249, 1356, 1378). However, in some studies carried out in ovariectomized female rats, GABA implanted directly into the arcuate nucleus fails to increase prolactin secretion (1318). Because the peripheral blood contains a significant amount of GABA, the question arose whether the GABA that affects the pituitary lactotrophs is of central or peripheral origin. Intracerebroventricular injection of anesthetized male rats with ethanolamine-*O*-sulfate, the specific inhibitor of GABA catabolism, causes a marked reduction in serum prolactin level and a three- to fourfold rise in the concentration of GABA in the pituitary stalk and in the hypothalamus (56). This demonstrates that GABA in the pituitary stalk plasma is derived from the CNS and that an abrupt increase in the concentration of GABA in hypophysial portal blood is associated with a suppression of prolactin secretion (56, 691). The effects of ethanolamine-*O*-sulfate on the hypothalamic and anterior pituitary GABA concentration and prolactin secretion occur much earlier than the increase of GABA concentration in the peripheral plasma, indicating that circulating GABA does not play a functional role in the control of prolactin secretion (56). It should be mentioned, however, that the physiological importance of GABA in the hypophysial portal blood has been subsequently challenged by others (1247, 1619). Nevertheless, the physiological role of GABA in regulating prolactin secretion is further supported by a close temporal relation between daily fluctuations in the activity of the tuberoinfundibular GABAergic system and the circadian prolactin surges (293). It has been suggested that changes in GABAergic activity might occur as a delayed response to prolactin circadian surges (293).

Treatment of ovariectomized rats with aminooxyacetic acid, a GABA-T inhibitor which elevates GABA levels in the CNS, leads to an increase in hypothalamic TH activity and a concomitant decrease in plasma prolactin concentration (96). Muscimol inhibits [^{3}H]dopamine release from the median eminence in vitro in a bicuculline-sensitive, strychnine-insensitive manner, indicating a presynaptic inhibition of dopamine release by $GABA_A$ receptors (37). When single-unit activity of neurons in the dorsomedial/ventrolateral part of the arcuate nucleus was examined, over 90% of these cells were inhibited by baclofen, a $GABA_B$ agonist (1049), suggesting a robust, functional inhibitory GABAergic input to the TIDA neurons. Studies in male rats indicate that although acute pharmacological activation of $GABA_B$ receptors inhibits TIDA neurons (1881), these neurons are under tonic inhibition mediated by $GABA_A$ but not $GABA_B$ receptors (1881). Taken together, these observations provide further evidence that the major central effect of GABA on prolactin secretion is exerted by inhibiting the neuroendocrine dopaminergic cells of the hypothalamus. Because the sensitivity of these dopaminergic neurons to neural inputs is sexually differentiated, that would explain the previously observed gender-related differences in the effects of GABA on prolactin secretion observed in most (1106, 1210, 1846), but not all (1469), laboratories.

Lactating female rats represent a unique model for the regulation of prolactin secretion (for references, see Ref. 1303) where the hypothalamo-pituitary GABAergic system seems to play an important role. Indeed, in lactating rats separated from their pups, reinstitution of suckling results in an increase in GAD activity in the medial basal hypothalamus and an increase in GABA content in the anterior pituitary (1439).

It was suggested that the major function of GABAergic neurons is negative-feedback regulation of prolactin secretion to prevent an exaggerated prolactin output during specific physiological situations (52, 477, 479). Indeed, hyperprolactinemia elevates central GABAergic activity as evidenced by an increase in hypothalamic GABA concentration and GAD activity (543). The effects of prolactin on GABAergic activity in vivo are mainly indirect and mediated by substance P and/or serotonin (11, 12, 1706). Immunoneutralization of endogenous substance P prevents prolactin-induced elevation of GABA in the anterior pituitary and diminishes the depolarization-induced GABA release from hypothalamic fragments in vitro (11). There are some indications that prolactin can affect tuberoinfundibular GABAergic neurons directly, suggesting that prolactin may influence its own secretion by stimulating the release of hypothalamic GABA, both through an increase of GABA synthesis and modification of GABA reuptake (478, 480). An activation of GABAergic neurons by prolactin in the hypothalamus is supported by the observations that prolactin induces a rapid elevation in intracellular free Ca^{2+} applied in primary cultures of rat embryonic diencephalon (970).

Hyperprolactinemia induced by pituitary grafts under the kidney capsule significantly reduces GABA concentration in the nucleus accumbens and the mediocortical amygdala (1117). In the case of sustained hyperprolactinemia, GABA turnover is reduced in the nucleus accumbens, whereas it is increased in the medial preoptic area (1117). Thus GABAergic systems in these brain areas might not be involved in regulating prolactin secretion per se, but rather mediate the prolactin-induced suppression of LH secretion, and/or elicit behavioral effects associated with hyperprolactinemia (1117, 1118). Centrally administered prolactin causes a delayed increase in GABAergic activity in the hypothalamus and GABA concentration in the hypophysial portal plasma (1071). This indicates that the activity of the tuberoinfundibular GABAergic neurons is regulated by circulating prolactin. Taken together, these results strongly support the notion that prolactin is capable of activating GABAergic neurons in the mediobasal hypothalamus, constituting a short-loop feedback

system by which prolactin regulates its own secretion (1071).

The activity of hypothalamic GABAergic neurons as well as the responsiveness of lactotrophs to GABA are both strongly affected by gonadal steroids, especially estradiol (53, 423, 441, 477, 859) and testosterone (669). The existence of a large number of estradiol-receptive, GABAergic neurons in the mediobasal hypothalamus suggests that these neurons are targets for the positive feedback action of estradiol on prolactin secretion (562). Indeed, estrogens induce hyperprolactinemia concomitantly with an increase of hypothalamic GAD and GABA-T activity, as well as GABA concentration (441). A single injection of estradiol does not change the activity of the tuberoinfundibular GABA neurons as assessed by the rate of GABA accumulation in the median eminence and the anterior pituitary following the blockade of GABA catabolism by ethanolamine-*O*-sulfate (53). However, a single injection of estradiol causes a shift of pituitary GABA receptors from low- to high-affinity state and results in a modest elevation of prolactin secretion. After the single estradiol administration, the GABA agonist muscimol causes a significant decrease in serum prolactin concentration. Chronic estradiol administration reduces the activity of the tuberoinfundibular GABA neurons and drastically decreases the number of high-affinity GABA receptors in the anterior pituitary, resulting in a robust elevation in plasma prolactin concentration. Under these circumstances, muscimol is ineffective in reducing plasma prolactin concentration (53), suggesting that the high-affinity population of anterior pituitary GABA receptors (presumably expressed by the lactotrophs themselves) are involved in the mechanisms whereby GABA inhibits prolactin release from the lactotrophs (53).

It is interesting to note that lactotrophs, as a result of an extended exposure to estradiol, tend to lose their responsiveness to inhibition by GABA (53), dopamine (1024), or endothelins (Kanyicska and Freeman, unpublished data) and became prone to malignant transformation. The precise molecular mechanisms underlying these changes in responsiveness toward endogenous PIF brought about by long-term exposure to estradiol is not yet understood. It seems likely that downregulation of a subset of G_i/G_o proteins is, at least in part, responsible for the estradiol-induced changes in lactotrophs' function (198, 199, 308, 1178, 1397).

The effects of GABA through $GABA_A$ receptors are thought to be initiated by an increase in conductance of cell membrane to chloride ions through activation of chloride channels, which leads to a hyperpolarization of the plasma membrane causing a decrease of Ca^{2+} influx through voltage-dependent Ca^{2+} channels. Patch-clamp studies on rat and bovine lactotrophs indicate that the main effect of GABA on lactotrophs is indeed mediated through modulation of chloride ion conductance. The chloride channel involved in lactotrophs is voltage insensitive and has a slope conductance of 20 pS (840, 841, 846). Muscimol mimics the effect of GABA on these channels, whereas baclofen is without effect, indicating a $GABA_A$ receptor-mediated activation of these channels (841). The $GABA_B$ receptors couple to potassium channels through GTP-binding proteins (41). Therefore, $GABA_B$ receptor activation also leads to membrane hyperpolarization by increasing membrane conductance to potassium ions. It has been suggested that GABA acting at $GABA_A$ and $GABA_B$ receptors might originate from distinct sets of GABAergic neurons (1699).

Isolated lactotrophs in primary culture respond to GABA or GABA mimetics with a transient increase of cytosolic free Ca^{2+} and depolarization of the plasma membrane (1082). The pharmacology of the latter effect of GABA is consistent with $GABA_A$ receptor involvement (1082). However, these effects of GABA seem inconsistent with the inhibition of prolactin secretion.

The role for GABA as the most important fast inhibitory neurotransmitter in the brain is so well established that the presence of the GABA-synthesizing enzyme GAD in axon terminals is usually interpreted as a sure sign of their inhibitory function (401, 1719). However, there are several observations that can challenge the view that GABA is always inhibitory (1362, 1403). For example, during early postnatal life, GABA is markedly stimulatory on GH and, to a lesser extent, on prolactin secretion when applied directly on pituitary slices or dispersed pituitary cells (6, 7). A similar observation has been made on cultured hypothalamic neurons using electrophysiological techniques (1847). Because GABA exerts its fast inhibitory action through activation of Cl^- channels, it can be assumed that in neonatal cells, the equilibrium potential for Cl^- is higher than the resting potential compared with that of adult cells. Therefore, activation of Cl^- channels will cause a depolarization of the cell membrane, an observation which offers a plausible explanation for the observed stimulation of Ca^{2+} influx by GABA or $GABA_A$ agonists on neonatal anterior pituitary cells (8, 9) and neurons as well (311, 1847). More recently, it has been reported that in mature neurons of the suprachiasmatic nucleus of the hypothalamus, GABA acts as an excitatory neurotransmitter during the day and as an inhibitory neurotransmitter at night (1847). Taken together, although the inhibitory function of GABA seems prevalent, under certain conditions, activation of $GABA_A$ receptors can result in stimulation of the target cell (355).

5. Gaseous transmitters

A) NITRIC OXIDE. Nitric oxide and, more recently, carbon monoxide have been shown to play a regulatory role in neuroendocrine function and prolactin secretion (207).

Among the gaseous neurotransmitters, nitric oxide is the most widely described as controlling prolactin secretion.

Unlike the classical neurotransmitters, nitric oxide is not stored in synaptic vesicles, is not limited to actions at synapses, and does not interact with classical receptor proteins, but it merely diffuses to nearby cells where it modulates the function of postreceptor transduction cascades (388, 389, 1083, 1213, 1254, 1293, 1576). Nitric oxide is synthesized from L-arginine by nitric oxide synthase (389, 1212). Although there are three major isoforms of the enzyme identified to date, only one, neuronal nitric oxide synthase (389), has been shown to play a role in control of prolactin secretion (171, 207).

Because nitric oxide synthase is identical to neuronal NADPH-diaphorase (387), cytochemical detection of NADPH-diaphorase activity is frequently used to study the distribution of nitric oxide synthase. Nitric oxide synthase is found throughout the CNS (1922). In the rat, nitric oxide synthase is present in the anterior pituitary (301), throughout the hypothalamus (51, 172), and colocalized in the locus coeruleus with norepinephrine (1893). Within the hypothalamus, nitric oxide synthase (NADPH-diaphorase) activity is found in the paraventricular and supraoptic nuclei as well as in the lamina terminalis (51, 172, 213, 1767). Moderate activity is found in the medial preoptic nucleus, ventromedial nucleus, suprachiasmatic nucleus, and median eminence (172).

Most of the studies examining a role for nitric oxide on the hypothalamo-pituitary axis focus on LH secretion (207). There is, however, some evidence that nitric oxide may play a role in the control of prolactin secretion as well. Administration of the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine blocks the preovulatory release of prolactin on proestrus (185). Likewise, administration of the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester blocks the steroid-induced proestrus-like release of prolactin in ovariectomized rats (185). Similar pharmacological blockade of nitric oxide synthase inhibits stress-induced prolactin secretion in male rats, while potentiating morphine-induced increase of prolactin secretion (1157). The latter results are somewhat unexpected, since stress is thought to affect prolactin secretion via activation of the endogenous opioid system (239, 1540, 1634, 1808). It should be considered, however, that systemic nitric oxide synthase inhibition likely affects several different pathways of neurotransmission mediating stress-induced prolactin secretion in addition to endogenous opioids. It is also conceivable that blocking of nitric oxide synthesis has differential effects on morphine-induced (activating a μ-type opioid receptor) versus an endogenous opioid-induced (perhaps activating a κ-opioid receptor) signaling (120).

Administration of the nitric oxide donor sodium nitroprusside to conscious male rats stimulates prolactin secretion (641). All in all, these data indicate that nitric oxide plays a stimulatory role in the control of prolactin secretion. In support of the former assertion, it has been shown recently that sodium nitroprusside enhances prolactin secretion by inhibiting tyrosine hydroxylase activity in the median eminence of male rats (642), while administration of the nitric oxide synthase inhibitor N^{G}-nitro-L-arginine blocks the estrogen-induced increase of prolactin secretion of ovariectomized rats by increasing dopaminergic activity in the median eminence (1912). These data, therefore, suggest that nitric oxide enhances prolactin secretion by diminishing the activity of TIDA neurons.

At the pituitary level, it seems that nitric oxide, formed either by inducible or constitutive isoforms of nitric oxide synthase (1803), may mediate the inhibitory effect of cytokines on prolactin secretion (1163–1165). Moreover, recent observations suggested that nitric oxide inhibits prolactin secretion by activating guanylyl cyclase-cGMP pathway and that this mechanism may be involved in the GABA-induced inhibition of prolactin secretion (481, 1161, 1162). In addition, incubation of male rat hemipituitaries with sodium nitroprusside inhibits basal prolactin secretion from these glands (482). Interestingly, when applied on dispersed cells from male rat pituitary glands, molsidomine, also a nitric oxide donor (1455), stimulates basal prolactin secretion (238). The opposing biological effects of nitric oxide observed in intact tissue (482) and dispersed cell (238) preparations indicate that cell-to-cell interactions may be important in determining the effects of nitric oxide on prolactin secretion.

Taken together, these data indicate clearly that nitric oxide plays a role in regulating prolactin secretion and argue for a stimulatory role of nitric oxide within the hypothalamus and a predominantly inhibitory effect within the anterior pituitary gland.

B. Intrapituitary Regulation

In addition to the intricate regulation by the hypothalamus and peripheral endocrine glands (reviewed in sect. VII, *A* and *C*), the secretion of prolactin is also influenced by local regulatory mechanisms (Fig. 3). It is now widely accepted that the anterior lobe of the pituitary gland has an intrinsic regulatory capacity through paracrine and autocrine signals and that this type of regulation can robustly affect lactotroph function (141, 1577). Because these local regulatory mechanisms of the pituitary gland have recently been extensively reviewed (141, 1577–1579), we will provide only a brief survey of local control of prolactin secretion and elaborate on recent developments in this quickly expanding research area.

1. Anterior lobe

a) AUTOCRINE AND PARACRINE REGULATION: AN OVERVIEW. Modes of local regulation of cellular functions, brought

about by the secretion of diffusible molecules, can be further divided based on the positional relation of the participating cells. The regulation is called autocrine when the secretory product of the cell regulates its own secretion. In the case of paracrine communication, the secretory product is transported by extracellular fluid and exerts a biological effect on target cells at some distance. Juxtacrine regulation is distinguished as a special case of paracrine regulation when the source and target cells are adjacent (juxtaposed) to each other. In addition, when the lactotroph lies in intimate physical contact with another anterior pituitary cell (which could be another lactotroph as well), interactions are also possible without diffusible messenger molecules, through gap junctions or extracellular matrix proteins (164, 165, 424, 494). Because gap junctions, to some extent, are permeable to intracellular messengers such as Ca^{2+}, inositol trisphosphate, or cAMP, it seems conceivable that a larger cell population can be synchronized through these intercellular channels (424). It appears that certain physiological situations promote the formation of reversible supracellular functional units within the pituitary gland. For instance, it has been reported that during lactation, lactotrophs and folliculostellate cells are functionally coupled through gap junctions (25, 26, 991, 1325). Although these types of communication between pituitary cells are extremely important (especially from a pathophysiological point of view), a detailed discussion is beyond the scope of this review. As for the rest, we discuss cell-to-cell communications through secreted diffusible messenger molecules pertaining to prolactin secretion.

A direct contact occurring between lactotrophs and other pituitary cell types in vivo (792, 1287, 1559) is suggestive of juxtacrine regulation. However, such intimate contact between cells does not seem to be required for a more general paracrine regulation of prolactin secretion (426). Paracrine interactions between different pituitary cell types have been studied extensively by Denef et al. (426). Four different cell types have been established as potential sources of paracrine signals affecting lactotroph function: lactotrophs, gonadotrophs, corticotrophs, and folliculostellate cells (101, 425, 1577).

To consider a factor as a potential intrapituitary messenger, proof of its local synthesis should be provided. For peptides and proteins, demonstration of the presence of immunoreactive material together with the respective mRNA through the combined application of immunocytochemical and in situ hybridization techniques is usually accepted as proof of local synthesis. To establish small nonpeptide molecules, such as acetylcholine, ATP or nitric oxide as autocrine/paracrine agents could be more complicated, and usually requires in vitro biochemical/pharmacological experimentation in addition to the demonstration of the synthesis enzyme(s) with immunocytochemistry and in situ hybridization.

Numerous peptides and other molecules have been detected in the pituitary gland that are known to be capable of modulating prolactin secretion (800), including VIP (1275), galanin (596, 909), endothelin (452, 905), prolactin (146, 890, 795), ANG II (426), substance P (89), neurotensin (89, 630), GnRH (129, 1227), TRH (320), corticotrophin releasing factor (1228), growth hormone releasing factor (1230), somatostatin (1229), gastrin (1458), secretin (1335), enkephalins (950, 1771, 1870), vasopressin (828), and acetylcholine (276, 276, 277, 1245, 1564, 1729). There is reason to believe that these messenger molecules are synthesized locally rather than being taken up after delivery through the portal circulation. Considering the high "spontaneous" rate of prolactin secretion, it probably is significant that most of these peptides are potent stimulators of prolactin secretion by acting directly on the lactotrophs (505, 512, 663, 734, 916, 918, 1046, 1154, 1754, 1820).

There is an ever-growing list of peptides with the potential to act as local regulators of prolactin secretion. However, establishing the precise mode of their actions in a physiological context presents a significant challenge. It is probably the most difficult to produce unambiguous data in support of autocrine control of prolactin secretion, since the presence of a biologically active molecule and its mRNA in the lactotroph is not sufficient to verify an autocrine role. Furthermore, demonstration of the biological effect of the putative autocrine agent by antagonism or immunoneutralization in most of the in vitro test systems still would not support such a role convincingly, since these methods are usually applied to a heterogeneous cell population in which a wide variety of cell-to-cell interactions can occur. It seems that the best methodological approach currently available to characterize autocrine regulation is a carefully designed reverse hemolytic plaque assay (572, 576, 1211, 1300). With the use of this method, the secretory activity of a single cell can be assessed quantitatively without interference from neighboring cells (190, 250, 573, 771, 862, 1030, 1090, 1275, 1282).

B) AUTOCRINE AND PARACRINE REGULATORS OF PROLACTIN SECRETION. *I) VIP*. VIP, a known hypothalamic stimulator of prolactin release (4, 1528, 1609), is also synthesized within the anterior lobe of the pituitary gland (87), more specifically, by the lactotrophs (978). Specific VIP antiserum, but not other hyperimmune sera, decreases basal secretion of prolactin in vitro, thus suggesting a paracrine and/or autocrine stimulation of prolactin secretion by locally produced VIP (715). An autocrine control of prolactin secretion by VIP has been demonstrated unequivocally using reverse hemolytic plaque assay (1275), by showing that under conditions in which the pituitary cells are plated at sufficiently low density to preclude paracrine interactions, VIP antiserum or a VIP antagonist suppresses prolactin secretion (1275). These findings likely

have far-reaching physiological and pathological relevance, albeit none has been firmly established yet. For instance, it seems conceivable that the peculiar ability of lactotrophs to secrete prolactin vigorously without any exogenous stimulant may be due to a positive feedback exerted by its own VIP secretion. With some stretch of imagination, it can be envisioned that VIP is a common autocrine mediator of all other PRF or PIF. In support of this notion, it has been found that the presence of a VIP antagonist attenuates TRH-stimulated prolactin secretion in vitro (113). Similarly, the stimulatory effects of serotonin on prolactin secretion from cocultures of anterior lobe and neurointermediate lobe cells can be blocked by simultaneous incubation with a VIP antagonist (115). In addition, it is also conceivable that dopamine may suppress prolactin secretion, at least in part, by antagonizing the stimulatory effect of VIP through an activation of inhibitory signaling or by inhibiting VIP secretion per se, or both (114). Taken together, it appears that VIP has a multifaceted role in the regulation of prolactin secretion that may involve an autocrine, paracrine, or neuroendocrine route of delivery (1275).

II) Galanin. Several lines of evidence indicate that galanin regulates prolactin secretion in a auto- and/or paracrine manner. Galanin-like immunoreactivities have been found in the anterior lobe of rat and human pituitary glands (803, 808, 818, 819, 909, 1840), and it appears that galanin is an estrogen-inducible secretory product of the anterior lobe of the pituitary gland (909, 1339, 1843). Specifically, galanin mRNA and peptide have been detected in lactotrophs (823, 1339). Interestingly, galanin secretion is also affected by prolactin secretagogues, in accordance with galanin's stimulatory effect on prolactin secretion. For instance, galanin secretion from the rat anterior lobe is inhibited by dopamine and somatostatin and stimulated by TRH (824) and estrogen (726, 749, 823, 1843). Exogenous galanin stimulates basal as well as TRH-induced prolactin release and lactotroph proliferation in rats (1360, 1889) and humans (628). Immunoneutralization of endogenous galanin attenuates the preovulatory release of prolactin on proestrus (1081). Although receptor autoradiography fails to detect specific galanin binding sites in the pituitary (820), data obtained by the more sensitive receptor-binding assay clearly indicate that high-affinity galanin receptors are indeed present in the anterior lobe (1890). Moreover, the recently cloned galanin receptor, GALR2, has been shown to be expressed in the anterior lobe of the pituitary gland (532).

Recent experiments provided direct evidence for a tonic autocrine and paracrine stimulatory action for intrapituitary galanin on prolactin secretion (1841, 1843, 1888). In an elegant study, Cai et al. (258) have shown that in estrogen-treated Fischer 344 female rats, more than 90% of the galanin-expressing cells are lactotrophs. Furthermore, with the use of the combination of reverse hemolytic plaque assay and in situ hybridization, it was found that galanin-positive lactotrophs secrete significantly greater amounts of prolactin compared with galanin-negative lactotrophs. The autocrine function of pituitary galanin has been further supported by in vitro immunoneutralization experiments showing that galanin antiserum significantly attenuates prolactin secretion from galanin-positive cells (258).

III) Endothelins. Endothelin-like peptides (especially ET-1) are potent inhibitors of prolactin release in vitro (452, 902, 903, 1140, 1543, 1544, 1689, 1689). Because endothelin-like peptides are present in all three lobes of the pituitary gland (452, 905) as well as in spent media from rat anterior pituitary cell cultures (1149), it seems plausible that these peptides contribute to the local regulation of prolactin secretion. Endothelin-like immunoreactivity is detectable in lactotrophs (905) as well as other cells of the anterior lobe (1292). Moreover, by using endothelin-specific reverse hemolytic plaque assay, it has been shown that endothelin is indeed secreted from lactotrophs. Interestingly, lactotrophs obtained from cycling female rats show signs of more vigorous endothelin secretion compared with lactotrophs from males (905). The amount of endothelin secreted by the lactotrophs is biologically significant, since it is sufficient to inhibit prolactin secretion, as attested by the fact that the presence of ET_A receptor antagonists markedly enhance prolactin secretion as detected by reverse hemolytic plaque assay (905). Because lactotrophs bear ET_A receptors (904, 1532), it is not surprising that ET_B antagonists were ineffective on prolactin secretion (905). Because in these experiments the reverse hemolytic plaque assay was performed under conditions that preclude paracrine interactions, the argument has been made that prolactin secretion is under autocrine control by endothelins (905). We should add, however, that these data, while strongly supporting the possibility of autocrine regulation by endothelins, by no means exclude paracrine control of prolactin secretion by endothelins.

IV) Prolactin. It is well established that prolactin can inhibit its own secretion by activating neuroendocrine dopaminergic neurons in the hypothalamus (65, 82, 773a, 1353, 1584). However, there is evidence that prolactin can also act directly at the lactotroph and inhibit its own secretion in an autocrine/paracrine manner, in both human and rat pituitary glands (146, 890, 795). Prolactin receptor is detected on the membrane of lactotrophs (323). Moreover, by using electron microscopy and autoradiography, it has been found that prolactin is bound to the plasma membrane and subsequently internalized and found in the Golgi apparatus, secretory granules, nucleus, and mitochondria of the lactotroph (627).

These data demonstrate clearly that lactotrophs have the capacity to perceive and respond to prolactin in their environment. It is interesting to note that in certain phys-

iological or pathological conditions, such as lactation or prolactinoma, lactotrophs apparently lose their autoinhibitory response to prolactin. It appears that the autoinhibitory function of prolactin is related to a particular isoform of the hormone (768) and that an impairment of the synthesis and secretion of this isoform is responsible for the lack of prolactin-induced autoinhibition (768). On the other hand, another isoform of prolactin can act as an autocrine growth factor in tumorous cells (980), resulting in unrestrained cell proliferation (980).

It seems well established that prolactin, together with VIP, galanin, and endothelin, can regulate lactotrophs' function in an autocrin*e* manner, and there is a high probability that such regulation is indeed operational in vivo. However, by confirming the autocrine regulatory function of these agents does not exclude the possibility that they also subserve a role as paracrine modulators of prolactin secretion as well. Indeed, simply by considering that a large proportion of the cells in the anterior lobe is lactotroph and many lactotrophs are actively secreting VIP, galanin, endothelin, and prolactin, there is reason to believe that paracrine type of interactions among lactotrophs through these peptides may also exist.

V) ANG II. There is abundant evidence that ANG II is formed in the anterior lobe of the pituitary gland (601, 602, 1290, 1674, 1677), specifically in the lactotrophs (1529, 1674). Moreover, ANG II receptors have been found in the pituitary (1244), presumably in lactotrophs (14, 273, 746, 1244). Because ANG II is a potent stimulator of prolactin release (14, 426, 1575), it seems quite likely that angiotensin stimulates prolactin secretion in a paracrine and/or autocrine manner (987, 1265, 1676, 1678).

VI) Substance P. Although substance P affects prolactin secretion through a neuroendocrine or neurotransmitter role (reviewed in sect. VII*A*), there is some evidence that it may also originate from a pituitary source. The preprotachykinin gene has been found in the anterior pituitary, and its expression is regulated by thyroid hormone (872) and estrogen (225). Moreover, substance P and other preprotachykinin gene products are also found in the anterior lobe (428, 1226). Finally, with a cell immunoblot assay, it has been shown that anterior pituitary cells actually secrete substance P (85). Unfortunately, in none of these studies was the endocrine phenotype of the anterior pituitary cell determined, nor was a substance P antagonist applied. Consequently, there is no direct proof to differentiate substance P as either an autocrine or paracrine regulator of pituitary prolactin secretion.

VII) Growth factors. There is strong evidence for an autocrine/paracrine role for transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and nerve growth factor (NGF) in the control of prolactin secretion.

A) TGF-β. TGF-β is a polypeptide of 25 kDa and exists as three isoforms (TGF-β1, TGF-β2, and TGF-β3). The anterior pituitary contains TGF-β1 and TGF-β3 (247, 1389, 1552). In lactotrophs, the presence of TGF-β1 protein as well as TGF-β receptor and its mRNA have been demonstrated (247, 391, 1552). The lactotroph expresses both forms of the TGF-β receptor, designated type I and type II (1389). Most of the biological activity of TGF-β1 can be attributed to the type I receptor, whereas the growth-inhibitory response is due to type II receptor activation (1553). Intrapituitary administration of TGF-β1 suppresses pituitary cell proliferation and decreases pituitary prolactin content and plasma prolactin concentration (1198). Moreover, TGF-β inhibits basal secretion of prolactin in a pituitary monolayer culture system (1262) as well as prolactin gene expression in GH_3 cells (408) and normal anterior pituitary cells (5, 1712), likely by a paracrine route (5). It is interesting to note that in rats in which pituitary tumors are induced by estrogen, the proteins and mRNA for TGF-β1 and the type II receptor are reduced (1389). This finding raises the possibility that pituitary tumorigenesis may be the result of suppression of TGF-β activity.

B) EGF. EGF is a single-chain polypeptide originally extracted from the mouse submaxillary gland. In the anterior pituitary gland, the presence of prepro-EGF mRNA (1444) and the secretion of EGF peptide has been demonstrated (988). Within the pituitary gland, EGF binding sites are restricted to lactotrophs (303, 536). Functionally, EGF promotes differentiation of lactotrophs at the expense of somatotrophs in neonatal rats (542) and stimulates prolactin gene transcription in and prolactin secretion from lactotrophs (1263). EGF also induces expression of functional D_2 dopamine receptors in lactotroph-like cell lines lacking the receptor (1204). Approximately 20% of the cells in the anterior pituitary gland of lactating rats secrete EGF, with 27% of those being lactotrophs (1239). Without reference to cell of origin, it has been suggested that EGF exerts its effects through autocrine and paracrine routes (1237). It is interesting to note that anterior pituitary cells from proestrous rats secrete the greatest amount of EGF and that estradiol is a potent stimulator of EGF secretion from rat pituitary cells (1238). With this in mind, it is tempting to speculate that estrogen induces the proestrous surge of prolactin secretion (1302) partly by stimulating intrapituitary EGF secretion, hence priming the lactotrophs for the massive hormone secretion brought about by hypothalamic factors.

C) NGF. The 26-kDa peptide NGF and its receptor are found in all three lobes of the pituitary gland, with greatest abundance in somatotrophs and lactotrophs (1202, 1395). Stimulation of these cells with VIP (1201) or interleukin-1β (1396) results in secretion of NGF. Much like EGF, NGF promotes differentiation of lactotrophs at the expense of somatotrophs in GH_3 cells (1203) and anterior pituitary cells from early postnatal rats (1201). NGF also promotes mitogenesis of immature pituitary cells (1437). Unlike EGF, NGF does not appear to be involved directly

in the control of prolactin secretion. It has been proposed that NGF plays a dual role in the pituitary gland: a local one as a stimulator of differentiation and proliferation of lactotrophs during pituitary development and a systemic one as a neurohormone that is cosecreted with prolactin into the bloodstream (1205). Furthermore, NGF is an autocrine differentiation factor for prolactin-secreting cells. Escape from NGF control appears to be one of the mechanisms involved in the development and progression of prolactinomas. Exposure of prolactinomas refractory to dopaminergic therapy to exogenous NGF results in their differentiation into lactotroph-like cells reexpressing the D_2 receptor protein (1205). This observation may open the way to a sequential therapy with NGF and bromocryptine for patients refractory to the conventional therapy (1205).

VIII) Calcitonin. Calcitonin-like immunoreactivity is present and released from rat anterior pituitary cells (514, 880, 1225, 1593–1595, 1597, 1631). Moreover, exogenous salmon calcitonin inhibits basal and TRH-stimulated prolactin release as well as prolactin gene transcription in cultured rat pituitary cells (514, 880, 1225, 1593–1595, 1597, 1631, 1894). Therefore, it has been suggested that calcitonin affects prolactin secretion by a paracrine mechanism (514, 880, 1225, 1593–1595, 1597, 1631). Administration of an antiserum to salmon calcitonin to ovariectomized rats enhances prolactin secretion (1595). Similarly, addition of the antiserum to cultures of rat pituitary cells enhances prolactin secretion in the presence or absence of dopamine (1595). Immunocytochemical studies reveal a nonuniform distribution of calcitonin-like immunoreactivity in the anterior lobe because the cells of the inner zone adjacent to the intermediate lobe contain the greatest salmon calcitonin-like immunoreactivity (1595). Although they are clearly not lactotrophs, the phenotype of these cells has not been determined unequivocally. Nevertheless, it has been suggested that they may be gonadotrophs that affect prolactin secretion by a paracrine and/or juxtacrine pathway (329). There may also be a feedback relationship between prolactin and calcitonin, since the circulating levels of calcitonin in male rats are enhanced by hyperprolactinemia produced by homotransplant of pituitaries to the kidney capsule (1084).

IX) TRH. Earlier we reviewed the extensive literature that TRH of hypothalamic origin is a potent stimulator of pituitary prolactin secretion. It is now apparent that some of the TRH may originate within the anterior pituitary gland. However, it is not clear if this is a source for TRH-stimulated prolactin secretion. Indeed, pro-TRH-derived peptides have been characterized in long-term cultures of anterior pituitary cells (232), while pro-TRH mRNA has been found in a subpopulation of somatotrophs (234) in which the gene expression is regulated coordinately with the growth hormone gene by glucocorticoids (233) and thyroid hormone (235). TRH appears to be most abundant in anterior pituitary glands obtained from 15-day-old female rats (235, 236). Although TRH is found in pituitary cell cultures, the peptide from this source apparently does not affect prolactin synthesis or secretion (237).

X) Cytokines. IL-6 is a cytokine found in the anterior pituitary gland (1669), likely produced by folliculostellate cells (1801). IL-6 has been shown to stimulate prolactin secretion, both in vitro (1095, 1667) and in vivo (1095). In addition to VIP (1665), IL-1 can also stimulate the release of IL-6 from anterior pituitary cells (1666, 1668). Taken together, these data imply that VIP-induced prolactin secretion may involve a VIP→IL-1→IL-6 cascade within the pituitary gland. However, further studies are required to confirm the role of this cascade in the intrapituitary regulation of prolactin secretion.

XI) GnRH. Perhaps the first example for paracrine modulation of lactotrophs described (425), is the stimulation of prolactin release by GnRH. The most prominent prolactin-releasing activity of GnRH could be detected during the early postnatal life when the relative proportion of gonadotrophs is much higher than in adults (425). Moreover, GnRH will only stimulate prolactin secretion when lactotrophs are cocultured with gonadotrophs (425), indicating that not GnRH itself but other gonadotroph-related products may be responsible for the GnRH-induced stimulation of prolactin secretion. Because all components of the renin-angiotensin system had been described previously to be present in gonadotrophs, the agent mediating this effect was thought to be ANG II (426). However, other experimental data (1486) do not support the role of ANG II in the GnRH-induced and gonadotroph-mediated paracrine influence on prolactin release. The physiological significance of the paracrine regulation of prolactin secretion by gonadotrophs is unknown. However, it probably operates in vivo, since GnRH has been reported to release prolactin in monkeys (609, 1350) and in women during the menstrual cycle (295, 1910).

In addition to the effect of GnRH on the secretory function of lactotrophs, it also affects cell mitosis and cytodifferentiation within the anterior lobe. Treatment of reaggregate pituitary cell cultures with GnRH enhances the total number of lactotrophs replicating DNA (1748) and containing prolactin mRNA (1787). These effects are mediated by growth factors present in the medium conditioned by gonadotroph-enriched cell population obtained from 14-day-old rats. This recruitment of lactotrophs may not be restricted to the early postnatal period of life. During the period of cytodifferentiation as well as in certain physiological situations such as pregnancy or lactation, recruitment seems to be due to the differentiation of progenitor or immature cells, rather than to a mitogenic action on preexisting lactotrophs alone (42, 1787).

Search for paracrine factor(s) mediating lactotroph recruitment by gonadotrophs has continued and yielded a number of candidates, such as the common α-subunit of the pituitary glycoprotein hormones (1478, 1686, 1786, 1787, 1862, 1883), the NH_2-terminal fragment of proopiomelanocortin [POMC-(1—74), isolated from conditioned medium of gonadotroph cell culture] (1749, 1750). Ongoing studies using transgenic animals targeting gonadotrophs likely will help to clarify the precise mechanism and physiological significance of the paracrine communication between lactotrophs and gonadotrophs (1802).

XII) Acetylcholine. An intrapituitary cholinergic system, acting through muscarinic receptors, exerts a tonic inhibitory influence on prolactin release (1245, 1564, 1729). Acetylcholine is produced within the anterior lobe, most likely in corticotrophs (276, 277). Although immunoreactivity for choline acetyltransferase (1637), the enzyme catalyzing the biosynthesis of acetylcholine, and cholinesterase activity (121) can be predominantly localized in corticotrophs, atropine, a potent muscarinic receptor antagonist, dose-dependently increases prolactin release in reaggregate cells of anterior lobe (276). Addition of cholinergic agonists to the cultures inhibits prolactin secretion (278, 1513). Both effects require the presence of glucocorticoids in the culture medium (278). Taken together, it appears that corticotrophs exert a tonic inhibitory influence on prolactin release that is mediated by acetylcholine acting through a muscarinic receptor (276). However, although the interaction between corticotrophs and lactotrophs and the role of acetylcholine in its mediation is one of the best-characterized paracrine mechanisms in the anterior lobe, it is still difficult to place in a physiological perspective. In addition to acetylcholine, galanin and TRH have also been detected in corticotrophs (808), indicating that, at least in certain species, corticotrophs might affect lactotrophs by these two potent prolactin regulatory peptides (905, 1577).

XIII) Factor(s) from folliculostellate cells. Folliculostellate cells (immunocytochemically identified as containing S-100 protein) suppress prolactin-secretory response to ANG II and TRH when they are cultured with lactotrophs as cell aggregates (101). As with paracrine interactions between gonadotrophs and lactotrophs (426), intimate contacts between lactotrophs and folliculostellate cells are not required for this inhibition, since it is still observed after dispersion of the coaggregates into single cells (101). These observations indicate that a diffusible inhibitory factor is secreted by the folliculostellate cells. However, the identity of this putative paracrine factor is unknown. It is also difficult to reconcile the observed inhibitory influence of the folliculostellate cells with the assumption that these cells are also the source of the prolactin-releasing IL-6 as we discussed above.

C) CONCLUSION. Several paracrine interactions between lactotrophs and other cellular phenotypes are now well established and likely more will soon be discovered. We are only beginning to place intrapituitary regulative networks into a physiological perspective. In general, it seems unlikely that paracrine interactions are responsible for acute regulation of the release of prolactin, since the dynamic regulation of prolactin secretion more likely relies on hypothalamic factors. Indeed, paracrine interactions seem more likely to be responsible for changes occurring within a much slower time domain, pertaining to cellular development and differentiation. In addition, autocrine and/or paracrine regulation likely play an essential role in changing of responsiveness to hypothalamic factors during the estrous cycle, pregnancy, or lactation.

2. Neural and intermediate lobes

There is abundant evidence in the literature that the lactotroph is influenced by the neural and intermediate lobes of the pituitary gland (141). Secretory products of the neural and intermediate lobes of the pituitary gland can reach the anterior lobe through the short portal vessels, which represents a vascular communication between these lobes and the anterior lobe of the pituitary gland. Thus the communication between the neurointermediate lobe and the anterior lobe of the pituitary gland is both neuroendocrine and endocrine. Several observations suggest that dopamine, oxytocin, vasopressin, α-MSH, and possibly other less well-characterized compounds as well, after being released at the posterior and/or intermediate lobes of the pituitary gland, can reach the anterior lobe and participate in the control of prolactin secretion.

A) NEUROINTERMEDIATE LOBE PROLACTIN-RELEASING FACTOR. Posterior pituitary lobectomy elevates prolactin levels in the blood of cycling and lactating rats (143, 1255, 1406). Because dopamine is found emanating from THDA axon terminals in the posterior lobe (176), the response might be due to the removal of dopamine of posterior lobe origin (420, 605–607, 1258), which is transported to the anterior lobe through short portal vessels. In the course of performing these studies, Ben-Jonathan and colleagues (1256) made the serendipitous observation that the suckling-induced release of prolactin was blocked when the neural and intermediate lobes were removed. The absence of a prolactin-secretory response is not due to the removal of oxytocin, since replacement of oxytocin failed to overcome the effects of removal of the neurointermediate lobe (1256). They therefore concluded that the neurointermediate lobe of the pituitary gland contains a nonoxytocinergic prolactin-releasing activity. Indeed, rat neurointermediate lobe extracts stimulate prolactin secretion in vivo (822) and in vitro (821, 827, 827). Bovine intermediate lobe extracts share the same property (1539). Similarly, cocultures of neurointermediate and anterior lobes enhance basal (483) as well as secreta-

gogue-induced (484) prolactin secretion. The prolactin-releasing activity has subsequently been localized to the intermediate lobe of the pituitary gland of the rat (1011, 1681).

Attempts have been made to chemically characterize the activity. It seems clear that the activity is due to a small peptide that is distinct from TRH, ANG II, VIP, arginine vasopressin, and oxytocin (821, 827, 1059). An interesting approach has been taken to produce a model for further purification of the intermediate lobe prolactin-releasing activity. Transgenic mice were generated with large tumors localized to the intermediate lobe (27). These animals were hyperprolactinemic. Inoculation of nude mice with the tumor cells resulted in large secondary tumors. Crude extracts of both primary and secondary tumors stimulated prolactin secretion from GH_3 cells in culture. With chromatography, the activity was found in two size classes: a large 70- to 80-kDa bioactive peak and two very small hydrophobic peaks. None of the elution profiles coincided with β-endorphin, α- or β-melanocyte-stimulating hormone, ACTH, TRH, oxytocin, ANG II, and VIP. Although these data suggest that the prolactin-releasing activity indeed arises from melanotrophs in the intermediate lobe, care should be taken when equating data derived from tumorous tissue to that obtained from normal cells.

B) α-MELANOCYTE-STIMULATING HORMONE. α-Melanocyte-stimulating hormone of intermediate lobe origin appears to play a unique role in the function of the lactotrophs within the anterior lobe. Among the cells of the anterior pituitary, the lactotroph possesses the greatest number of α-melanocyte-stimulating hormone binding sites (1923). Rather than act as a pure PRF, α-melanocyte-stimulating hormone appears to act as a lactotroph-responsiveness factor that plays two roles. With the use of the reverse hemolytic plaque assay it was shown that α-melanocyte-stimulating hormone is responsible for the "recruitment" of lactotrophs from a nonsecretory to a secretory pool as well as enhancement of the sensitivity of lactotrophs to known secretagogues for prolactin (497, 760, 761). The enhanced responsiveness of lactotrophs is due to stimulation, by α-melanocyte-stimulating hormone, of calcium entry from extracellular sources (1330). These effects require *N*-acetylation of α-melanocyte-stimulating hormone for full biological activity (498). It has been suggested that the enhanced prolactin-secretory responsiveness of the pituitary gland of suckled dams to secretagogues (760, 761) and the estrogen-induced release of prolactin (497) are both mediated by α-melanocyte-stimulating hormone.

C. Peripheral Organs

1. The ovaries

A) ESTRADIOL. Ovariectomy has a dramatic effect on the lactotroph (reviewed in Ref. 1768). Removal of the ovaries is followed by a decrease in lactotroph size and number as well as the intracellular abundance of prolactin-secretory granules (429). Estradiol is the dominant ovarian hormone that reverses these effects and subsequently stimulates prolactin secretion (309). Indeed, in the rat, immunoneutralization of the rising blood levels of estradiol on diestrus through early proestrus blocks the preovulatory release of prolactin on proestrus (1302). Moreover, administration of estradiol to ovariectomized rats results in proestrus-like prolactin-secretory release daily for a number of days (1297, 1305).

Estradiol affects the secretion of prolactin at two levels. Directly at the pituitary lactotroph, estradiol controls prolactin gene expression and modifies its sensitivity to physiological stimulators and inhibitors of prolactin secretion. Within the hypothalamus, estradiol modifies the activity of the neuroendocrine neurons known to control prolactin secretion.

It has been suggested that estradiol is responsible for the differentiation of lactotrophs from a pluripotent pool of somatotrophs and mammosomatotrophs (191), an effect which requires the presence of the neurointermediate lobe of the pituitary gland (496). Estrogen regulates prolactin gene expression within the anterior pituitary gland (1045, 1159, 1627, 1628) by binding to its nuclear receptor and subsequently conferring DNA binding and transcriptional activation of the gene (1867). Progesterone (326) or androgens (1759) in turn inhibit estrogen-induced prolactin gene expression. The transcription of the prolactin gene results in increased synthesis of prolactin, and the increased prolactin secretion may be a reflection of spillover of newly synthesized hormone from the estrogen-stimulated lactotrophs. Although estrogen increases the percent of prolactin-releasing cells in the anterior pituitary, it does not increase the percent of total pituitary cells expressing prolactin mRNA (1562). This would suggest, in contrast to earlier observation (191), that lactotrophs are not differentiated from a pluripotent pool by estrogen. However, other studies have shown that differentiation occurs posttranscriptionally (1428) and thus resolves this discrepancy. Nevertheless, there is a direct relationship between the amount of prolactin secreted by and the amount of prolactin mRNA in lactotrophs obtained from estrogen-treated rats (1009). Moreover, estradiol enhances the secretion of prolactin through a constitutive pathway since nifedipine, a blocker of voltage-sensitive calcium channels which are required for secretion, does not interfere with the estradiol-induced enhancement of prolactin mRNA/lactotroph (1009).

Estrogens modify the response of the rat lactotroph to physiological inhibitors and stimulators of prolactin secretion. Estradiol is antidopaminergic at the lactotroph (1024, 1454, 1454, 1875); that is, dopamine is less potent as an inhibitor of prolactin secretion when lactotrophs are exposed to estradiol in vitro (1454, 1454, 1875) or in vivo

TABLE 1. *Neurotransmitters regulating prolactin secretion*

Neurotransmitter	Receptor in the CNS	CNS Target	Effect on PRL Secretion*
		Biogenic amines	
Dopamine	D_1 (155, 475) D_2 (156, 474, 486, 1124)	↓ TIDA (155, 475) ↑ TIDA (156, 474, 486, 1124)	↑ Basal (155, 475) ↓ Basal (474)
Norepinephrine and epinephrine	α_1 (400) α_2 (1047, 1436, 1780) †(884, 885, 983)	PVN (? TRH) (1780)	↓ Basal (400, 1012) ↑ Basal (1047, 1436, 1736) ↑ Ovx+E_2 (1012) ↑ Proestrus (1003) ↑ Suckling (1436) †(286) ↑ Stress (1003)
	β (974)	TIDA (775, 805)	↑ Basal (392) †(102, 392, 393) ∅ Ovx+E_2 (1734)
Serotonin (5-HT)	$5HT_{2A}$, $5HT_{2C}$ (108, 1040) $5HT_{1C}$ (108, 1040)	PVN (104–107, 1200) SCN (921) TIDA (1152, 1420)	↑ Basal (551, 999, 1085, 1788) ↑ E_2/proestrus (260, 313) ↑ Suckling (600, 972, 1181)
Histamine	H1 (59, 644, 1044, 1780) H2 (58, 457, 460, 1468, 1780)	TIDA (558, 622, 1571)	↑ Basal (1780) ↑ Stress (961, 1656)
Acetylcholine (ACh)	ACh_N (58, 180, 1696) ACh_M (58, 180, 1696)	TIDA (504, 665, 1261, 1696, 1885) †(622)	↓ Basal (662, 665, 1043) ↓ E_2/proestrus (58, 180, 1696) ↓ Suckling (180)
		Peptides	
Thyrotropin releasing hormone	TRH-R (836)	↑ TIDA (227, 836, 1342)	↓ Basal (836, 1342)
Oxytocin and vasopressin	(246)	↑ TIDA (1919) †(1209) SCN (842)	↓ Basal (1087, 1235) ↓ Stress (1235)
VIP/PHI	(163)	Hypothalamus (849, 917, 977, 1823) SCN (123) ↑ TIDA (813)	↑ Basal (813) ↑ E_2/proestrus (74, 1547, 1794)
PACAP	(653, 654, 1344, 1623)	↑ TIDA (40, 813)	↓ Basal (40, 813) ↑ Basal (anesthetized) (858, 1900)
Opioids (OPI)	μ, κ (245, 261, 934, 984, 985) κ (937) ORL1, opioid receptor-like receptor (240, 1189)	PVN, SON, MBH (1119) ARC (48, 49) ↓ TIDA (31, 70, 83, 86, 440, 472, 547, 693, 742, 908, 965, 1121, 1123, 1467, 1806, 1836)	↑ Basal (240, 742, 1175, 1804, 1805) ↑ E_2/proestrus/PSP (18, 833, 1525, 1554) ↑ Lactating (70, 473) ↑ Nonsuckled (1278) ↓ Suckled (1278) ↑ Stress (473, 540, 541, 866, 908, 1504, 1540, 1634, 1789, 1891)
Angiotensin II	AT-R (194, 1751) AT_{1A} (869, 871, 1022, 1521, 1673, 1777)	TIDA (871a, 1586, 1916)	(↓) Basal (1265, 1266, 1521, 1675, 1678) ↓ Ovx+E_2 (1265, 1266, 1521, 1673) ↓ Stress (1265, 1266, 1521, 1673)
Substance P (SP)	Tachykinin receptors (932, 1120, 1456)	mPOA (1120, 1416) ARC (1775) SON/PVN (175)	↑ Basal (489, 1416, 1820) (80, 81, 701) †(402) ↓ Basal (low dose) (80, 81, 701)
Galanin (GAL)	GAL-R (136, 915, 1890)	MBH (136, 1188) TIDA (806) ↓ DA release/ME (1327) ↑ VIP release/MBH (844)	↑ Basal (973, 975, 976, 1177) †(1360) ↑ Proestrus (1079, 1188)
Neurotensin (NT)	NT-R (1328, 1507)	PVN/ARC-ME (831) ↑ TIDA (692, 751, 964, 1167, 1373, 1856)	↓ (964, 1166, 1167, 1482) ↓ E_2/proestrus (1166) ↓ Stress (1166, 1167, 1753)
Neuropeptide Y (NPY)	Y_1, Y_2 (897, 1381)	↑ TIDA (592, 714)	↓ Basal (592, 618, 1466)
Somatostatin (SST)	SSTR1-5 (390, 463, 671, 1190, 1195, 1334, 1375, 1744) SSTR2 (135, 1588)	CNS (556, 1462) ↓ TIDA (135, 898, 1588, 1645)	↑ Basal (898)
Calcitonin (CT) and calcitonin gene-related peptide (CGRP)	CT and CGRP receptors (1644)	CNS (1679) ↑ TIDA (341)	∅ Basal (341, 1347, 1348, 1679) †(531) ∅ E_2/proestrus (371, 372) ↓ Suckling (495, 1348) ↓ Stress (370, 1633)

TABLE 1— *Continued*

Neurotransmitter	Receptor in the CNS	CNS Target	Effect on PRL Secretion*
Bombesin-like peptides (gastrin-releasing peptide and neuromedin B and C)	(126, 1671)	↑ TIDA (95, 257, 886, 929, 1099, 1100, 1122, 1757)	↓ Basal (912, 928, 929, 1705, 1757) ↓ Ovx (95) ↓ E_2 (1099) †(700, 1483) ↓ Stress (1705)
Cholecystokinin (CCK)	CCK-R (1115, 1410) $CCK_B > CCK_A$ (hypothalamus) (1860)	ARC/TIDA (1049, 1371) ↑ VIP (1714)	↑ Basal (1714, 1821, 1822) †(912)
Atrial natriuretic peptide (ANP)	ANP-R (713, 1522)	TIDA (566, 1534) †(1536)	↓ Basal (1531, 1533)
		PVN (713)	∅ Proestrus (1604) ↓ Stress (571, 1531, 1533)
		Amino acids and nitric oxide	
Glutamate/aspartate	NMDA (91)	PIF (TIDA) and/or PRF (PVN) (91)	↓ Basal (91) ↓ Cycling (1, 208, 209) ↓ Suckling (91) ↑ ↓ (1)
γ-Aminobutyric acid (GABA)	$GABA_A$ (39, 588, 661, 1826, 1881) $GABA_B$ (1049)	↓ TIDA (37, 1049, 1881) SON/PVN (1174, 1737) TIDA (643, 1912)	↑ Basal (588, 998, 1106, 1210, 1249, 1356, 1378, 1846) †(1318) ↑ Suckling (1439)
Nitric oxide (NO)		SON/PVN (51, 172, 213, 1767)	↑ Basal (641, 642) ↑ E_2/proestrus (185, 1912) ↑ Stress (1157)

Arrows indicate the nature of the effects of the neurotransmitters: ↑ increase/facilitation, ↓ decrease/inhibition (arrows in parentheses indicate a less than robust effect); ∅, no effect. ARC, arcuate nucleus; MBH, medial basal hypothalamus; mPOA, medial preoptic area; PVN, paraventricular nucleus; TIDA, tuberoinfundibular dopaminergic system; SON, supraoptic nucleus. Reference numbers are given in parentheses. * Only those data are considered where the experimental paradigm indicates that the observed effects on prolactin secretion are probably mediated within the central nervous system (CNS). These experimental approaches usually involve intracerebroventricular administration of a neurotransmitter, its precursor, its selective agonists and/or antagonists, as well as specific antibodies developed against the endogenous transmitter or modulator. The effects of these manipulations were evaluated on nonstimulated (basal) as well as stimulated prolactin secretion. The latter group is further divided according to the cause of elevated prolactin secretion: estradiol and/or proestrus (E_2/proestrus), pseudopregnancy (PSP), suckling stimulus in lactating animals (suckling), or stress. † Conflicting observations.

(346, 1024). Apparently, estradiol exerts this effect by decreasing the number of dopamine receptors (1454). In contrast, estradiol enhances the sensitivity of the lactotroph to TRH (623). It does so by increasing the number of TRH receptors (406). Estradiol depresses the inhibitory input the hypothalamus exerts over pituitary prolactin secretion. Long-term treatment with estradiol lowers the concentration of dopamine in hypothalamo-hypophysial portal plasma bathing the anterior pituitary gland (365). Similarly, the concentration of dopamine in portal blood is diminished coincident with the beginning of the preovulatory release of prolactin on proestrus (140). In addition, treatment with estradiol decreases the activity of TH, the rate-limiting enzyme of dopamine biosynthesis, in TIDA axons terminating in the median eminence (181, 873, 1027, 1236, 1385). Likewise, the activity of these neurons decreases concomitant with the release of prolactin on proestrus (287, 1027). The surge of prolactin released in response to estradiol increases the activity of these dopaminergic neurons that subsequently terminates prolactin secretion (44, 416, 417, 1218, 1220, 1758).

B) PROGESTERONE. A direct role for progesterone in the synthesis and release of prolactin is not as well described as that of estradiol. Some studies report no effect (309, 1550), whereas others report inhibition (623, 745) or enhancement (1911) of prolactin secretion in response to progesterone. On the other hand, progesterone is capable of advancing the time of day in which an estrogen-induced surge of prolactin occurs (259, 1911). It appears to exert this effect by actions within the hypothalamus. Progesterone stimulates dopamine release into hypophysial portal blood (365). However, progesterone has a dual effect on TH activity in TIDA neurons. Acutely, progesterone negatively modulates TH activity (61, 62, 68, 134, 1911). Such observations are consistent with the advancement of the estradiol-induced surge of prolactin by progesterone. Subsequently, progesterone enhances TH activity (66), a finding which is consistent with the inhibition of prolactin secretion by progesterone.

C) CHANGING RATIO OF OVARIAN STEROIDS: ESTROUS CYCLE. We can now place all of these observations in a physiological context. During the afternoon of diestrus-2 of the rat's estrous cycle, the rising titers of ovarian estradiol (1647) stimulate the hypothalamo-pituitary axis to release a "surge" quantity of luteinizing hormone and prolactin on proestrus (1302). The surge of luteinizing hormone stimulates an increase in ovarian progesterone secretion (583)

that initially participates with estrogen in decreasing the activity of TIDA neurons (61, 62, 68, 134, 1911). The resulting estradiol-induced surge of prolactin (1758) along with progesterone (66) activates TIDA neurons which, in turn, extinguishes the surge of prolactin.

2. The adrenal cortex

A rarely discussed aspect of the inhibitory influences on adenohypophysial prolactin secretion is the potential role of the adrenal gland. It is well known that in rats, plasma levels of prolactin increase significantly after adrenalectomy, whereas the effect of adrenalectomy can be reversed by administration of corticosteroids (94, 94, 139, 206, 312, 1032, 1438, 1798). Similar effects of adrenalectomy and the synthetic glucocorticoid dexamethasone have been shown in estrogen-induced (284, 285), stress-induced (521, 739, 1504), and TRH-induced (1581) prolactin responses. Moreover, consistently high levels of plasma prolactin have been found throughout the entire lactation period in adrenalectomized dams (1798). Significantly higher plasma prolactin response to the dopamine receptor blocker haloperidol could be detected in adrenalectomized lactating mothers (936). Dexamethasone pretreatment of lactating rats completely blocks suckling-induced prolactin release (122). This effect is transient, since it cannot be detected 24 h later. In contrast to the dramatic effect on the suckling-induced prolactin response, dexamethasone does not inhibit domperidone-induced pituitary prolactin release, indicating that dexamethasone cannot interfere with the antagonist binding and its effect at the level of dopamine receptor of lactotrophs. Dexamethasone also suppresses prolactin release induced by the suckling stimulus when it is implanted into the medial basal hypothalamus (122). Blockade of glucocorticoid receptors by the administration of RU486 (mifepristone) enhances prolactin secretion (1799). RU486 is also a progesterone antagonist. However, immunoneutralization of circulating progesterone does not affect prolactin secretion (284). Long-term elevation of the serum glucocorticoid level by chronic administration of ACTH (541, 908) or hydrocortisone (937) or by prolonged stress (540) decrease opioid-induced prolactin secretion. These effects of glucocorticoids are taking place predominantly within the CNS. It is assumed that the decreased responsiveness of the TIDA neurons to inhibitory inputs brought about by the elevated glucocorticoid levels (908) may be responsible for the blunted responses of prolactin secretion. Thus the regulatory pathway mediating neurogenic stimuli (suckling or stress)-induced prolactin release is extremely sensitive to glucocorticoid feedback mechanisms, and the adrenal glands of an animal provide a physiologically important signal to the hypothalamo-hypophysial mechanisms regulating prolactin secretion.

Aside from the regulation of prolactin secretion, glucocorticoids also influence the differentiation (1557) and morphology (289) of lactotrophs. Indeed, glucocorticoids stimulate the differentiation of somatotrophs but suppress that of lactotrophs in the fetal rat pituitary gland (1557). Adrenalectomy increases the cellular and nuclear areas of prolactin-immunoreactive cells. Glucocorticoid replacement in vivo reverses these effects (289). In cultured cells, exposure to glucocorticoids reduces numerical density and cellular, cytoplasmic, and nuclear areas of prolactin-immunoreactive cells (289). These actions of glucocorticoids may merely be a reflection of another site at which the steroid regulates the immune system: inhibition of secretion of the immunomodulatory hormone prolactin.

3. The placenta

As noted earlier, there is abundant evidence that the rat placenta secretes a lactogen that is similar in biological activity to pituitary prolactin. Aside from maintaining pregnancy and preparing the mammary gland for subsequent lactation, this lactogen also plays a major role in regulating pituitary prolactin secretion (64, 561, 649, 1755, 1756, 1760–1763, 1832–1834, 1838). For example, it is well known that the two surges of pituitary prolactin secretion last appear on *day 10* of a 21-day pregnancy (1648). Coincident with this is the increase in the concentration of placental lactogen in the blood of the pregnant rat at mid-pregnancy (1760–1763). Although rat placental lactogen (1834), spent placental culture media, or maternal serum (649) will inhibit prolactin secretion from pituitary cells in culture, injection of rat placental lactogen will not inhibit prolactin secretion in vivo (1837). On the other hand, injection of spent incubation media (1832) or surgical implantation of a lactogen-secreting choriocarcinoma (1146, 1756) will effectively inhibit prolactin surges in vivo. Although placental lactogen will diminish the surges of prolactin in pregnant or pseudopregnant rats as well as suckling-induced prolactin secretion (560, 561), it will not inhibit the ante-partum secretion of prolactin (561, 668). This implies some alteration that occurs within the hypothalamo-pituitary axis to change its response to placental lactogen.

Aside from the pituitary gland as the obvious site at which placental lactogen exerts its effect on prolactin secretion, there is ample evidence that the effect may also be exerted within the hypothalamus. Indeed, human placental lactogen is quite effective in activating TH in TIDA neurons (410) and consequently suppressing the surges of prolactin during early pregnancy (668) when injected into the cerebral ventricles. Similarly, transplantation of lactogen-secreting rat choriocarcinoma cells also increases TH activity in TIDA neurons and suppresses prolactin

TABLE 2. *Neurohormones regulating prolactin secretion*

Neurohormone	Receptor/G Protein in the Lactotrophs	Signal Transduction	Direct Effect on PRL Secretion
		Established prolactin releasing and release-inhibiting neurohormones	
Dopamine (DA) as PIF *(140, 142, 621)	D_2 (279, 280, 1171) $G_{i3\alpha}$, $G_{o\alpha}$ (100, 1065)	↑ I_K (492, 847) ↓ I_{Ca} (407, 754, 847) ↓ AC/cAMP (398, 508, 565, 619, 1002, 1355) ↓ PLC (272, 510, 513, 1002, 1635)	↓ In vitro (140, 1096–1098) ↓ In vivo (140, 395, 1281, 1421, 1423)
Thyrotropin releasing hormone (TRH) *(520, 553)	TRH-R (763, 1129, 1917) $G_{q/11}$ (807) G_s (943)	↑ PLC/Ca^{2+} (57, 529, 563, 564, 747, 807, 1002, 1558, 1684) ↓ I_{Kir} (127, 128, 1565)	↑ In vitro (17, 924, 1723) ↑ In vivo (178, 405, 963, 1419)
Oxytocin *(620)	OT-R	↑ PLC/Ca^{2+} (246)	↑ In vitro (827, 1537) ↑ In vivo (867, 1087, 1235, 1243, 1537, 1542) †(1371)
Vasoactive intestinal polypeptide (VIP) *(1313)	VIP-R (125)	↑ AC/cAMP (1314, 1349, 1354, 1355) ↑ I_{Ca} (856)	↑ In vitro (1535, 1538, 1608–1610) ↑ in vivo (4, 891, 892, 1313, 1343, 1506, 1611, 1873)
		Putative prolactin releasing and release-inhibiting neurohormones	
Somatostatin (SST) *(3, 319, 724)	SST-$R_{1–5}$ (390, 463, 671, 1190, 1195, 1334, 1375, 1391, 1392, 1463, 1613, 1744)	↓ AC/cAMP (941, 1715) ↓ I_{Ca} (941, 1715) ↑ $I_{K(Ca)}$ (1878)	↓ In vitro (461, 462, 466, 509, 733, 824, 826, 941, 1783) †(1394, 1460) ↓ In vivo (359, 507, 651, 913, 1001, 1018)
γ-Aminobutyric acid (GABA) *(1206, 1716, 1719, 1827) †(1247, 1619)	$GABA_A$ (52, 54, 679, 841) $GABA_B$ (378, 1091, 1092) ↓ In vivo (55, 96, 378, 394–396, 459, 1092, 1168, 1632, 1881)	↑ I_{Cl} (841, 846) ↑ $I_{K(GTP)}$ (41)	↓ In vitro (56, 511, 679, 691, 1441, 1569) †(38, 39)
Atrial natriuretic hormones (ANH) *(1604)	ANH-R (713)	↑ GC/cGMP (305, 321, 713, 1345)	↓ In vitro (482) ↑ In vivo †(571)
Vasopressin (VP) *(782, 789, 966, 1424)	VP-R (47, 957) V_1 (50, 952) V_2 (954, 955)	↑ PLC/Ca^{2+} (246) ↑ AC/cAMP (246)	↑ In vitro (734, 1616) ↑ In vivo (829, 1276, 1283, 1372, 1616, 1785, 1809)
Calcitonin (CT)		↓ PLC/PLA_2 (514, 880, 1660, 1661) ↑ Fast $[Ca^{2+}]_i$ (1660, 1661) ↓ In vivo (495, 531, 1348, 1595, 1633, 1660) ↓ Sustained $[Ca^{2+}]_i$ (1660, 1661)	↓ In vitro (514, 880, 1225, 1593–1595, 1597, 1631, 1894) ↑ In vivo [in the absence of T_3] (1905)
Neuropeptide Y	Y_1, Y_2 (897)	↑ PLC/Ca^{2+} [Y1] (528, 1849) ↓ I_{Ca} [Y2] (528, 1849, 1857) ↓ AC/cAMP [Y1, Y2] (897)	↑ In vitro [cycling female] (302) ↓ In vitro [ovx or lactating] (1857)
Angiotensin II	AT_{1B} (1022) G_i/G_o (513)	↑ PLC/Ca^{2+} (269, 270, 506, 513, 610, 1075, 1572, 1902) ↑ AC/cAMP (93)	↑ In vitro (14, 36, 409, 746, 1575)
Galanin (GAL) *(1078)	GAL-R (136, 915, 1890)	↑ PLC/Ca^{2+} (727)	↑ In vitro (465, 697, 1890)
Substance P (SP)	SP-R (930, 1006–1008)	↑ PLC/Ca^{2+} (932, 1158)	↑ In vitro (1819, 1820) ↑ In vivo (1482)
Bombesin-like peptides (gastrin-releasing peptide, neuromedin B and C)	(126, 796, 1671, 1845, 1877)	↑ PLC/Ca^{2+} (177, 461, 462, 1766)	↑ In vitro (797–799, 1876)
Neurotensin (NT) *(946, 1866)	NT-R (1180)	↑ PLC/Ca^{2+} (1179) ↑ I_{Ca} (1179) ↑ PLA_2 (271, 1179)	↑ In vitro (505) ↑ In vivo (964, 1166, 1167, 1482)
Dopamine as PRF	D_2 (252) G_s (251)	↑ I_{Ca} (248, 582)	↑ In vitro (252, 346, 427, 761, 979, 1614) ↑ Ex vivo (761, 1280, 1282) ↑ In vivo (72)

Neuroendocrine regulators of prolactin secretion were selected based on the following (pharmacological, neuroanatomical, and physiological) criteria. *1*) They are capable of affecting prolactin secretion by acting directly at the lactotrophs; *2*) produced by neurons, usually residing within the so-called "neuroendocrine hypothalamus," which project to the external zone of the median eminence; and *3*) their concentration in the pituitary portal blood is significantly higher than in the peripheral circulation. Putative releasing and release-inhibiting hormones only partially fulfill these criteria. Arrows indicate the nature of the effects of the neurohormones: ↑ increase/facilitation, ↓ decrease/inhibition. AC, adenylyl cyclase; GC, guanylyl cyclase; PLA_2, phospholipase A_2; PLC, phospholipase C; I_K, potassium current/channel; $I_{K(Ca)}$, Ca^{2+}-dependent potassium current/channel; $I_{K(GTP)}$, G protein-gated potassium channel; I_{Kir}, inward rectifying potassium channel; I_{Ca}, calcium current/channel; I_{Cl}, chloride current/channel. Reference numbers are given in parentheses. * Detected in the portal blood and/or in the external zone of the median eminence. † Conflicting observations.

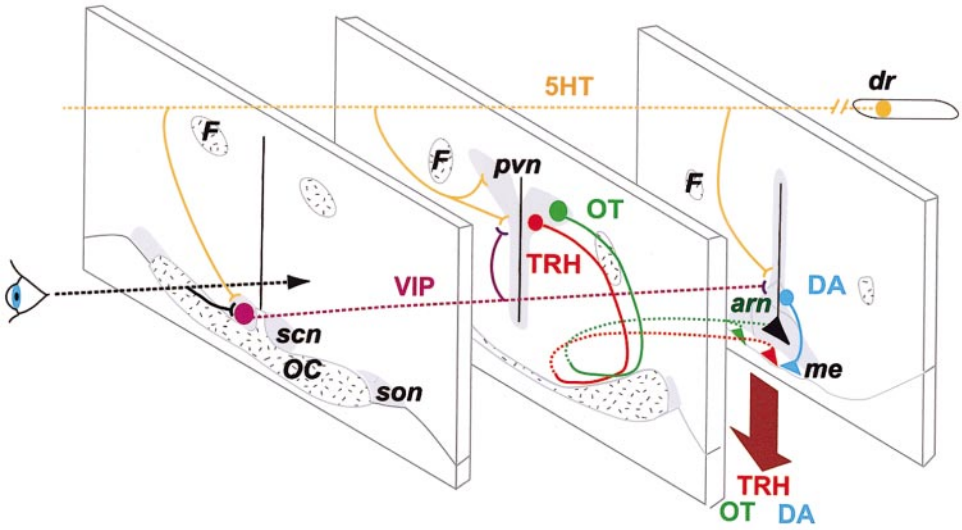

FIG. 6. Schematic representation of the major regulatory pathways to the neuroendocrine neurons controlling prolactin secretion. The most important prolactin inhibiting factor (PIF) is dopamine (DA), synthesized by the tuberoinfundibular dopaminergic neurons of the arcuate nucleus (arn). The two most potent prolactin releasing factors (PRF), thyrotropin-releasing hormone (TRH) and oxytocin (OT), are produced by the parvi- and magnocellular neurons of the paraventricular nucleus (pvn). These neuroendocrine neurons project directly (TRH) to the external zone of the median eminence (me), or send axon collaterals there in passage through the internal zone of the median eminence en route to the posterior lobe of the pituitary gland (OT). These axons in the median eminence terminate around the perivascular spaces of the portal capillary system. The circadian rhythms of PIF and PRH release are paced by the (VIPergic?) neurons of the suprachiasmatic nucleus (scn) receiving entrainment from the retinohypothalamic pathway. Both the PIF and PRF producing neurons receive serotonergic (5-HT) innervation ascending mainly through the median forebrain bundle from the dorsal raphe nucleus of the brain stem. These serotonergic pathways participate in regulation of prolactin secretion during stress, pregnancy, and lactation. F, fornix; OC, optic chiasma; son, supraoptic nucleus.

secretion (1146). Taken together, there is little doubt that this trophoblast-specific factor (64) activates dopaminergic neurons and thus suppresses pituitary prolactin secretion during the latter half of pregnancy.

4. The nonpregnant uterus

It has long been appreciated that removal of the uterus prolongs the life span of corpora lutea in a large number of mammals (1176, 1508). In many, this has been attributed to removal of a luteolytic hormone of uterine origin. In humans, sheep, rats, and rabbits this hormone has been identified as prostaglandin $F_{2\alpha}$ (1322). Although there is no doubt that this is the mechanism of luteolysis, there are data indicating that the uterus also contributes to luteolysis by depressing the secretion of the luteotrophic hormone prolactin (577, 578, 646, 647, 650).

Artificial stimulation of the uterine cervix initiates recurrent surges of prolactin secretion for 13 days in ovariectomized animals (585). When the uterus is removed, this same stimulus eventuates in recurrent surges for 21 days (577). Because there is no corpus luteum in place whose life could be prolonged to release progesterone and maintain the surges (645), the only interpretation of these data is that the uterus secretes a substance that acts at the hypothalamo-pituitary axis to directly inhibit prolactin secretion. Indeed, even the steroid regimen that extinguishes the mating-induced surges of prolactin secretion (645) requires the uterus (650). This PIF is extractable from the uterus and actively inhibits only prolactin secretion from cultured anterior pituitary cells (647). After enzymatically separating and culturing uterine epithelial, stromal, and myometrial cells and placing them in culture, coincubation of the spent media from only epithelial cell cultures inhibits prolactin secretion from cultured pituitary cells in a dose-dependent manner (648). Similarly, addition of serum from rats with their uteri intact resulted in a greater inhibition of prolactin secretion than serum from a hysterectomized animal (648). These data suggest that the uterus secretes a factor into blood that acts directly at the lactotroph to inhibit prolactin secretion. On the other hand, a central effect of a uterine factor has not been excluded since hysterectomy at the early stage of lactation significantly delays the extinction of suckling-induced prolactin secretion (907). The chemical nature of the material has yet to be identified.

5. Adipose tissue (leptin)

It has long been recognized that nutritional status and reproductive capacity are related (377, 569). Leptin, the product of the obese (*ob*) gene, is a humoral signal secreted by adipose tissue to act in the CNS to regulate

food intake and body weight (15, 268, 294, 802, 1685). It seems that leptin provides the link between nutritional and reproductive function (117, 316, 339, 377, 569, 1742).

Leptin stimulates prolactin secretion from cells isolated from the anterior lobe of the pituitary gland (1918). Given intracerebroventricularly, leptin-(116—130) stimulates prolactin (and LH) secretion in fasted adult male rats (640). In addition, leptin restores the starvation-eliminated prolactin (and LH) surges in estradiol/progesterone-implanted ovariectomized animals (969). Restoring circulating leptin concentration of starved animals to the physiological level by administering leptin subcutaneously with osmotic minipumps also restores the estradiol/progesterone-induced prolactin (and LH) surge (1865). In addition, antileptin serum significantly delays the onset of the secretory surge of prolactin in normally fed animals (969). These observations indicate that physiological concentrations of leptin in the peripheral circulation can exert a stimulatory effect on steroid-induced (1865) or spontaneous (969) prolactin (and LH) secretion.

Increased serum prolactin concentrations, induced by pituitary graft or exogenous ovine prolactin injection, stimulate leptin secretion (690). Moreover, prolactin is able to increase leptin mRNA in white adipose tissue (690). These recent observations indicate that both prolactin and leptin are intricately involved in the complex regulation of energy balance and reproduction.

Taken together, these data indicate that leptin plays an important permissive role in the generation of steroid-induced prolactin (and LH) surges in female rats. However, the mechanism whereby leptin alters prolactin secretion is not yet known. Several hypothalamic neuronal systems (e.g., oxytocin/vasopressin, NPY, POMC, Agouti-related peptide) express leptin receptors and are affected by leptin in the peripheral circulation and/or in the cerebrospinal fluid (500, 559, 1743, 1898). Recent evidence indicates that the effects of leptin on prolactin secretion are mediated by melanocortins, possibly through MC4 melanocortin receptors (1864).

There is little information on the intracellular signaling mechanisms activated by leptin. However, because the leptin receptor (Ob-R) is a member of the cytokine receptor family (1720), the Jak/STAT pathway (for further details, see sect. IV) presumably plays an important role in this respect (723). In glucose-sensitive neurons of the lateral hypothalamus, leptin induces a long-lasting hyperpolarization by activating ATP-sensitive potassium (K_{ATP}) channels (1670). It has been suggested by the authors (1670) that the K_{ATP} channel may function as an end point of the intracellular pathway(s) elicited by leptin.

VIII. EPILOGUE

It has been well recognized that prolactin ensures survival of the species through its reproductive role and survival of the individuals of the species in its homeostatic roles. While we know a great deal about the chemistry, biological actions, and controls in its reproductive role, there is a paucity of similar information in its homeostatic roles. Hopefully these voids articulated in this review will be filled in the near future.

Most of the active endogenous substances regulating prolactin secretion have multiple sites of action: they can act at the hypothalamic level as neurotransmitter (Table 1) and also at the pituitary as a neurohormone (Table 2).

At the hypothalamic level, many of these substances can directly affect the activity of neuroendocrine dopaminergic and PRF neurons and/or presynaptically regulate neural inputs to these neuroendocrine cells (summarized in Figs. 5 and 6). The precise mode of communication between different modules of the regulative circuitry and the integration of the multifarious neuronal and humoral inputs is still not well understood. Ongoing research with insightful combinations of electrophysiological techniques, tract tracing, and immunocytochemical identification (both light and electron microscopic levels) hold much promise for further advance in this field.

At the pituitary level, only a few substances play a role as primary neurohormones by robustly affecting hormone secretion (e.g., dopamine, TRH), while many others can act as modulators by amplifying or diminishing the effect of a primary neurohormone (e.g., neuropeptide Y, galanin, enkephalin). The distinction between the two modes of action is rather intuitive, and the possibility to shift from one mode to another remains open; under different physiological circumstances (e.g., proestrus, pregnancy, lactation, long-term exposure to a noxious stimulus, aging), a modulator can became a principal factor in regulating hormone secretion.

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