0031-6997/85/3703-0249$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 37, No. 3
Printed in U.S.A.

Neurotransmitter Regulation of Anterior Pituitary Hormones

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I. Introduction

IT HAS BECOME clear during the last 15 yr that most known central nervous system (CNS) neurotransmitter substances participate in the regulation of pituitary secretion. This regulation is concentrated in, but by no means limited to, the hypothalamus-median eminence-pituitary axis (fig. 1). In some instances, "neurotransmitters" behave more like releasing hormones. For example, dopamine (DA) is released from nerve endings of tuberoinfundibular neurons in the median eminence and pituitary stalk to stimulate dopamine receptors at the pituitary level after being transported there by blood vessels. Hence, the definitions of neurotransmitters and hormones are partially intermingled. This is not a completely new concept, since the peripheral adrenergic receptors are influenced both by the neurotransmitter of sympathetic nerve endings and the hormone of the adrenal medulla.

The present review has been written with pharmacologists in mind. It is structurally different from previous reviews dealing with the regulation of anterior pituitary secretion. It was considered important to proceed by transmitter rather than by hormone, in order to obtain a clearer overall view of the functions of the CNS in the regulation. Since dopamine is by far the most extensively studied transmitter, most of the general principles are illustrated in the context of dopaminergic systems.

In recent years, there has been a boom of literature on neurotransmitter regulation of pituitary hormones. Hence, to be manageable, the topic was restricted and gonadotropins were excluded, but their regulation would be worth a review of its own. Even so, it seems this is about the ultimate hour to write a general comprehensive review on these regulatory mechanisms.

Several excellent reviews have been published on the morphology of the hypothalamo-hypophyseal system (1004, 1297b) as well as on general principles and earlier literature (361, 776, 1018, 1474, 1488). These aspects are thus covered only to an extent considered essential for understanding. The emphasis is clearly on experimental studies in animals and man, but clinical applications are occasionally included.

The area of neuroendocrinology very much borders on physiology, endocrinology, and pharmacology. Pharmacological methods have been widely used in trying to study regulation of body homeostasis, often with bewildering results. Nonspecificity of drugs, especially at high doses, complexity of several successive steps of regula-

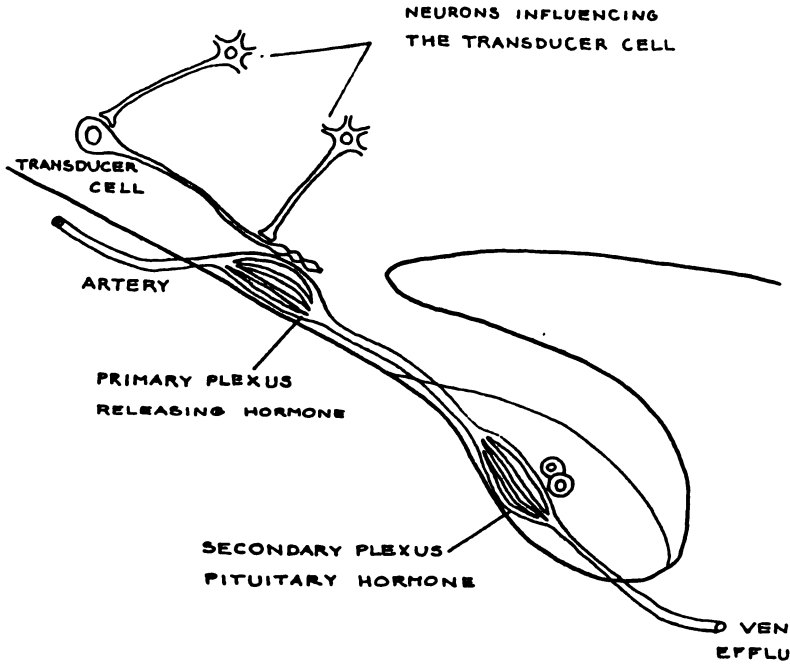

FIG. 1. The basic hypothalamic pituitary unit. Various neuronal systems influence the "neuroendocrine transducer cell" which receives neuronal input and forwards hormonal input via the portal vessels to the pituitary trophic cells. These, in turn, are either stimulated or inhibited by the hypothalamic factor, and they increase or decrease the release of pituitary hormone to the peripheral circulation, respectively.

tion, feedback mechanisms, and sometimes unsound pharmacological experimental principles have added to the confusion. Perhaps more than in any area of physiology, joint interdisciplinary efforts are needed here to solve the problems and to give a clear overall understanding. An attempt is made to emphasize the pharmacological aspects of the common topic.

From the pharmacological point of view, it is also of interest that pituitary hormone responses offer a unique monitoring tool for studying the physiology, pharmacology, and toxicology of the central nervous system. Presently, there are relatively few functional methods to monitor the actions of neurotransmitters in the CNS, since many of the synaptic connections are interneuronal. Hence, most of the information available is either morphological or neurochemical. The functional approach will gain even more importance, after methods to measure the concentrations of all releasing hormones, neurotransmitters, or their metabolites in the pituitary portal circulation have been developed, providing similar possibilities as do the classical perfusion experiments of autonomic ganglia or peripheral organs. This research area may be of importance for all pharmacologists interested in the functions of the CNS.

II. Dopaminergic Regulation of Pituitary Hormone Secretion

A. Prolactin

1. Tuberoinfundibular dopamine (TIDA) neurons as part of the feedback loop of prolactin secretion. It has been demonstrated that prolactin secretion is mainly under inhibitory hypothalamic control (454, 945, 1018). Hypothalamic lesions (56, 779) or stalk transection (703, 813) cause an increase in prolactin secretion. Furthermore, when the anterior pituitary is transplanted to, for example, the kidney capsule, it continues to secrete high amounts of prolactin (356, 414), as do cultured pituitary cells in vitro (948). Any factor that disconnects the anterior pituitary from the hypothalamus (surgical-morphological or pharmacological) appears to increase prolactin secretion.

Several lines of information suggest that one of the basic functions of TIDA neurons is to form a link in the feedback loop which guarantees a stable low basal prolactin level. A high prolactin level activates the TIDA neurons to synthesize dopamine and to release it into the hypophyseal portal circulation. Dopamine molecules attach to dopaminergic receptors on pituitary mammotrophs and inhibit the adenylate cyclase system which normally activates the cell to secrete prolactin. Decreasing prolactin secretion decreases the drive. Several factors such as estrogens and/or androgens are able to set this feedback regulation at different levels of prolactin balance. It is unclear to what extent this dopaminergic regulatory system is involved in rapid fluctuations (1291), such as those induced by suckling during lactation. An attempt is made in the following to illustrate the different stages of this feedback regulation of basal prolactin secretion (fig. 2). The evidence is presented vertically, starting at the level of the regulation of the pituitary mammotroph. Information on the dopaminergic regulation of prolactin release is already widely utilized in clinical therapy (for review, see 1017).

2. Autoregulation of prolactin at the pituitary level. Several investigators have considered the possibility that prolactin directly inhibits its own secretion at the pituitary level. In rat pituitary tumor cells, an inhibition of prolactin release of 80% has been reported in the presence of low levels of ovine prolactin in the incubation medium (611). In other studies, a small, transient inhibition was reported by high prolactin levels (953). However, several other authors (167, 1445, 1457b) could not find any indication of prolactin autoinhibition in vitro in primary cultures of normal rat pituitary cells. Vician et al. (1445) remark that the rat prolactin released by the cultured cells in the study of Herbert et al. (611) far exceeded the ovine prolactin levels studied. This, together with the fact that prolactin levels in vivo far exceed those reported by Herbert et al. (611) to cause a full inhibition, casts considerable doubt on the conclusions. Also, the prompt and marked increase of prolactin in vivo after the removal of dopaminergic inhibition speaks against an effective direct autoregulation (249). Prolactin-secreting tumors cause inhibition of host pituitary prolactin synthesis, but this inhibition is prevented by dopamine receptor blocking agents (877) or reserpine (807). A complete reversal could not be expected, if prolactin directly inhibited its own synthesis. Perhaps short loop inhibition is not flexible enough for the needs of the organism. A multicomponent regulation gives more possibilities for a multifactorial setting of the system. Hence, it is not likely that there would be a short feedback loop of prolactin synthesis or secretion in the pituitary. This renders the regulation through the TIDA system all the more important.

3. Dopamine receptors on prolactin-secreting pituitary cells. It has been known for years that neuroleptic drugs cause pseudopregnancy (77) and lactation (702) in experimental animals and gynecomastia and menstrual disorders in clinical use (361). By the early and mid-1970s, it had become clear that dopamine (or at least a catecholamine) (1427) is the key transmitter in the inhibition of prolactin secretion, and this could explain the effects of antidopaminergic drugs. It was not at all clear, however, whether dopamine stimulated the release of a separate prolactin inhibiting factor (698, 1063) or if it was itself released to the hypophyseal portal system, exerting its effects directly on the pituitary cells (104; for discussion, see refs. 1018 and 1406).

MacLeod and Lehmeyer (877, 878) were the first to unequivocally indicate that dopamine acts at the pituitary level. They incubated pituitary glands in vitro and

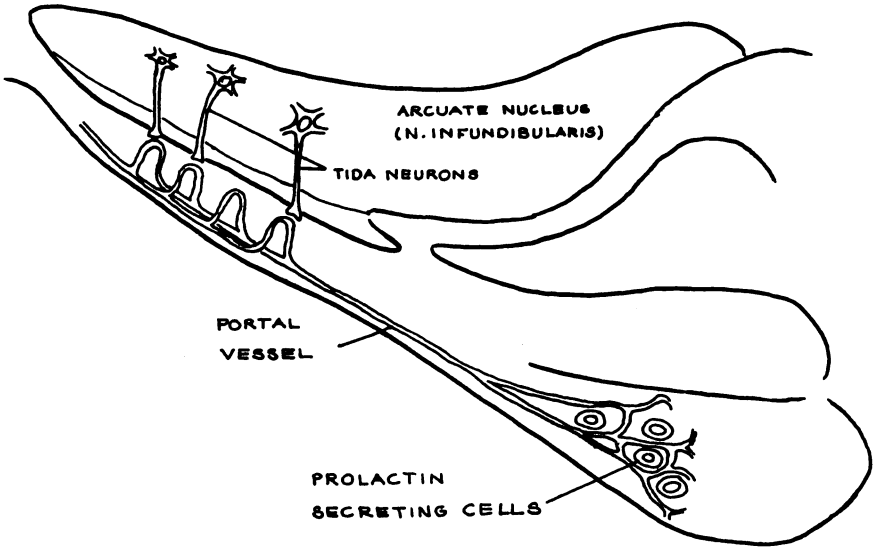

FIG. 2. Schematic presentation of TIDA neurons and their portal connection to the anterior pituitary.

showed inhibition of prolactin synthesis and release by dopamine and dopaminergic drugs. This inhibition could be abolished by dopamine receptor blocking agents. Also, Shaar and Clemens (1278) and Takahara et al. (1365) showed that the prolactin release inhibiting factor (PIF) activity in hypothalamic extracts was due to catecholamines. Even today there is uncertainty as to the existence of other prolactin release-inhibiting factors, dopaminergically activated or otherwise. These will be dealt with later.

4. Dopamine receptor binding studies. The existence of dopamine receptors on the pituitary releasing cells has been demonstrated in many binding studies by using either dopamine or dopamine agonists as radioactive ligands. Brown et al. (137) found abundant stereoselective binding sites for haloperidol and dopamine in the rat pituitary, while none were detected in the rat medial basal hypothalamus. In the monkey pituitary, haloperidol binding was stereoselective and at least as sensitive to displacement by neuroleptics as that in rat striatum. These results supported the notion that dopamine is a PIF. Subsequently the high-affinity binding of dopaminergic ligands both to normal pituitary cells in various species (169, 181, 277, 312) and to pituitary tumor cells (131, 275, 279) has been demonstrated in a number of studies. These include studies on normal human pituitaries and pituitary adenomas (131, 272). Dopamine receptors inhibiting prolactin release are pharmacologically different from classical postsynaptic receptors in the brain and rather similar to presynaptic autoreceptors (412).

Dopamine itself was demonstrated to bind to bovine pituitary membranes in a saturable manner with two K_d values according to the Scatchard plot, 0.44 nM and 47 nM (169). The binding was reversible, and high concentrations of nonradioactive dopamine rapidly displaced the radioactive ligand. Various dopaminergic agonists or dopamine receptor blocking drugs inhibited binding, although only at high concentrations (169).

In primary cultures of rat and bovine anterior pituitary cells, Caron et al. (181) used [^{3}H]dihydroergokryptine as the dopamine agonist ligand. This binding, too, was saturable, reversible, and specific. The Scatchard plot gave a single apparent K_d of 2.2 nM. The dissociation rate constant K_2 after adding 10 μM (+)-butaclamol was 3.3×10^{-3} min^{-1}. Displacement and inhibition of binding by various dopaminergic agonists and antagonists exhibited a typical pattern of a dopamine receptor binding ligand. The ability of dopaminergic agonists to inhibit prolactin release from cultured cells in vitro correlated well with their ability to compete for dihydroergokryptine binding. An interesting finding in this context is that haloperidol and pimozide seemed to have partial dopaminergic agonist activity. The same was true of 5-HT receptor antagonists, cyproheptadine and methysergide. Such agonist-like activity of dopamine receptor antagonists leading to inhibition of prolactin secretion was also noted by other groups (876, 970, and references therein). These paradoxical responses may be unrelated to dopamine receptor actions and due to calmodulin inhibition by high concentrations of neuroleptic drugs (968b–970; see also section II A 5). The anterior pituitary cell is a very useful tool for dopamine receptor binding studies, since simultaneous effects on the biological response can be monitored. With neuronal membranes, this is not possible.

Cronin et al. (277) found a K_d for dopamine (DA) of 50 nM in rat and 80 nM in sheep anterior pituitary, and only one binding site in each case. Dihydroergokryptine also exhibited a single-site high-affinity binding with a

K_d of about 5 nM. The binding satisfied the requirements of a specific binding to a receptor: it was saturable and reversible by competing ligands, such as apomorphine and other dopaminergic agonists and antagonists but only by high concentrations of other catecholamines or adrenergic receptor blocking drugs. N-Propylapomorphine is another dopaminergic agonist used in binding studies on anterior pituitary membranes. It binds to a single high-affinity site with a K_d of 0.22 nM (311).

These studies strongly suggest that there are specific dopamine receptors in the normal anterior pituitaries of several species, and the K_d of dopamine is about 50 nM in binding studies (169, 277). Other agonists, e.g., apomorphine and dihydroergokryptine, exhibit even lower K_d values (181, 277, 311, 448).

Studies with a selective dopamine receptor blocking drug, spiroperidol (spiperone), a butyrophenone derivative, confirm the results obtained with dopaminergic agonists. Creese et al. (271) found specific binding with a very high affinity to a single species of receptors in steer anterior pituitary membranes: the K_d was 0.2 nM, and the inhibition pattern by various drugs was very similar to that in bovine caudate nucleus. In support of these results, Cronin and Weiner (280) found a K_d of 0.85 nM in sheep and 0.38 nM in steer anterior pituitary. The K_d of 0.23 nM was found in rat anterior pituitary (1336). The K_d for spiperone in human pituitaries (obtained at hypophysectomy due to prostatic or breast cancer) was 2.2 nM (272). In another study on human pituitaries (collected 2 h after death), two binding sites were found for [^{3}H]domperidone with K_d values of about 0.2 and 4 nM (131). These were similar to those found in pituitary adenomas (see below). Also in the rat pituitary, the high-affinity K_d for domperidone is very low, 1.2 nM (448).

Several pituitary tumors of the rat have also been demonstrated to contain spiperone binding sites. It is of interest that some tumors which are refractory to dopaminergic inhibition do contain high-affinity receptor sites (275, 279), whereas others do not (274).

Spiperone binding was also assessed in human prolactin-secreting adenomas (272). The K_d was not significantly different from that of the normal anterior pituitary (3.1 ± 1.4 nM and 2.2 ± 0.7 nM, respectively), but the number of sites was higher in adenomas. However, if corrected for prolactin content, there was no difference. Hence, the difference may only reflect the higher relative number of mammotrophs in adenomas.

In 26 human prolactin-secreting pituitary adenomas, dopamine receptors were also discovered by using domperidone as the ligand (131). The K_d was 0.29 nM, which was very close to that found in normal pituitaries (0.18 mM). The densities of the binding sites varied in adenomas in contrast to those in normal pituitaries.

Dopamine receptors labelled by agonists (181) seemed different from those labelled by antagonists (271), since the affinity of agonists for the former was much lower than for the latter. The ability of dopaminergic agonists to displace [^{3}H]spiperone was still reduced by some guanine nucleotides, notably guanine triphosphate (GTP) (1293). Recently, it has been suggested (311, 312, 1294, 1295) that a single dopamine receptor population can, in fact, exist in two affinity states. These are discriminated clearly by the agonists which have a high affinity for only one type, but also to some extent by antagonists, although in the latter case the difference in affinity is only 2- and 10-fold. The agonist high affinity state exhibits a lower affinity for the antagonists and vice versa. The proportion of high-affinity and low-affinity agonist states seems to be about equal. Because of the marked difference in affinities (30- to 200-fold), agonists bind practically to receptors in the high-affinity state only. Antagonists bind more easily to both. This causes an apparent 2-fold difference in maximal binding.

The two states of affinity mentioned above can be influenced by guanine nucleotides (312), N-ethylmaleimide, and heat (733). According to these authors (312), 1 mM GTP converts the agonist high-affinity state to the agonist low-affinity state. This causes the maximum binding of the agonist to decrease by more than 75%. By the same token, however, the antagonist high-affinity binding is increased. These interesting data suggest that the heterogeneous population of receptors is converted to a single population with high affinity for antagonists but very low affinity for agonists. A similar change has been reported for other receptors (1195), notable adrenergic beta-receptors (842, 843). During solubilization of anterior pituitary binding sites, the agonist high-affinity binding is lost (732).

Haloperidol binding to dispersed anterior pituitary cells has been visualized by an immunocytochemical method (522). Haloperidol appeared to be bound mainly to mammotrophs, although some positively stained somatotrophs and gonadotrophs were also seen. Similar results were obtained on human pituitaries by autoradiographic localization of [^{3}H]spiperone (357).

Libertun et al. (837) reported an increased number of dopamine receptors in the pituitaries of median eminence-lesioned rats and a simultaneous supersensitivity to dopamine. This may be related to reports that lesioned rats exhibit supersensitivity to prolactin release-inhibiting effects of apomorphine 2 wk after the operation (225). Supersensitivity was also demonstrated in vitro (226), and the potency of dopamine to inhibit both synthesis of prolactin and release of newly synthesized prolactin was found to be increased in pituitaries of long-term lesioned animals (224).

Application of the above information to pharmacology and toxicology is only in its infancy. Understanding the differences between dopamine receptors in the brain and pituitary may help in designing more specific drugs (412). These receptors may also be targets of neurotoxic agents,

such as metals, which often interfere with reproductive ability (528).

5. The mechanisms of action of dopamine on prolactin secreting anterior pituitary cells. The mechanism by which dopamine inhibits prolactin secretion from mammotrophs is not clear. Some investigators suggest that dopamine *stimulates* adenylate cyclase (16), while other authors report *no effect* on adenylate cyclase of anterior pituitary cells (727, 1267, 1325, 1337, 1515). Dopamine has also been suggested to *inhibit* adenylate cyclase in enriched rat anterior pituitary mammotrophs (75, 1355) or in homogenates of human prolactin secreting adenomas (307) or to *block* the stimulation of adenylate cyclase by TRH (1093). Dopamine receptor blocking drugs have been shown to stimulate adenylate cyclase activity in prolactin secreting tumor cells (250). Some results suggest that the response depends both on dopamine concentration and on the hormonal status (1092).

Even researchers who find some inhibitory effects on adenylate cyclase have doubted its importance for the regulation of prolactin secretion (1161, 1372), and it has been suggested that calcium, rather than cAMP, might be the more important mediator of the dopamine-induced inhibition (1162, 1392). Hence, the results of studies of the anterior pituitary are contradictory in contrast to the unanimous results on the inhibition of adenylate cyclase by dopamine in the intermediate lobe (457, 973, 1022). However, the cAMP and Ca^{2+} hypotheses are not necessarily mutually exclusive (968a, 968b, 1260), and recently the view that dopamine also *inhibits* adenylate cyclase in pituitary mammotrophs has gained some support.

Since the relative number of mammotrophs in the pituitary gland varies, Giannattasio et al. (503) compared the dopamine sensitivity of anterior pituitary adenylate cyclase in mature female rats (with high contribution of mammotrophs to total cell population) with that in male rats (with few mammotrophs). In both lactating and nonlactating female rats, the basal adenylate cyclase activity in anterior pituitary was about 3-fold that in males, and a significant (39 to 48%) inhibition was achieved with 10 μM dopamine, whereas no significant inhibition was seen in males. The apparent K_d of inhibition was 625 nM. The inhibition was blocked by trifluoperazine and sulpiride and mimicked by dopaminergic agonists. Dopamine was also shown to inhibit adenylate cyclase in conditions of stimulated adenylate cyclase activity after treatment with vasoactive intestinal peptide (VIP) (1069), even if the basal activity in the male rat pituitary used was not changed.

Enjalbert and Bockaert (403) recently reinvestigated the role of dopamine receptor coupled with adenylate cyclase in prolactin secretion as well as its classification as a D_2-receptor. They found an inhibition by dopamine in both male and female rats, and the apparent K_d values were 160 nM and 560 nM in males and females, respectively. In males, the inhibition was stronger after VIP stimulation of prolactin secretion than in basal conditions. Sulpiride, a D_2-specific antagonist, blocked the dopamine inhibition, and a specific dopaminergic D_2-agonist, RU-24926, inhibited prolactin secretion with a K_d of 20 nM. Comparison of various antagonists showed a good correlation between the inhibition of prolactin release and the inhibition of adenylate cyclase. These and other results (403, 616b) strongly favor the view that dopamine inhibits adenylate cyclase in rat anterior pituitary through D_2-receptors, and this causes the inhibition of prolactin release. Furthermore, the GTP-sensitive binding of various agonists to pituitary D_2-receptors (312, 1293–1295) is compatible with the existence of a coupling of these receptors with an adenylate cyclase (1195).

Several studies have shown that prolactin release is inhibited by high concentrations of neuroleptic drugs, and these drugs also inhibit calmodulin activity (968b–970, 1262). Schettini et al. (1260) recently suggested that the Ca^{2+}-calmodulin and cAMP systems are interrelated in the regulation of prolactin secretion. There seemed to be a complicated interaction between these factors, since (*a*) Ca^{2+}-ionophore increased the pituitary cAMP content as well as prolactin release, (*b*) dopamine inhibited cAMP accumulation as well as prolactin release, and (*c*) dopamine also inhibited calcium-induced cAMP accumulation and prolactin release. Also calmodulin inhibitors reduced cAMP accumulation and prolactin release. These results were summarized in a hypothesis presented in fig. 3 (1260).

Also, a non-adenylate cyclase-linked dopamine receptor has been proposed to mediate the prolactin release

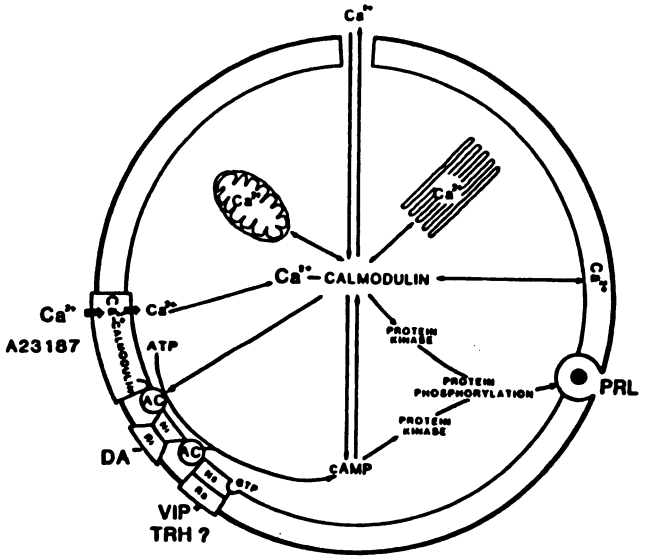

FIG. 3. Diagrammatic representation of the interrelation among Ca^{2+} calmodulin, cAMP, and dopamine in the control of prolactin secretion (for details, see ref. 1260). Reproduced from Schettini et al. (1260).

(727). These receptors could be coupled to membrane-bound chloride ionophores (1122).

Another approach to the mechanism of the inhibitory action of dopamine is to study the actual release process of prolactin. It has been suggested that lysosomal enzymes are involved and that they are activated by dopamine (1036, 1037) and bromocriptine (338). This mechanism has also been disputed (1027), and the data are at best circumstantial (349). Whatever the mechanism, lactotrophs can be inhibited for as long as the inhibitory hormone or analogue is bound to its receptors (273). This lack of tachyphylaxis is quite exceptional.

6. Evidence of dopamine being a prolactin release-inhibiting hormone in pituitary portal blood. The early evidence of dopamine being the crucial neurotransmitter/factor in the inhibition of prolactin release initiated a debate of whether it is the inhibiting factor released into the hypophyseal portal circulation (671, 878, 1278, 1365) or whether there is a separate prolactin release inhibiting factor or hormone (PIF, PRIH) either under dopaminergic control (697, 698)) or independent of it (1255). For this differentiation, it was crucial to show that pituitary portal blood contains dopamine at concentrations which are known to influence prolactin secretion at the pituitary level. Ben-Jonathan et al. (85) showed by cannulation of the rat pituitary stalk and radioenzymatic assay of catecholamines that dopamine is secreted into portal circulation at concentrations of 0.5 to 20 ng/ml (3 to 130 nmol/liter) in various conditions. The concentrations of noradrenaline and adrenaline were undetectable. The dopamine concentration was clearly higher in females than in males and increased from proestrus to estrus (1.32 and 3.87 ng/ml, respectively). During pregnancy, the concentrations varied up to about 20 ng/ml. Simultaneous concentrations in arterial blood were very low in all these circumstances.

By and large, these findings have been confirmed in later studies in the rat by radioenzymatic assay (266, 558) and liquid chromatographic-electrochemical detection (504, 1119). A similar pattern has been shown in the monkey (1045).

One of the problems of measuring dopamine in hypophyseal portal blood is that it must be carried out in anesthetized animals, and anesthesia may alter the activity of tuberoinfundibular neurons (1109). Nevertheless, it seems safe to state that enough dopamine is secreted from the median eminence into hypophyseal portal blood so as to have inhibitory effects on pituitary mammotrophs. Dopamine has also been shown to inhibit prolactin secretion when infused directly into a single portal vessel (1365). Recently, it was demonstrated that hypophyseal portal vessels, which contain the venous effluent of the medial median eminence, contain significantly more dopamine than those coming from the lateral parts of median eminence (1176). This may also cause topographic differences in both dopamine concentrations at the pituitary level and prolactin secretion.

Dopamine concentrations in hypophyseal portal blood can be altered by various treatments. The release is dependent on continued synthesis of dopamine, and α-methyltyrosine causes a marked reduction of dopamine concentration with subsequent elevation of serum prolactin (504, 555), When dopamine is infused into α-methyl-*p*-tyrosine-treated rats to achieve arterial plasma concentrations of dopamine that approximate those normally formed in hypophyseal portal plasma, serum prolactin decreases, approaching normal values (504). This demonstrates the interrelationship of prolactin and dopamine concentration. *d*-Amphetamine increased dopamine concentration in pituitary stalk plasma of male rats from 0.25 ng/ml to 1.5 ng/ml, and α-methyl-*p*-tyrosine prevented this stimulatory effect (555). Reserpine lowered dopamine concentrations, and amphetamine reversed this effect, but the concentrations did not reach those obtained with amphetamine alone. Since α-methyl-*p*-tyrosine caused a rapid and marked reduction in the concentration of dopamine and blocked the amphetamine-induced release of dopamine more effectively than did reserpine, it was suggested that amphetamine preferentially released newly synthesized dopamine and that the presence of dopamine in pituitary stalk blood results from preferential release from a small, newly synthesized pool of this neurotransmitter (555). These changes in dopamine concentrations can be correlated with changes in prolactin release after respective treatments, i.e., amphetamine antagonizes the reserpine-induced elevation in prolactin levels but does not reverse the increase in prolactin concentrations seen after α-methyl-*p*-tyrosine (638, 955). The changes in dopamine concentrations caused by reserpine were also counteracted by pargyline, a monoamine oxidase inhibitor, and also prolactin levels were reduced (550). This indicates that the release of dopamine is dependent on intact storage and monoamine oxidase (MAO) activity in addition to continued synthesis.

The secretion of dopamine into the hypophyseal portal blood varies throughout the estrous cycle (85, 266). In ovariectomized rats, dopamine release is suppressed by estradiol (266); hence, the high estradiol concentrations during proestrus may contribute to concomitant low dopamine secretion.

Ovariectomy of adult female rats had no significant effect on hypophyseal portal plasma dopamine, but prepubertal ovariectomy significantly decreased dopamine concentrations (558). In male rats, orchiectomy did not cause any change, whether performed at the age of 1 day or at an adult age, but a 3-day treatment with estradiol increased dopamine concentration significantly (558). These results suggest that the higher dopamine levels in the females than in the males are due to estrogen stimulation during the sexual differentiation rather than

inhibition by androgens in the male. A higher dopamine concentration may be needed to compensate for the reduced effectiveness with which dopamine inhibits the secretion of prolactin from the female anterior pituitary gland (558).

Intracerebroventricular administration of prolactin increased dopamine in the portal blood (from 0.2 to 1.1 ng/ml in male rats) (557). Haloperidol (2.5 mg/kg s.c.), which increased serum prolactin concentration from 31 ng/ml to 139 ng/ml, elevated the portal dopamine similarly to prolactin intra-cerebroventricularly (i.c.v.) (to 1.2 ng/ml). The effect of haloperidol on DA was mediated through prolactin increase, since antiserum to rat prolactin was able to attenuate the effect of haloperidol (557).

These examples of variations of dopamine concentrations in hypophyseal portal blood due to various physiological factors or after drugs convince one that dopamine indeed functions as a prolactin release-inhibiting hormone.

7. Synthesis, storage, and release of dopamine in the TIDA neurons. Anatomy and blood supply of tuberoinfundibular neurons have been authoritatively reviewed recently (29, 741, 1004, 1080, 1175). Hence, these items are only briefly dealt with here. The tuberoinfundibular (TIDA) and tuberohypophyseal dopamine neurons have their perikarya in the A_{12} region within the hypothalamus, as visualized by fluorescence microscopy (290, 469, 470, 474, 627), i.e., in arcuate and periventricular nuclei (741, 1327, 1364). Cell bodies of the tuberohypophyseal dopamine neurons are believed to be located in the more rostral regions of these nuclei. Tuberoinfundibular dopamine neurons have short axons that project ventrally to terminate in the median eminence. Dopamine nerve terminals are most abundant in the external layer of the median eminence (19). Here, they are packed in a palisade-like manner close to the pericapillary spaces of the primary plexus of the median eminence. The external layer has been divided into the medial palisade zone on both sides of the midline, and the lateral palisade zones on both sides of the medial palisade zone (855). Dopamine released in the medial palisade zone seems to be transported via the hypophyseal portal system to the anterior hypothalamus, whereas dopamine terminals in the lateral palisade zone terminate near the neurosecretory terminals which contain gonadotropin releasing hormone (630). Hence, the terminals in the medial palisade zone seem to be those involved in the inhibition of prolactin secretion, whereas those in the lateral palisade zones may be involved in the secretion of gonadotropin releasing hormone. Biochemical studies seem to confirm this, and dopamine is mainly found in the medial median eminence (736, 1273). This is also reflected as a higher dopamine concentration in portal vessels located medially on the pituitary stalk (1176).

Tuberoinfundibular dopamine neurons seem to differ neurochemically from nigrostriatal dopamine neurons in several respects (43). Since the terminals in the medial palisade zone do not form synapses, but dopamine is released into portal vessels, there is no synaptic cleft with pre- and postsynaptic receptors (344) and no effective high-affinity amine uptake system (50, 205, 343). These differences cause a number of consequences in the neurochemical behavior and feedback regulation of these neurons. They are not sensitive to neurotoxic actions of 6-hydroxydopamine, apparently because the neurons are not able to concentrate the agent (287a, 339, 683, 1301). Since dopamine released from the nerve ending is not transported back into the neuron, the concentration of metabolites, such as dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), is relatively low in the median eminence and cannot be used to monitor the turnover rate of dopamine (50, 343, 426, 1412).

The lack of presynaptic autoreceptors in TIDA neurons renders them insensitive to the inhibition of dopaminergic agonists and activation by dopamine receptor antagonists. In nigrostriatal neurons, apomorphine, piribedil, bromocriptine, and other agonists cause an immediate decrease in dopamine turnover, release, and discharge activity (158, 242). Dopamine receptor antagonists, e.g., neuroleptics, increase these activities (661).

In tuberoinfundibular neurons, neither piribedil, a dopaminergic agonist, nor haloperidol, an antagonist, changed dopamine turnover in the median eminence, although changes were seen in the striatum, as expected (344, 551, 552). Since there seems to be no immediate feedback regulation either via presynaptic dopamine receptors or via neuronal feedback loops, an obvious possibility of the regulation of these neurons is by the product of the cells they are regulating, i.e., prolactin. The function of D_1 receptors recently suggested to exist in the median eminence (471) remains to be settled.

Tuberoinfundibular neurons are destroyed by neonatal treatment with monosodium glutamate (1048, 1461), but since this lesion is somewhat nonspecific and dopamine, β-endorphin, and acetylcholine neuronal systems are affected (51, 1048), the endocrinological responses are complex and difficult to interpret. Lesioning of the infundibular nucleus in monkeys by stereotaxic coagulation suggested that regions involved in the regulation of prolactin secretion are different from those which control gonadotropin release (1114).

8. Feedback regulation of TIDA neurons by prolactin. Studies on the activity of TIDA neurons are difficult because of the peculiarities of these cells. Their dopamine turnover rate cannot be measured by assaying dopamine metabolites, DOPAC or HVA, since dopamine is not primarily metabolized within the area of release. Electrical recordings have so far not given specific information on the activity of tuberoinfundibular dopamine neurons. Various methods and their advantages and disadvantages have been reviewed recently (999). Three methods have

been used to estimate DA turnover; (*a*) assaying the activity of tyrosine hydroxylase in vitro or the rate of accumulation of L-dihydroxyphenyl alanine (L-dopa) after administration of decarboxylase inhibitor in vivo; (*b*) measuring the decline of dopamine after administration of tyrosine hydroxylase inhibitor; and (*c*) measurement of dopamine concentrations in hypophyseal portal blood.

Release and/or increase of turnover rate of dopamine after prolactin administration have been demonstrated by all the above-mentioned methods. Systemic prolactin injections increase the α-methyltyrosine-induced decline of dopamine in the median eminence, as first shown histochemically (629). This observation has been confirmed biochemically both by giving prolactin systemically (559, 625, 1273) and intracerebroventricularly (49). There was a latent period of several hours. Prolactin injected i.c.v. increased L-dopa accumulation in animals treated with a decarboxylase inhibitor (674). In agreement with earlier results, a significant increase was seen only 12 h after the prolactin injection. Cycloheximide reduced the prolactin-induced increase in L-dopa accumulation in the median eminence, which suggests the involvement of protein synthesis, possibly that of tyrosine hydroxylase (674). Tyrosine hydroxylase activity was also shown to be increased in the median eminence 12 to 24 h after i.c.v. injection of prolactin (1052).

Demarest et al. (347) provided evidence that there is also a rapid component in the increase of dopamine turnover in TIDA neurons by prolactin. Only the delayed-type component required protein synthesis as indicated by cycloheximide sensitivity (347). It is interesting that the delayed component only gives a potential for increase. Such increase is only expressed if prolactin is high shortly before the measurement. Prolactin has even been demonstrated to enhance the electrically induced release of dopamine in hypothalamic slices (1100).

Secretion of dopamine into hypophyseal portal circulation was increased in rats bearing prolactin-secreting tumors or ectopic pituitary glands (267, 1468) as well as in rats after prolactin administration (557). Also in vitro, superfused medial hypothalamic fragments released increased amounts of dopamine after prolactin (450). This augmentation was an immediate effect in contrast to most turnover measurements, where a latency of 10 to 26 h was seen.

Neuroleptic drugs cause a delayed increase in dopamine turnover in TIDA neurons as indicated by a decrease in DA levels after α-methyltyrosine (549, 552), conversion of [^{3}H]tyrosine to [^{3}H]dopamine (1101), or release of dopamine to portal blood (557). This suggests an indirect mechanism through increased prolactin secretion, whereas the turnover change in the striatum and olfactory tubercle is rapid due to direct neuronal effects of dopamine receptor blocking drugs (180, 552, 1101).

A chronic stimulation of hypothalamic dopamine neurons by prolactin may even lead to depletion of dopamine concentrations (1002, 1300), damage to TIDA neurons (1224, 1225), and reduced stalk blood dopamine (1226). This may be of relevance in states connected with chronic hyperprolactinemia. On the contrary, dopamine levels were also significantly decreased in the median eminence of hypophysectomized rats, and the levels were further reduced by anterior pituitary implants or prolactin administration (1003). In hyperprolactinemia, the reduced level of dopamine may be due to the inability of synthesis to keep pace with increased release (1003), whereas in hypoprolactinemia, the cause may be a reduction of dopamine synthesis (1003). In old animals, TIDA neuronal activity seems to be reduced (1226), and it will be of interest to see if this is the primary step leading to altered control of prolactin secretion and development of prolactinomas.

It seems that in certain physiological conditions, the feedback stimulation of dopamine neurons by prolactin is suppressed. This is the case with lactating animals. In rats, 12 days postpartum, prolactin concentration is high, but the TIDA neuronal activity is low. Even direct i.c.v. administration of prolactin fails to increase dopamine turnover in the median eminence (342). Furthermore, haloperidol fails to increase the dopamine turnover (342).

There are no direct data on the feedback regulation of TIDA neurons in humans. Prolactin can be suppressed in normal subjects both by L-dopa, the immediate dopamine precursor, and by L-dopa plus carbidopa. The latter inhibits peripheral dopamine synthesis, but since it does not penetrate the blood-brain barrier, it does not prevent the increase of dopamine synthesis after L-dopa in the central nervous system. In hyperprolactinemic patients with pituitary tumors, L-dopa more effectively inhibits prolactin secretion than L-dopa plus carbidopa (281, 442). These observations have been interpreted to indicate a reduction in central dopaminergic inhibition of prolactin secretion in patients with prolactinomas (1159). It would be more logical, however, that an increased prolactin secretion in patients with prolactinomas would increase the central dopaminergic tone. A further increase in this already high dopaminergic turnover by L-dopa would less effectively decrease the prolactin levels than would an increase in a normal turnover in normal subjects. There seems to be no direct evidence for this hypothesis, since there are no data on dopamine concentrations in human pituitary portal plasma, but there is some circumstantial evidence to support it. (*a*) Carbidopa seems to also partially inhibit dopamine synthesis in TIDA neurons, since carbidopa alone increases prolactin, and a greater inhibition of prolactin is seen after L-dopa alone than after L-dopa plus carbidopa (136, 281). This partial dopadecarboxylase inhibition in TIDA neurons obviously blunts the effects of L-dopa which may be more crucial in patients with adenomas than in normal subjects. This would explain the greater potency

of L-dopa alone. This carbidopa effect has not been observed in all studies, however (442, 1159, 1214). This may be a matter of dose.

(*b*) In microprolactinoma patients, the reduction of prolactin during a low-concentration dopamine infusion was significantly lower than in normal individuals (1277, 1467), although a high-concentration dopamine infusion caused a similar relative decrease (1145, 1467). This suggests that the lowered sensitivity to dopa plus carbidopa is not attributable to inappropriate central dopaminergic tone but to relative resistance to dopamine at the pituitary level. Dopa alone causes a more massive increase in dopamine secretion. In macroprolactinomas, a resistance to dopamine was not seen (1277). However, it is difficult, due to vascular changes and other abnormalities in macroprolactinoma, to know whether the preinfusion dopamine concentrations were decreased or increased.

(*c*) There is suggestive evidence that dopamine is more potent in inhibiting prolactin secretion from normal human pituitary cells in vitro than from adenoma cells (100). A reduced numer of dopamine receptors in pituitary adenomas has been suggested (131). In rat pituitary tumor cells, this refractoriness to dopamine is well established (274, 275, 279, 422, 807, 891).

(*d*) There is evidence that metoclopramide, a dopamine receptor blocking drug, increases TSH levels in patients with hyperprolactinemia more than in normal subjects (1146, 1235, 1238). One explanation for this would be an increased dopamine secretion into the portal vessels which forces the thyrothrophs to adapt to an inhibitory high-dopamine environment. Abolition of this inhibition by a dopamine receptor blocking drug would result in an overshoot of TSH. An inverse situation is seen in physiological puerperal hyperprolactinemia where the TSH increase after metoclopramide is reduced, supposedly due to a reduced dopaminergic tone in this condition (1196).

(*e*) Dopamine receptor blocking drugs have been shown to be relatively less potent in increasing prolactin levels in prolactinoma patients than in normal subjects (70, 71, 173, 1144, 1145, 1467). This would be an expected result of a competitive antagonist if the agonist (dopamine) concentration was increased, although there may be other explanations such as aberrant vascular arrangement of portal vessels (1145).

On the other hand, α-methyl-*p*-tyrosine increased prolactin only in normal women, but not in hyperprolactinemic patients, and dopamine infusion after α-methyl-*p*-tyrosine decreased prolactin in both groups (1054). This may favor a normal peripheral response to dopamine, but again it is difficult to know on the basis of only one dose level whether or not the same dose causes an equivalent antagonism in both groups. Recent results on the insensitivity of prolactin levels to thyrotropin releasing hormone (TRH) in hyperprolactinemic patients and normalization of this response during dopamine infusion also favor the possibility of relative or absolute dopamine deficiency in these patients (1053). The difficulty here is to know the effect of the very different baseline to the sensitivity to TRH.

Admittedly none of the above mentioned studies excludes the possibility of an impaired dopaminergic tone and thus impaired feedback regulation of prolactin at the level of TIDA neurons, at least in some hyperprolactinemic patients. This has been suggested as a primary reason for the initiation of prolactinomas (1418). However, neither can it be excluded that the defect is peripheral rather than central (791) and that dopamine would be secreted in increased amounts into the portal vessels in hyperprolactinemic patients.

9. Antagonism of dopamine inhibition of prolactin secretion by estrogens. Estrogens are known to increase prolactin secretion in humans (455) and rats (20, 219). These effects could, in principle, take place either at the pituitary level or within the brain. A direct action on the pituitary was demonstrated in the 1960s (83, 597, 1055).

A sexual difference in the ability of drugs to increase prolactin has been known for a long time. The inhibitor of dopamine synthesis, α-methyl-*p*-tyrosine (377), and dopamine receptor blocking drugs, such as chlorpromazine and pimozide (249, 1062), were more effective prolactin releasers in female than in male rats. After ovariectomy, the prolactin response to pimozide was clearly blunted, and estrogen treatment facilitated it (1062). Moreover, the TRH-induced prolactin response was blunted by ovariectomy and restored by estrogen (1062).

Raymond et al. (1163) demonstrated with cultured anterior pituitary cells in vitro that estrogens have a potent antidopaminergic activity on prolactin secretion. Their results indicated a decreased sensitivity of prolactin secreting cells to dopamine. Therefore, higher dopamine concentrations in portal blood would be required under conditions of high estrogen secretion. Similar antagonism has also been demonstrated between estrogen and dopamine agonist compounds, such as dihydroergokryptine (1478). Dopamine receptor antagonists, such as pimozide, increase prolactin levels in estrogen-treated pituitary cells in the same manner as in untreated cells, but the setting of regulation is at a higher level (1106). These effects are also seen in vivo (790). The permissive effects of estradiol may be mediated via pituitary conversion to 2-hydroxyestradiol, a catechol estrogen (10, 1252, 1497). On the other hand, these results have also been disputed, and catecholestrogens have been suggested to have dopamine agonist effects, decreasing prolactin (845, 1266) or having no immediate effects on prolactin release (1096).

Gudelsky et al. (554) extended the investigation of these mechanisms in vivo in ovariectomized rats treated with estrogen or its vehicle. They observed in estrogen-treated rats a 20 to 25-fold increase in serum prolactin

concentrations, a 2.5-fold increase in dopamine concentrations in pituitary stalk plasma, a 3-fold increase in pituitary prolactin content, and a marked decrease in pituitary dopamine contents *versus* ovariectomized control rats. In vitro dopamine only slightly inhibited prolactin release from anterior pituitary tissue after a 5-day estrogen treatment of the animal in vivo. These results are in agreement with those of Raymond et al. (1163) and render it unlikely that the elevated prolactin level would be due to a suppressed release of dopamine, since dopamine concentration in portal blood was increased. Instead, this change in dopamine secretion may be secondary to the prolactin increase. This, in turn, may be due to a reduced responsiveness of prolactin cells to the inhibitory effect of dopamine, as well as to an increased capacity of the anterior pituitary to secrete prolactin.

The mechanism of densensitization to dopamine inhibition is not clear. According to Di Paolo et al. (369), estrogen does not alter the concentration of dopamine receptors or their affinity. 2-Hydroxyestradiol also weakly inhibited spiroperidol binding in rat pituitary homogenates (1252) and did not inhibit dopamine antagonist binding in prolactinomas at all (1096). However, a decrease in dopamine receptors after estrogens has also been observed (609), as well as changes during the estrus cycle (608, 1088a) and gestation (276).

It has been suggested that prolactin cells have the capacity to internalize dopamine and to incorporate it into prolactin secretory granules (553, 1035). Estrogen treatment reduced the capacity of prolactin cells to incorporate dopamine into secretory granules (554). Nansel et al. (1037) suggested that estrogen suppresses dopamine inhibition by reducing its capacity to stimulate lysosomal enzyme activity in the anterior pituitary gland.

De Quijada et al. (353) showed that tamoxifen, an antiestrogenic compound, rendered dispersed rat pituitary tumor cells more sensitive to dopamine and bromocriptine. These cells are less sensitive to dopaminergic inhibition than normal mammotrophs. The partial restoration of dopamine sensitivity to tamoxifen was reversed by estradiol.

Apparently complicated synergistic effects are involved, since Pilotte et al. (1108) observed no effect on spiperone receptor binding by estrogen or progesterone alone, but a significant increase after a sequential treatment with both hormones.

In human studies, prolactin sensitivity to dopamine is increased when circulating estradiol levels are high (691). In agonadal women, prolactin suppression during dopamine infusion was clearly lower than in normally cycling women (Day 2), and estrogen treatment augmented basal prolactin release and clearly reinforced the dopamine-induced suppression (692). Also, in Rhesus monkey, estrogen has been suggested to reinforce the inhibitory effect of dopamine in contrast to its antagonistic effect in rodents (1045). Hence, primates and rats may differ in the mechanisms by which estrogen regulates prolactin secretion.

The complex interrelationship of dopamine and estrogen in the pituitary was also demonstrated by the reduction in estrogen receptor concentration after the destruction of median eminence (1475). This reduction was reversed by bromocriptine, a dopaminergic agonist (352). However, the decrease of estrogen receptors in the pituitary transplanted to the kidney capsule did not return to normal (352); hence, dopaminergic stimulation alone does not explain these changes. Also, α-methyl-*p*-tyrosine and haloperidol, which are known to decrease dopamine concentrations in hypophyseal portal blood, reduced the estrogen receptor concentration in the pituitary as did neonatal treatment with monosodium glutamate, which destroys the arcuate nucleus. Bromocriptine partially reversed these effects (184). The above findings suggest that dopamine may have a stimulatory or trophic influence on estrogen receptors in the pituitary gland. None of the treatments cited above changed hypothalamic estrogen receptor concentrations (184).

10. Changes of dopamine turnover in the hypothalamus caused by steroid hormones. There is a clear sex-related difference in prolactin responses to interruption of dopaminergic control. Blockade of this control caused a much greater increase in the serum concentration of prolactin in female rats than in male rats (377, 1062, 1306b). This difference may be due in part to the sensitivity at the pituitary level. However, also dopamine synthesis and turnover of TIDA neurons are higher in female rats (341), and the dopamine concentration in hypophyseal portal blood is clearly higher in female rats than in males. The difference to males is about 6- to 7-fold during estrus or diestrus (85, 558). Adult ovariectomy or androgen sterilization had no significant effect on dopamine, but prepubertal ovariectomy resulted in significantly reduced dopamine concentrations in pituitary plasma. In males, neither neonatal nor adult orchiectomy had any effect, but estrogen treatment increased the dopamine levels (558). A similar effect was reported in ovariectomized female rats (554). Hence, the crucial hormone would appear to be estradiol.

The effect of estrogen is also seen in changes of dopamine turnover in the median eminence. Three daily injections of estradiol into male rats elevated serum prolactin concentrations and increased the rate of turnover and synthesis of dopamine exclusively in the median eminence (282, 345, 394). The turnover of dopamine in the median eminence of ovariectomized rats also increased after estrogen and progesterone injections (670) or after the implantation of silastic tubing containing estrogen and progesterone released in approximately physiological amounts (1154, 1491). However, the effects of estrogen did not occur in hypophysectomized animals, which has also been interpreted to suggest that the

activation of dopamine turnover is secondary to the increase of prolactin (345, 346, 394).

Contrary to short-term experiments, dopamine turnover in the median eminence decreased after long-term estrogen treatment (348, 387). This decrease which is also followed by a decrease in dopamine levels is not caused by neuronal loss as previously suggested (190, 387), since the effect is clearly reversible (348). It may be due to a decrease in the responsiveness of TIDA neurons to prolactin.

There are conflicting reports on the effects of estrogen on the steady-state concentrations of hypothalamic dopamine. Increased dopamine has been reported in the median eminence but not in other parts of the hypothalamus after long-term ovariectomy. No changes were found between different days of the estrous cycle (548). Estrogen treatment decreased dopamine levels in the median eminence (348, 387, 1306a). Hence, it is possible that dopamine concentrations are not so strictly regulated by the end-product inhibition of synthesis in TIDA neurons as in other dopamine neurons (348).

The higher dopamine turnover in cycling females does not seem to be due to continuous feedback activation by prolactin alone. L-Dopa accumulation (a measurement of dopamine turnover) in the median eminence of females remains elevated 3 wk after castration, although the serum concentration of prolactin is reduced to that in the male (341). Neonatal androgen exposure affects the tuberoinfundibular dopamine neuronal activity and might also contribute to the sexual differences in prolactin secretion (341).

Another explanation for the increased activity of TIDA neurons in the female is that they may be more responsive to the stimulatory actions of prolactin than the neurons in the male. In gonadectomized females, dopamine synthesis increased to a much greater extent in response to a number of manipulations that increase serum prolactin (e.g., haloperidol, estradiol, or i.c.v. prolactin) than in the gonadectomized male (346). The female was also more sensitive to decreased levels of prolactin; i.e., dopamine synthesis in the median eminence decreased more in females than in males after hypophysectomy or bromocriptine, a dopamine agonist which decreases prolactin (346). These results are consistent with the proposal that the dopamine turnover of female rats is related to plasma prolactin concentrations. Also, i.c.v. effects of prolactin indicate that dopamine turnover is more sensitive to prolactin in female than male rats (346).

Secretion of dopamine into hypophyseal portal blood is highest in estrus and lowest in proestrus of the rat (85, 268), whereas estrogen levels are higher during early proestrus than at any other time of the estrous cycle (165, 1302). Administration of estrogen to adrenalectomized and ovariectomized rats leads to a transient reduction in the secretion of dopamine (266). On the other hand, progesterone stimulates dopamine secretion (268) and decreases prolactin if given with estradiol (836). Restoration of physiological estrogen levels in ovariectomized rats did not affect dopamine release, but an increase was seen after subsequent prolactin treatment (1108). During gestation, dopamine secretion has been shown to be elevated to even higher levels than during estrus (84, 85). These results suggest that dopamine release into hypophyseal portal circulation is controlled by a delicate interplay of both estrogen and progesterone effects. Most results also agree in that even if there is an inverse correlation between dopamine and prolactin (84, 1108), the correlation is not perfect; hence, other factors must be involved as well.

Changes in dopaminergic activity in the hypothalamus associated with hormonal changes have also been demonstrated by histochemical methods. A marked increase in the number and intensity of dopaminergic cell bodies of the tuberoinfundibular system was demonstrated in pregnant, pseudopregnant, and lactating rats (476–478). On the other hand, the rate of α-methyltyrosine-induced decline in dopamine fluorescence indicated an increased turnover rate during gestation (856). In ovariectomized rats, estradiol increased serum prolactin and catecholamine turnover, especially in the medial palisade zone and to a lesser extent also in the lateral palisade zone (853).

11. Dopamine in the regulation of prolactin surges during the estrous cycle. As stated above, secretion of dopamine into rat hypophyseal portal blood is highest in estrus and lowest in proestrus (85, 235, 268). This may suggest that a reduced dopaminergic tone participates in the induction of the late afternoon prolactin surge in proestrus.

The decline of catecholamine fluorescence following administration of α-methyltyrosine also revealed fluctuations in dopamine turnover in the median eminence: a lower turnover during proestrus-estrus than during diestrus (17). With subsequently refined methods, a lower dopamine turnover was observed in the lateral palisade zone during proestrus than at any other time during the cycle (853).

Biochemical dopamine turnover studies have also revealed a decrease in the early afternoon of proestrus (183, 340). Not all results agree, however. Dopamine turnover has also been found to be identical between 16.00 and 17.00 h in the mediobasal hypothalamus on the days of diestrus and proestrus (637), but since only one time point and gross dissections were used, the changes may have been missed (1155). However, a decrease in dopaminergic activity in TIDA neurons has been demonstrated mostly during the afternoon of proestrus, although the exact timing is controversial (183, 340, 999, 1155). With the information presently available, it is very difficult to know how these changes correlate with other physiological fluctuations in endocrine status and

to decide which is cause and which is effect. It would be logical that a lowered dopaminergic tone would precede the prolactin surge in the late afternoon of proestrus. Other regulators such as 5-HT may participate (1111), since there is no direct correlation between the concentration of dopamine in the stalk plasma and the release of prolactin (1108).

12. Dopamine in suckling-induced prolactin release. Suckling-induced prolactin release seems to involve serotonergic neurons (756) and TRH (443, 542), but dopamine may have a permissive role as well. The results have been conflicting, and this has been recently explained by the existence of several variants of prolactin (cf. 829).

Dopamine turnover was initially reported to increase during lactation as measured by histofluorescence (478). Contrary to these histochemical data, most biochemical studies suggest that TIDA neurons are less active in lactating rats in spite of their high prolactin levels and that suckling further reduces their activity. The dopamine concentrations in hypophyseal portal plasma were lower during lactation than during gestation of rats, being increased at 24 h after pup separation (84). Hence, there may be an inverse correlation between plasma prolactin and dopamine concentrations in portal blood.

The stimulus of suckling which causes an increase in prolactin secretion with a few minutes (112, 1349, 1384) can be simulated by electrical stimulation of the isolated mammary nerve of lactating rats (964, 1046). This slightly, but significantly, decreased dopamine concentrations in the hypophyseal stalk plasma and increased blood prolactin concentrations (309, 310). A similar decrease was suggested by continuous monitoring of pituitary blood by means of microelectrodes (1118, 1120). It seems clear on the basis of dopamine concentrations in the pituitary portal plasma that dopamine alone cannot account for the rapid and substantial prolactin surge, since there is no perfect mirror image correlation. However, dopamine may have a permissive role along with other factors in causing a release.

There are conflicting data on hypothalamic dopamine concentrations after suckling. Some workers have observed depletions of dopamine in the hypothalamus (310, 963), median eminence (234), ventromedial but not arcuate nucleus (1010), and anterior pituitary (234, 310, 342). Others report no changes in hypothalamic dopamine concentration (342, 1274, 1456). In any case, transmitter levels are not a reliable index of activity. Since there is no synthetic activity in the anterior pituitary (677, 1216), dopamine found there is thought to measure hypothalamic release. However, correlation of suckling to the decrease of dopamine concentration in the anterior pituitary is also relatively poor (349).

Dopamine turnover studies have indicated a decreased L-dopa accumulation in the median eminence of pup-deprived lactating rats and a further decrease after suckling (342, 999).

In studies utilizing α-methyltyrosine-induced decrease of dopamine concentrations, no significant change in dopamine turnover was noted after suckling (1010). Selmanoff et al. (1274) found a decrease in dopamine turnover in the median eminence during the first 30 min after suckling as well as 30 to 60 min after suckling 10 days postpartum. The decreases were no longer significant 20 days postpartum. At the latter time, the prolactin response to suckling was markedly blunted and sluggish as compared to that on the tenth day. The prolactin response was demonstrated to increase due to α-methyl-*p*-tyrosine, as shown earlier by Voogt and Carr (1457a). Since the prolactin release due to α-methyl-*p*-tyrosine and suckling was no greater than that due to α-methyltyrosine alone, Selmanoff et al. (1274) concluded that the blockade of dopaminergic mechanism may fully account for the prolactin levels seen with suckling. The decreased dopamine turnover in the median eminence after suckling was confirmed by Demarest et al. (342).

Grosvenor and coworkers have suggested that prolactin is released in two phases in the pituitary (544, 545) and that only the first phase is regulated by dopamine (546). This hypothesis is based on the observation that depletion of prolactin in the pituitary gland occurs in a matter of minutes after suckling (543) or electrical stimulation of the mammary nerve (544, 964), whereas the increase in plasma prolactin is much slower (547, 1384). This hypothesis was tested by administering either median eminence extract or bromocriptine before suckling or after the commencement of suckling. These agents inhibited prolactin release only if given before suckling, even if the increase in prolactin continued for at least 20 to 30 min after the administration (546). This was interpreted to mean that dopamine inhibits only the first phase of prolactin secretion, rapidly transforming prolactin within the pituitary into a releaseable form. The following steady discharge into the circulation would not be inhibited by dopamine.

Leong et al. (829) recently offered an alternative explanation for this finding. Since the rapid pituitary release of prolactin has been shown by bioassay or disc electrophoretic assays and the slowly increasing plasma prolactin has been measured by radioimmunoassay, they may not represent the same hormone at all. There seems to be no firm evidence for this attractive and provocative hypothesis yet, but it is supported by the finding that the depletion of pituitary prolactin stores cannot be detected by radioimmunoassay (829).

13. Dopamine in the regulation of prolactin surges during gestation. Prolactin surges occur twice a day during early gestation in rats (166). The regulation of this activity is not well worked out. In the most thorough study so far, McKay et al. (942) measured the circadian rhythms of plasma prolactin and dopamine turnover in

the median eminence. They found two prolactin surges on Days 2 and 6 of gestation: a nocturnal surge which peaked at 0300 to 0600 h, and a diurnal surge at 1800 h. This circadian pattern had disappeared by Day 13 of gestation. Two low points in dopamine turnover (as measured by L-dopa accumulation and in part supported by dopamine levels in the anterior pituitary) were found on Days 2, 6, and 7, at 0600 and 2100 to 2400 h. This pattern also disappeared by Day 13. These results suggest that there is a relationship between the prolactin surges and changes in the rate of dopamine synthesis. After midgestation, when the surges of prolactin are no longer required (1504), dopamine turnover increased to a consistently high level, and prolactin remained low throughout the day. Since the decreases in dopamine turnover did not clearly precede the prolactin surges, there may be other contributory factors, and dopamine may be assumed to have a permissive rather than dominantly regulatory role.

B. Thyrotropin (TSH)

1. Influence of dopamine on thyrotropin secretion in vivo in rats. There is by far less information on the dopaminergic regulation of TSH secretion than on the inhibition of prolactin release. Based on circumstantial evidence, we suggested that dopamine might inhibit TSH secretion in the rat (1408). Dopaminergic drugs such as apomorphine, bromocriptine, and sufficiently high doses of L-dopa given systemically decrease plasma TSH levels and blunt cold-induced release of TSH in rats (778, 896, 897, 1008, 1011, 1070, 1158, 1241, 1407, 1447). This inhibition can be reversed with dopamine receptor blocking drugs, e.g., chlorpromazine or pimozide (896, 1070, 1158). All these results suggest that dopamine is inhibitory but do not indicate the level of action. In some conditions, dopaminergic drugs have not been found to decrease plasma TSH (48), and in all studies, higher doses have been required than those which inhibit prolactin secretion. The ineffectiveness of dopamine receptor blocking drugs, such as haloperidol (48), metoclopramide (421), or pimozide (1158), to increase TSH basal levels also indicates a completely different system from that seen in the case of prolactin. It is obvious that dopamine does not play a major part in tonically inhibiting TSH release, and dopamine is probably not the dominant transmitter in its regulation. Another clear difference from prolactin regulation is the existence of an effective feedback system which does not involve the central nervous system. Thyroid hormones exert a powerful inhibitory effect on TSH secreting cells in the pituitary (1006), and this complicates any effort to disturb the balance via the CNS. TSH secretion is therefore much less sensitive to drug effects than prolactin secretion. It has proved particularly difficult to increase TSH secretion with drugs in euthyroid animals. In slightly hypothyroid animals, this seems to be easier (899), highlighting the importance of feedback systems. Even then, pimozide given alone did not increase plasma TSH (899).

Intracerebroventricular dopamine was shown to decrease plasma TSH in ovariectomized female rats, ovariectomized-estrogen-progesterone-treated female rats (1447), and male rats (896). Also the dopaminergic agonists, apomorphine and piribedil i.c.v., decreased plasma TSH at low doses (1447). All these agonists also suppressed TSH when given systemically. These results suggested that their site of action is the median eminence which has no effective blood-brain barrier (97), and into which dopamine readily penetrates if injected into the brain ventricle. This view is supported by the finding that dopaminergic drugs do not inhibit the effect of TRH at the pituitary level in vivo (778, 1158, 1407), although not all studies agree (815). Interestingly, TSH caused a dose-dependent increase of dopamine turnover in the median eminence (32d).

On the other hand, there is evidence that the site of action is higher in the CNS, since systemically administered dopamine did not decrease TSH levels or blunt cold response (896, 901), and domperidone, a dopamine receptor blocking drug unable to penetrate the blood-brain barrier, did not inhibit the decremental effects of apomorphine (896). The unilateral destruction of substantia nigra leading to supersensitivity to apomorphine and bilateral destruction to complete abolishment of cold response suggests the involvement of the nigral dopamine tracts (896). However, there is no information on the destination of these neurons, but since dopamine infusions to the third ventricle decrease TSH (see above), some periventricular area may be involved. There are recent data suggesting that dopamine terminals in the median eminence influence TRH secretion (32d). This would also provide a mechanism for short-loop negative feedback by TSH (32, a and d). Results on TRH release from synaptosomes are unclear; both inhibitory (687) and stimulatory (87, 1251) effects have been reported.

2. Direct dopaminergic inhibition of rat thyrotrophs. Whether there are direct effects of dopamine on the thyrotropin-secreting cells of the pituitary is disputed. Most in vivo results (see above) suggest inhibition at the suprapituitary level. It has been suggested on the basis of in vitro stimulation of cultured rat pituitary cells that dopamine and bromocriptine may inhibit TSH secretion from both TRH-stimulated and nonstimulated cells (449). The inhibitory effect was blocked by metoclopramide and domperidone. In a later study by the same authors, the inhibition was compared with that of prolactin (448). It was found that secretion of TSH and prolactin was inhibited at the same concentration range with dopaminergic agonists and that their rank order of potency was the same for both hormones. The pattern of inhibition by various dopamine receptor blocking drugs was similar. Functionally, the thyrotroph was less sensitive even if the effective concentration (EC50) and

inhibitory concentrations (IC50) were similar. There was only one class of dopamine receptors involved in both cases, which suggests that the different sensitivity is not a function of the dopamine receptor type (448). A different sensitivity was also suggested by another study (1133), in which domperidone was shown to increase TSH secretion in vitro and to antagonize the effects of dopamine on TSH and prolactin secretion.

On the other hand, dopamine did not influence TSH secretion when it was applied to a solution used to perfuse dispersed rat anterior pituitary cells (1138). The dose-response curve for TRH stimulation did not change in the presence of either dopamine or bromocriptine (1138). It is somewhat difficult to compare these quite different techniques. Receptors may develop (or possibly become sensitive) in culture or as a response to high TSH concentrations in the suspension as contrasted to the dynamic perfusion system. However, the number of dopamine receptors increases in the pituitary of hypothyroid rats, and the increase is associated with the increase in the number of thyrotrophs (447). TSH secretion by anterior pituitary cells derived from hypothyroid rats can be inhibited by dopamine to a greater extent than that by cells from euthyroid animals (447). These recent findings support the view that dopaminergic inhibition at the pituitary level is physiological in the rat.

3. Dopaminergic inhibition of TSH release in man. A number of studies indicate that dopamine inhibits TSH secretion in man. However, as emphasized by several authors (1006, 1233, 1406), powerful feedback effects tend to mask any drug effects on TSH levels. Hence, the effects were first seen in hypothyroid patients in whom L-dopa suppressed TSH levels (863, 985, 1160, 1167, 1367). This decrease was also seen after dopamine agonists such as bromocriptine (431, 863, 992). In euthyroid subjects, these changes were not initially noted. Neither were any TSH increases initially demonstrated after dopamine receptor blocking drugs, such as neuroleptics or metoclopramide (326, 690, 834, 1073, 1334), or dopamine-depleting drugs, such as 3-iodo-L-tyrosine (1306b, 1308).

Along with changes in other hormones, however, small but significant elevations of TSH were seen in some studies after dopamine receptor blocking drugs such as metoclopramide (599, 1320). These changes were more apparent in women than in men (926).

In a series of studies on volunteers, Scanlon and coworkers have studied the effects of dopaminergic agonists and antagonists on TSH secretion in man (1233). They demonstrated an increase in TSH levels in hypothyroid patients by metoclopramide, a dopamine receptor blocking benzamide drug (1234). Somewhat smaller increases in TSH were subsequently found in euthyroid subjects after metoclopramide, domperidone, or monoiodotyrosine (1236, 1238). The degree of TSH response was significantly greater in females than in males (1238) and inversely correlated with the basal TSH level. This was interpreted to mean that dopamine contributes to maintaining low daytime TSH levels (1238).

However, in a subsequent study (1237), a greater disinhibition was not seen after metoclopramide during the day than at night as was expected if dopamine causes daytime TSH level to be low. This was taken to dispute the hypothesis that dopaminergic inhibition would be the cause for a lower daytime TSH level.

On the other hand, Sowers et al. (1319) showed that a dopaminergic agonist, bromocriptine, abolished the daily rhythm in TSH, fixing its level slightly lower than the usual daily low. Hence, during the daytime, the difference between controls and bromocriptine-treated male subjects was modest, but at midnight it was more than 2-fold. This again would favor the view that dopamine may be responsible for the low daytime levels of TSH. However, the pattern is not identical to that of prolactin, which peaks several hours later (1322).

There are two basic difficulties in trying to show that dopamine regulates the daily rhythm of TSH. (*a*) Metoclopramide is a competitive inhibitor. Hence, the inhibition to be expected is less (not more) if the concentration of dopamine (agonist concentration) is higher. This means that, at a higher dopamine concentration phase, a higher dose of inhibitor would be needed to cause the same degree of inhibition than what is needed during a low concentration phase. It is virtually impossible to predict the net result if the concentrations of both agonist and antagonist at the receptor site are not known. (*b*) It seems unlikely that changes in hormone levels would be caused by a single regulatory agent. This complicated interplay necessitates the use of simplified experimental arrangements in an effort to reduce confounding factors as far as possible.

It is obvious that the daily rhythm of TSH is one of the problems that confounds results if proper controls are not used. Normal TSH is on the decline during the hours of the day when most experiments have been performed (423, 1237, 1238, 1319). Under these circumstances, if only compared to the baseline level, a small increment is concealed, or rather there is a decreasing trend even after dopamine receptor blocking drugs.

Several studies have shown that dopamine (i.v.) decreases TSH levels in humans (313, 316, 711, 826, 928), and that this effect is abolished by domperidone (316).

There are relatively few studies of dopamine receptor agonists in euthyroid subjects, but a decrease in TSH levels has been demonstrated after bromocriptine (314, 1319). Furthermore, nomifensine, a dopamine uptake inhibitor, slightly decreased both basal and TRH-induced TSH levels (516). On the other hand, a number of studies clearly demonstrate an increase in TSH after dopamine receptor blocking drugs, even though the increment is relatively small in euthyroid subjects, and in some studies seen only in females (78, 316, 317, 423, 926,

1146, 1232, 1236, 1238, 1321, 1503, 1510). The increase is greatest in mild or subclinical hypothyroidism and declines with increasingly severe hypothyroidism (423, 599, 1232, 1233). This may suggest that in mild hypothyroidism the subnormal peripheral negative feedback allows a greater response to dopamine receptor blockade. With increasingly severe hypothyroidism, the dopaminergic tone may already be so low that its blockade will not make much difference. This "therapeutic window" may explain why increases of TSH by dopamine receptor blockade have been positively (700, 926) and negatively (1234) correlated with the severity of hypothyroidism.

Since dopamine and some of its antagonists such as domperidone (317, 924, 1132, 1321) do not penetrate the blood-brain barrier, the site of action of the dopaminergic regulation has been suggested to be the pituitary. Massara et al. (924) compared the ability of domperidone and sulpiride to increase plasma TSH in a cross-over study in hypothyroid women and found almost superimposable responses. Surprisingly enough, however, there was no intraindividual correlation between the domperidone-induced TSH and prolactin rises. Hence, if the mechanism of inhibition by dopamine is assumed to be the same for thyrotrophs and lactotrophs, the simultaneous presence of other contributing factors must be assumed. The most obvious of these is the feedback system at the pituitary level by thyroid hormones.

It is remarkable that, during a 48-h infusion of dopamine in healthy male subjects, both TSH and prolactin decreased to levels that were maintained for the whole period, and a significant and immediate rebound increase in both hormones occurred after the cessation of infusion (711). This could be partly due to the decrease of endogenous dopamine release from the median eminence.

4. Concurrency of TSH and prolactin secretion. Assuming that both TSH and prolactin are inhibited by dopamine released into the hypophyseal portal circulation from the median eminence, one would expect a certain degree of concurrent behavior in these two hormones. This is even more likely given the fact that TRH can release both of these hormones (see below). It is obvious that they both are regulated by separate factors as well. Hence, the pattern would not be identical. However, artificial intervention, e.g., by drugs, may be expected to have some effects that would either strengthen or dispute the idea of shared regulation by dopamine.

Foord et al. (448) investigated dispersed rat pituitary cells in vitro and used both dopaminergic agonists and dopamine receptor blocking drugs to compare the secretion of TSH and prolactin. Maximal inhibition of TSH secretion by dopamine and apomorphine was about 30%, while prolactin secretion was inhibited by about 60%. Bromocriptine was a more efficacious inhibitor, but again the inhibition of TSH was lower. The EC50, however, was about the same for both hormones. Also the rank order of antagonists in reversing dopamine-induced inhibition of release was the same for both hormones, though higher concentrations were needed to reverse TSH. No important differences were found to indicate different sensitivity of receptors, but the thyrotroph was functionally less sensitive to the dopaminergic regulation (448). These findings suggest that dopamine inhibits both prolactin and TSH secretion through similar receptors in the pituitary, but the functional range of reactivity is smaller for TSH.

Fukuda et al. (463) investigated the pituitary-thyroid axis during gestation and lactation in rats. Several interesting findings were noted. Thyroxine (T_4) levels, and to a lesser extent 3,5,3′-triiodothyronine (T_3) levels, decreased during gestation, but this was not fully accompanied by respective TSH increases. TSH levels were significantly higher in lactating than in nonlactating, pup-deprived rats. Neither plasma prolactin nor pituitary portal dopamine was assayed, but it is plausible that high dopamine concentration in pituitary portal vessels attenuates the TSH increase during gestation (85). During lactation, the dopamine concentration in pituitary portal blood is low (84), which may contribute to the slightly elevated TSH levels.

Suckling causes an acute increase in TSH, in addition to prolactin release (111, 163).

In one study, acute exposure to cold caused an increase in plasma prolactin in addition to TSH (672). The time pattern was different for the effects on the two hormones, the prolactin increase being faster and more short-lived. Since the TSH cold response seems to be mainly regulated by noradrenergic systems which may release TRH (see section III A), it is difficult to know how (or whether) the dopaminergic system contributes to these increases. It would be important to obtain information of the synchronization of inhibitory and stimulatory effects.

There are many studies illustrating the interplay of TSH and prolactin secretion in humans. The TSH release induced by dopamine receptor blocking drugs is greater in patients with hyperprolactinemia due to prolactinomas than in normoprolactinemic subjects (926, 1146, 1235, 1238). This suggests that dopamine secretion into the pituitary portal circulation is increased in adenomatous hyperprolactinemia, and blockade in these conditions causes an exaggerated response. Conversely, in females with physiological puerperal hyperprolactinemia, the response to dopamine receptor blockade was delayed and decreased as compared to controls (1196). This suggests that the dopaminergic tone was reduced and contributed less to controlling the TSH level in puerperium than in controls. Hence, a reduced dopamine level could be interpreted as one of the reasons for high prolactin, and TSH had by other regulatory means adapted to the lowered dopamine balance.

Spitz et al. (1333) recently reported an interesting division of hyperprolactinemic patients into two groups. In one group, metoclopramide increased TSH but not

prolactin, whereas, in the other group as well as in the controls, metoclopramide increased prolactin but not TSH. It is possible that the first group represents patients with prolactinomas and increased dopamine secretion, whereas in the other case, a hypothalamic rather than hypophyseal cause for hyperprolactinemia should be searched for.

Nomifensine, a dopamine uptake inhibitor, was recently shown to decrease TSH in normal subjects but not in hyperprolactinemic patients (516). Also, TRH-induced increase of TSH was attenuated in normal subjects but not significantly in hyperprolactinemic patients (516). Nomifensine did not change prolactin secretion either in normal or hyperprolactinemic subjects, which is in line with the hypothesis that TIDA neurons are not sensitive to uptake inhibitors (see section II A 7). Further studies are needed to determine whether the differences between prolactin and TSH responses indicate dopaminergic inhibition of TSH release at some other level than the pituitary.

The sex difference in the effect of dopamine receptor blocking drugs on TSH favors the suggestion that pituitary portal dopamine affects TSH secreting cells. The dopamine levels in portal blood are much lower in male than in female rats (85). It is unanimously agreed that dopamine receptor blocking drugs increase TSH more in female than in male subjects (1237, 1238), and in several studies, a significant increase in euthyroid subjects was noted in females only (78, 926). Also, in hypothyroidism, the response is greater in females (700), although in this study the males exhibited higher basal TSH levels than the females, and the groups may not be comparable (see above). Unfortunately, there are no controlled animal studies to elucidate the sex difference in TSH responses, and there is no direct information on the sex difference in pituitary portal dopamine concentrations in humans.

Just as hyperprolactinemia alters TSH regulation, abnormalities in the hypothalamo-pituitary-thyroid axis may affect prolactin secretion. This has not been the subject of any extensive investigation. Feek et al. (423) studied the effects of metoclopramide or L-dopa on prolactin and TSH secretion in hypothyroid patients. The prolactin response to metoclopramide was significantly greater in patients with subclinical hypothyroidism than in patients with overt hypothyroidism. On the other hand, serum prolactin levels decreased after L-dopa in patients with overt hypothyroidism but not in patients with subclinical hypothyroidism. These data agree with the concept of decreasing dopaminergic inhibition of TSH with increasing severity of hypothyroidism and also with the concept that this inhibition is due to an influence of dopamine in the portal circulation of both TSH and prolactin.

Sawers et al. (1228) studied the prolactin response to metoclopramide in euthyroid and hyperthyroid subjects. Hyperthyroid patients responded less than the euthyroid controls. This puzzled the authors, since they had assumed a higher dopaminergic tone in hyperthyroid patients and, hence, expected a greater response. However, as stated before, metoclopramide is a competitive inhibitor, and their data are completely in line with inhibition being weaker if the agonist concentration is higher. A higher degree of inhibition is supported by the negligible prolactin-releasing effect of TRH in the hyperthyroid patients (1228), although not all studies agree (1354).

These considerations emphasize the well-established pharmacological principle that inhibition by a certain dose of antagonist is greatest within a limited range of agonist level, since at very low agonist concentrations, it does not matter physiologically whether a small effect is blocked or not, and at very high agonist concentrations, a competitive antagonist fails to inhibit unless its dose is also increased. Since the agonist or inhibitor concentrations at the receptor site are not usually known, endocrinological studies utilizing receptor antagonists are bound to involve uncertainties. This is especially true in human studies, since the doses cannot be increased at will. Dose-response studies, whenever feasible, would probably better clarify the situation.

In this context, it is also of interest that the TSH response to TRH was enhanced after domperidone and pimozide (316) or sulpiride (1510). Dopamine infusions and bromocriptine, on the other hand, blunt TSH responses to TRH (99, 164, 928, 1498, 1502). This emphasizes the interaction of TRH and dopamine at the pituitary level. The effect of dopamine to reduce prolactin response to TRH is also well documented (164, 1059). Thus, these two hormones behave similarly in this respect, and dopamine and TRH play mutually antagonistic roles in their regulation. A clear dissociation was, however, found by Nilsson and coworkers (1058). Apomorphine blunted the TRH-induced prolactin response but left the TSH response undisturbed.

The acute effect of dopamine receptor antagonists is at variance with the clinically known suppression of the TRH-induced TSH response during long-term neuroleptic treatment (797, 1503). Since both dopamine receptor blocking drugs and L-dopa cause this inhibition of TSH response (797), the mode of action cannot be directly derived from their pharmacological effects but may be a result of a complicated feedback balance.

The clinical discrepancy that neuroleptic drugs increase prolactin levels (299) but not TSH levels (260, 797) may be explained by the powerful feedback systems that rapidly restore TSH levels. There can be no such correction of prolactin levels, if prolactin is assumed to be mainly under inhibitory hypothalamic regulation maintained by dopamine and if no direct feedback regulation of prolactin secretion at the pituitary level is assumed to exist.

In Parkinson's disease, the activity of the nigrostriatal dopaminergic system is decreased, and L-dopa or L-dopa

plus a peripheral decarboxylase inhibitor alleviate the symptoms. In a recent study, no significant differences were found in basal TSH or prolactin levels of controls, untreated Parkinsonian patients, and L-dopa plus carbidopa or L-dopa plus benzerazide-treated patients with the exception of a slight increase of TSH in the L-dopa plus benzerazide group (917). However, TRH-induced releases of both TSH and prolactin were lower in untreated patients than in controls, suggesting an increased dopaminergic tonus. The responses were virtually normalized by L-dopa plus benzerazide and to some extent increased by L-dopa plus carbidopa. The interpretation of the results is somewhat complicated by the uncertainty of whether dopamine is increased in TIDA neurons due to L-dopa or decreased due to the peripheral decarboxylase inhibitor. It is plausible, however, that it is decreased and more so in the benzerazide group (1123, 1214); hence, the TRH responses are augmented. It is noteworthy in this context that the responses of TSH and prolactin are virtually identical in both cases, which favors the same sort of dopaminergic inhibition for both, i.e., release of dopamine from TIDA neurons and effects at the pituitary level.

C. Growth Hormone (GH)

1. General considerations. Secretion of growth hormone (GH) from anterior pituitary somatotrophs is under the dual control of the stimulatory GH-releasing hormone (GRH) and the inhibitory factor, somatostatin. The former has only recently been isolated and characterized (562, 1331). Several other hypothalamic peptides such as TRH, luteinizing hormone-releasing hormone (LRH), and opioid peptides can release GH, at least under certain conditions. Other less well-documented peptide stimulators of GH release include vasopressin, α-melanocyte-stimulating hormone (α-MSH), substance P, and neurotensin (for review, cf. refs. 912 and 913).

One of the physiological roles of GH is to promote protein synthesis at the expense of carbohydrates and fat. Somatomedins (insulin-like growth factors), notably somatomedin C, are presumed mediators of some of the growth-promoting actions of GH (299). Presently, it is not possible to state whether somatomedins function as conventional peripheral hormones or not. It is established, however, that somatomedin C stimulates somatostatin release (93) and inhibits GH secretion (5). GH causes impairment of glucose utilization, and it can be considered a physiological antagonist of insulin. GH stimulation is conventionally tested by insulin-, glucagon-, or arginine-induced hypoglycemia. Another well-known stimulator of GH release is sleep. Consequently, several sedative drugs and anesthetics elevate GH levels. L-Dopa, which also elevates GH levels in man within a few minutes, is used as a pharmacological tool in clinical practice. Another stimulant of GH release in man is physical exercise (285).

The tonic effect of the hypothalamus on GH is stimulatory, since disruption of the connections between the hypothalamus and the anterior pituitary gland decreases GH secretion (517). Hypothalamic destruction causes growth retardation and defective responses to hypoglycemia, arginine, and L-dopa in man. Similarly, sleep-associated GH release can be abolished by hypothalamic lesions. In the squirrel monkey, even small lesions in the median eminence and the basal hypothalamus block insulin- and stress-induced GH release (915). More specific studies have shown that lesions in the ventromedial nucleus result in growth failure and falls in plasma and anterior pituitary GH levels. The episodic pulses of GH secretion are also abolished (458). Electrical stimulation of the ventromedial nucleus and arcuate nucleus elicits a prompt GH secretion both in baboons (1396) and in pentobarbital anaesthetized rats (459, 910), which further supports the crucial role of this area in the mediation of GH release.

Based on bioassays, the amount of GRH in the ventromedial nucleus also seems substantial (782). A detailed topography of the neurons containing GRH-like immunoreactivity has recently been demonstrated in both the monkey (114a) and the rat (114b, 1303b). There are many immunoreactive cell bodies in the arcuate and ventromedial nuclei. Presumably, neurons of both cell groups send fibers to the median eminence (114a, 1303b). The hippocampus and amygdala are other loci the electric stimulation of which can release GH. As a matter of fact, there seems to be a catecholaminergic link between the limbic system and the hypothalamus (910–912).

The inhibitory activity of GH secretion appears to arise from the preoptic area the stimulation of which causes a decrease of GH release (914). Somatostatin cell bodies are now known to locate in the preoptic but also in periventricular nuclei of the rostral part of the third ventricle. About 90% of the somatostatin content of the median eminence is derived from cells in the periventricular nucleus (for review, cf. 1078).

The physiological significance of somatostatin in the regulation of GH secretion is undisputable. Passive immunization of the animals with somatostatin antiserum elevates basal GH levels and partially reverses the stress-induced decrease in GH (1388). However, the histamine-induced GH fall was not antagonized by passive immunization (1050). Exogenous somatostatin inhibits the GH release caused by various stimuli such as electrical stimulation, hypoglycemia, sleep, and hypnotics (915). Moreover, somatostatin effectively suppresses elevated plasma GH levels in acromegaly and diabetes (915). Somatostatin reduces the episodic pulsatile GH secretion (129). In the dog, the secretory bursts may be initiated by somatostatin withdrawal (265). This episodic secretion, also seen with thyrotropin and prolactin (1487), is easily identified in freely moving, nonstressed rats. Surges of GH secretion occur at intervals of 3 to 4 h. The surges are associated with the light-dark cycle. Sleep, exercise,

age, and several other factors may have some influence on these surges, but basically they are considered to be spontaneous. The bursts do not have any clear relationship to variations in glucose, amino acids, corticosterone, prolactin, TSH, or insulin. It seems that the timing of the secretory peaks is regulated by a rhythm intrinsic to the central nervous system which is cued by the light-dark cycle but not by the sleep-wake rhythm (1485). Monoclonal antibodies against purified GRH were found to abolish the GH pulses (1470).

2. Dopaminergic regulation of growth hormone secretion in humans with normal growth. It is well established that dopaminergic stimulation enhances basal GH secretion. This has been demonstrated with various dopamine (DA) agonists such as apomorphine (125, 138, 794, 1029, 1056, 1209, 1309), bromocriptine (15, 68, 69, 175, 334), and piribedil (350, 1393). The action of apomorphine was effectively reversed by pimozide but not by methysergide or hyperglycemia (795, 796, 1056). Even amitriptyline was able to decrease the action of apomorphine (125). Bromocriptine has, however, also yielded negative results in euthyroid and hypothyroid subjects (431). Even buspirone elevated basal GH levels, evidently due to its DA agonist activity in man (958).

The results with DA infusions vary, but most studies favor GH stimulation (68, 69, 164, 174, 826, 880). The action of DA was antagonized by metoclopramide (68, 69), but there are also negative results (1066). The stimulatory action of DA infusion was significantly potentiated during late alcohol withdrawal and restored again by domperidone (44). The action of DA must be outside the brain, since DA does not penetrate the blood-brain barrier, but paradoxically DA infusions are particularly effective in diabetic patients whose blood-brain barrier is weak (864). In vitro studies suggest that DA inhibits anterior pituitary somatotrophs; thus, the median eminence may be the locus of DA's stimulatory action. In sharp contrast to the above reports (68, 69, 164, 174, 826, 880), Bansal and coworkers (69) have found that both DA and bromocriptine decrease the elevated GH levels induced by hypoglycemia. This action was effectively antagonized by metoclopramide. This unexpected finding corroborates an earlier result (826). Several other GH bursts can, however, be eliminated by DA antagonists (see below).

The action of L-dopa is usually stimulatory in normal subjects (15, 118, 123, 324, 389, 788, 920, 984, 1209, 1299, 1506), but the stimulation is considered to be caused mainly by noradrenaline and possibly to a lesser extent by dopamine (see below). In one study, i.v. L-dopa did not alter GH levels (86). The L-dopa response is attenuated in blind (82) and extremely obese persons (168a, 291, 817). Several studies have shown that L-dopa usually retains its GH-elevating activity in Parkinson's disease in spite of chronic L-dopa treatment (123, 823, 1086), but there are some exceptions (889, 1455). Similarly, the GH-enhancing effects of bromocriptine (1086, 1285), apomorphine (139), and L-dopa (202) are retained at least to some extent in Parkinson's disease.

The action of various DA agonists in elevating GH has also been studied in patients with diseases other than Parkinsonism. In schizophrenic patients, apomorphine was either equally effective (959, 1028) or less effective (413) than in the healthy controls. However, the GH response to apomorphine may correlate with psychosis ratings (959). The results in Huntington's disease have been variable as well. In one study, the GH response to bromocriptine was low (211), while in another the GH response to apomorphine, L-dopa, and bromocriptine was actually enhanced (1019). A few studies have been done in cirrhotic patients. In one study, the basal GH levels were high, and hence L-dopa did not elevate GH levels at all (120), while in another study, nomifensine, an inhibitor of DA neuronal uptake, was superactive (996). The latter finding was thought to be caused by an impaired metabolism of nomifensine. Finally, nomifensine has retained its GH-elevating activity in hyperprolactinemic patients (292).

Amphetamine (814) and methylamphetamine (1166) augment GH secretion, but both noradrenaline and DA may be responsible for this action. Amantadine is ineffective alone but seems to potentiate the action of L-dopa on GH (203, 927). Finally, pyridoxine, a coenzyme of L-dopa decarboxylase, raises GH levels (327) while it seems to antagonize the action of L-dopa (324, 983).

Further evidence that DA stimulates GH secretion in man has been obtained from studies with DA antagonists. Sulpiride (587) and chlorpromazine (1289) decreased basal GH levels. This action of sulpiride was not confirmed (14). Flufenazine (210) attenuated hypoglycemia-induced GH rise. Pimozide abolished the actions of L-dopa (849) and apomorphine (795, 796). Pimozide also reduced arginine- and exercise-induced GH bursts, although it did not affect episodic GH secretion (1271). In further studies, pimozide partially reversed the GH-elevating actions of glucagon (571) and diazepam (761), while in other studies, it did not counteract the effect of L-dopa (920), glugacon, or insulin (921). Metoclopramide was similarly active in single administration studies (694, 1320), but not in chronic use (566) or during pregnancy, when estrogen levels are high (1194). Sleep-associated GH elevations were strongly decreased by several antipsychotics in one study (569) but not in another (1360). Finally, reserpine inhibited the action of insulin-induced hypoglycemia on GH (201, 1014).

3. Humans with acromegaly or growth retardation. In acromegaly, L-dopa and dopaminergic agonists usually inhibit GH secretion (174, 175, 240, 329, 335, 384, 633, 802, 847, 848, 1066, 1094, 1107, 1218, 1391, 1465, 1466). However, the GH response to metyrapone is enhanced by L-dopa in acromegalic patients (640). Bromocriptine treatment did not change the qualitative characteristics

of GH (620). Similarly, GH binding properties to human lymphocytes remained unchanged (620). It is also noteworthy that only 50 to 60% of acromegalic patients respond to bromocriptine therapy (cf. 1014, 1018). Pergolide treatment has yielded positive results even less often (512, 737). Although bromocriptine causes a clinical improvement in most acromegalic patients, normalization of elevated GH or somatomedin C occurs only in the minority. Hence, some of the beneficial effects of bromocriptine may be independent of GH secretion or somatomedin generation (179, 620, 844, 1009, 1140, 1282, 1326, 1465, 1466, 1476). Reduction in tumor size occurs in only a minority of patients (1074).

The inhibition of GH secretion by bromocriptine was reversed after removal of the GH-secreting adenoma (418, 639, 1367), suggesting acromegaly to be characterized by abnormalities in pituitary somatotrophs and their receptors. These receptors (DA, CRH, or other) seem to lose their selectivity in this disease, responding to several types of stimuli (see below). It is noteworthy that [^{3}H] domperidone does not bind specifically to GH-adenoma cells (132) and that these cells also lack [^{3}H] spiperone-binding sites (274).

The paradoxical inhibitory action of DA agonists in acromegaly is attributable to the somatotrophic cells themselves. DA infusions have proved effective in lowering GH levels in acromegalic patients responding to bromocriptine (925, 1066, 1436). DA also inhibits the anomalous GH response to TRH (174). Not all dopaminergic compounds are effective in decreasing GH levels in acromegaly. It has become evident that only the DA agonists with direct action on the postsynaptic DA receptors are active, i.e., DA itself, L-dopa, apomorphine, bromocriptine, piribedil, and lisuride. The compounds with indirect or presynaptic activity, such as amphetamine, amantadine, and nomifensine, are ineffective (cf. 1018). Acromegalic patients exhibit a good, homogenous GH response to bromocriptine and TRH, an agent which acts at the anterior pituitary level (848). Selective adenomectomy abolishes or reverses both responses (418, 639). A nearly complete dissociation of the action elicited by dopaminergic drugs and by insulin hypoglycemia, glucose, or arginine infusion, mediated through the central nervous system (848), provides another piece of indirect evidence. Although dopaminergic compounds generally act at the brain level, it is well documented that DA can inhibit the secretion of another pituitary hormone, prolactin, in the anterior pituitary gland (see section II A), and L-dopa decreases GH levels in rats bearing transplanted GH-secreting tumors with no connections to the central nervous system (890).

Finally, as discussed below (see section II C 6), DA has a direct inhibitory action on GH release from both normal and acromegalic anterior pituitaries or pituitary cells in vitro, although the DA receptors on GH adenoma cells seem to differ from those on prolactin-secreting cells (132, 274). It seems that, in normal persons, the dual action of DA is directed so that the hypothalamic stimulatory component overcomes the peripheral negative signals. In acromegaly, however, the hypothalamic drive is more or less disconnected; hence, the inhibitory action at the anterior pituitary level prevails.

The pathophysiology of acromegaly is still unknown, and the disease is extremely variable and nonhomogenous, a characteristic feature being its paradoxical responses to various stimuli (770). Glucose loading, for instance, causes a GH increase, not decrease (284, 285). Tater and coworkers (1378) reported quite peculiar results with GH responses to L-dopa and domperidone. Acromegalic patients responded similarly to a dopamine agonist and to an antagonist: four of eight had raised GH levels, and three of eight had decreased levels after both treatments. A further example is the GH-enhancing activity of TRH and even LRH in acromegalic patients (254, 417, 653, 1253), although these releasing hormones do not affect GH release in normal subjects (31, 1253). It should be pointed out, however, that a pathological GH response to TRH is known to occur in a variety of other conditions, e.g., anorexia nervosa (583, 881), mental depression (127, 880), renal failure (524), primary hypothyroidism (584), and severe liver disease (1083). In these conditions, GH responds normally to dopamine agonists. In the first few weeks of life (263), DA agonists actually decrease GH levels just as they do in acromegaly. This time of life is characterized by rather high GH levels in plasma. In adults, however, DA and bromocriptine unexpectedly decreased the hypoglycemia-induced GH levels in one study (69).

The variability of the GH responses in acromegaly has given support to the view that at least some patients may have a primary hypothalamic disorder which chronically elevates GH secretion through enhanced release of GRH (284). This theory was supported by observation that circulating GRH levels are elevated in acromegalic patients (567, 568). The results of these early and indirect assays have not been confirmed to the best of our knowledge.

Based on the above theory, the inhibition of the hypothalamic stimulatory transmitters, noradrenaline and DA, plus stimulation of the β-adrenergic activity have subsequently been tried in the treatment of acromegaly. The results with phenothiazines have, however, been disappointing (368). Recently, Arosio et al. (61) reported that sulpiride actually elevated GH levels in the presence of DA. Phentolamine plus isoprenaline infusions have suppressed GH levels in some but not all patients, and the effect was very short-lived (285, 1030). Hence, this approach does not seem clinically useful.

On the whole, these clinical results do not convincingly support the importance of the central origin of acromegaly, but they rather encourage the view that the basic failure is in the somatotrophic cells.

An opposite condition to acromegaly, growth hormone deficiency, may also be characterized by abnormal response of GH to metoclopramide: GH levels are increased (256). However, a majority of the patients with retarded growth respond to L-dopa with enhanced GH secretion (441, 1174), while cortisol and TSH remain unchanged (598).

4. Other primates, cats, and dogs. The fundamental difference between GH regulation in humans and in other species is the difficulty in demonstrating a significant GH stimulation by the dopaminergic system in the latter. In monkeys, apomorphine enhanced GH secretion only at emetic doses (212), or it was ineffective (666). The stimulatory action of amphetamine was not blocked by pimozide, suggesting a stimulatory role for noradrenaline rather than for DA (904). In cats, apomorphine was quite ineffective as well (1212).

Ganong and coworkers have thoroughly studied the role of DA in both pentobarbital-anesthetized and unanesthetized dogs. L-Dopa was effective as a stimulant of GH, more effective in conscious than anesthetized dogs. The action was, however, antagonized neither by pimozide nor by butaclamol (634, 866–868, 1474). Similar results with L-dopa and amine antagonists were obtained in monkeys (666) and cats (1212). In anesthetized dogs, apomorphine had no effect; in conscious dogs, it elevated GH concentrations but only at emetic doses, suggesting that release was a function of severe discomfort and stress (634). Some have found that intracerebroventricular DA and apomorphine were not able to modify GH levels in anesthetized dogs (866–868), while in an early study, Toivola and Gale (1395) found a decrease of GH secretion.

L-Dopa elevated basal GH levels in conscious trained dogs, evidently by a central action of its metabolites (585). In another study, both apomorphine and nomifensine enhanced GH secretion in conscious dogs. The action of nomifensine was attenuated by phentolamine, atropine, and haloperidol but not by domperidone (188).

Lovinger et al. (867) found i.v. DA infusions not to affect GH stimulation in anesthetized dogs. This disagrees with the results of Takahashi et al. (1370), who reported a marked GH increase after 1 mg of DA per kg i.v. to trained, conscious, fasted dogs. This action was not abolished by fusaric acid, which inhibits the conversion of DA to noradrenaline. Also, in baboons (649, 1339), DA infusions elevated GH levels. Similar findings have sometimes been observed in man (see above). As a whole, these results favor a dopaminergic stimulatory action outside the blood-brain barrier.

Studies with DA antagonists are few. In an early study by Meyer and Knobil (975), the stimulatory action of chlorpromazine in dogs was interpreted to be caused by a nonspecific noxious stimulus.

5. Other species. Numerous studies have been performed in rats. Unfortunately, rat GH is easily depressed by various types of stress (261, 1254) as well as by urethane and ether anaesthesia (cf. 915, 1018). Hence, the variability of the results is enormous and exact conclusions are hard to reach.

It seems, however, that in conscious, cannulated rats, intracerebroventricular infusion of DA itself (1016, 1020, 1445) and a DA agonist, piribedil (1446), causes a clear-cut stimulation of GH secretion. In urethane-anesthetized rats, however, DA infusions into the brain ventricles caused GH release to decrease (259). Kakucska and Makara (696) found GH stimulation by DA only in rats with anterolateral cuts which excluded somatostatin effects (among others). Several studies have further shown that peripheral apomorphine (1011, 1446), piribedil (1011, 1446), and even a high dose of DA itself (1446) enhanced basal GH levels. In another study, DA (100 mg/kg) decreased GH levels in 10-day-old rats (1389). It should be pointed out that, at high doses, both apomorphine and piribedil lost their stimulatory activity (1011). L-Dopa restored low GH levels in old rats to the levels found in young adults (1310). Otherwise, L-dopa and sometimes even apomorphine reduced GH levels (751) or had no effect (116, 720). In anesthetized rats, peripheral apomorphine was inactive (116).

The results with DA antagonists have also been rather conflicting. In a few cases, GH stimulation by pimozide and chlorpromazine has been observed (232, 718, 720). However, several reports have given more expected results with haloperidol (390, 1011) and perphenazine (1165). Moreover, the stimulatory action of DA was successfully antagonized by haloperidol (1011). Finally, the studies with 6-hydroxydopamine lesions and α-methyl-*p*-tyrosine treatment have given evidence of a positive relationship between the hypothalamic DA concentrations and the diurnal GH rhythm (1014, 1298). Episodic GH bursts were attenuated by α-methyl-*p*-tyrosine, reserpine, and haloperidol but not by *p*-chlorophenylalanine (390). The secretory bursts returned to normal in 24 h, although the brain amine levels remained rather low.

DA seems to be a stimulatory transmitter in GH regulation in rats, but its effect is certainly less significant than that of noradrenaline. No such conclusion is possible in sheep (301, 382).

6. In vitro studies. As far as we know, there are ten in vitro studies testing direct anterior pituitary actions of DA. It seems quite clear that, in human anterior pituitary cell cultures, DA has a negative action on basal GH release, since both DA and various dopaminergic agonists have yielded uniform results in six independent studies (9, 132, 655, 822, 1323, 1371). The inhibition was rather potent with an IC50 of 5×10^{-8} M for bromocriptine (9) and 10^{-7} M (655) or 5×10^{-8} M (132) for DA. There was no great difference between normal and adenomatous tissues. Prolactin secretion was inhibited even at lower

concentrations than GH secretion in both types of tissues (132, 655, 1371).

In sheep pituitaries, only GRH-stimulated (818) or TRH-stimulated GH release was inhibited by DA, not basal release (1366). In cultured ovine pituitary cells, the GH elevation caused by synthetic GRH was inhibited by DA (IC50 10^{-7} M), while cyclic adenosine monophosphate (cAMP) levels were decreased (818). Two studies on pigeon (575, 577) and two on rat anterior pituitaries in vitro (104, 873) have given negative results. In two other studies with rat anterior pituitary preparations, bromocriptine (278) or a high concentration of DA (1147) decreased GH liberation. However, in the presence of hypothalamic fragments, DA stimulated GH release from pigeon anterior pituitaries (575, 577) and rat pituitary halves (1147).

These results show clearly that in man DA has a direct inhibitory action on anterior pituitary somatotrophs, resembling that regulating prolactin release. However, prolactin release can be inhibited at much lower concentrations than GH release. Finally, there seems to be no important difference between normal and adenomatous pituitaries. In the rat, dopamine's action is unclear. The lack of effect of DA on somatotrophs is supported by the report of Abe and coworkers (3). L-Dopa infusions into the pituitary portal vessels did not affect GH release. DA antagonists also were inactive.

7. Regulation of somatostatin secretion. a. RELEASE OF SOMATOSTATIN FROM MEDIAN EMINENCE INTO THE HYPOPHYSEAL PORTAL BLOOD. Highly sophisticated techniques of collecting blood samples from hypophyseal portal vessels have made it possible to monitor somatostatin release in vivo. The acidified plasma must be extracted with acetone before radioimmunoassay. These studies have shown that the elevation of somatostatin levels in portal plasma by urethane anesthesia is severalfold that produced by pentobarbital anesthesia (229). It is noteworthy that somatostatin concentrations in peripheral plasma were similar in both groups, while GH levels were much decreased under urethane anesthesia. Urethane also abolished episodic GH secretion (720) as well as the rise of GH otherwise induced by electric stimulation (915).

It may be of physiological significance that intracerebroventricular glucose injection diminishes (2) and glucagon elevates somatostatin levels in portal plasma (228).

In a series of experiments, Chihara et al. (228) tested the effect of i.c.v. neurotransmitters on somatostatin liberation into portal vessels. Dopamine, noradrenaline, and acetylcholine increased somatostatin secretion. The effect of dopamine was the most potent and prolonged. Somatostatin release was slightly inhibited by 5-HT. A short feedback seems also to be working here, since i.c.v. GH infusion increases somatostatin release into the portal system (230). Andersson et al. (39, 42) also concluded that somatostatin release was enhanced after i.v. GH, but their statement about the decreased dopamine activity in the median eminence does not fit into the results given above (228).

b. SOMATOSTATIN RELEASE FROM NEURAL TISSUES IN VITRO. Subcellular mapping has revealed that somatostatin is mostly located in synaptosomes isolated from the median eminence, hypothalamus, or extrahypothalamic brain tissue (406, 628, 1346). Like conventional neurotransmitters, somatostatin can be released from synaptosomes and brain slices or fragments by K^+ in the presence of Ca^{2+} (65, 91, 92, 660, 825, 1089, 1460). Somatostatin can also be released from brain slices by electric stimulation in the presence of Ca^{2+} (825, 1089). There also seems to be a short-loop, positive feedback in this system, since addition of GH increases somatostatin liberation from hypothalamic fragments (1287). TSH did not have a similar effect.

Release experiments with various neurotransmitters have given fairly, but not completely, uniform results which agree to some extent with those obtained by somatostatin analysis in portal plasma. Bennett et al. (88) found opposite results in somatostatin release from the synaptosomes isolated from brain cortex (enhanced somatostatin release) and from hypothalamus (decreased somatostatin release) by dopamine, noradrenaline, and 5-HT. Noradrenaline enhanced somatostatin release in brain slices prepared from amygdala or preoptic hypothalamus, while it was not active in slices from medial basal hypothalamus. The stimulatory effect was antagonized by propranolol in amygdala and by phentolamine in preoptic hypothalamus. DA, 5-HT, GABA, and morphine did not alter somatostatin release (407). Negro-Vilar et al. (1044) showed increased release of somatostatin by both noradrenaline and dopamine. These actions were antagonized by phentolamine and pimozide, respectively. In a further study (1460), dopamine enhanced somatostatin release from hypothalamic synaptosomes. As to other neurotransmitters, 5-HT and melatonin decreased somatostatin release from rat hypothalamus in vitro (1181), while GABA was inhibitory in both hypothalamic (486) and cortical cell cultures (1193). Bicuculline reversed the action of GABA only in hypothalamic cells. In the latter report, glutamine and aspartate stimulated somatostatin liberation, while a number of other amino acids were inactive. The action of acetylcholine (10^{-10} to 10^{-7} M) was clearly inhibitory in the rat hypothalamic segments in short-term tissue culture. A similar action was seen with neostigmine. Atropine, but not hexamethonium, attenuated the effect of acetylcholine, demonstrating the involvement of muscarinic receptors (1180). Completely opposite results were reported in dispersed fetal rat hypothalamic cells in monolayer culture (1103). Acetylcholine, oxotremorine, and carbacholine enhanced somatostatin liberation. This stimulation was prevented by atropine but not by hexamethonium. Surprisingly, 5-HT and GABA also blocked the stimu-

latory effect of carbacholine. The action of GABA was abolished by bicuculline and picrotoxin. GABAergic antagonists enhanced somatostatin release.

Finally, several peptides such as neurotensin (1, 1288) and substance P (1288) stimulated, while vasoactive intestinal peptide inhibited (407), somatostatin release from brain fragments in vitro. Opioid peptides or morphine did not affect basal somatostatin release from superfused medial basal hypothalamic slices, while K^+-stimulated (383) and cold-stimulated (995) somatostatin secretion was blocked by β-endorphin, leu-enkephalin, D-ala-met-enkephalinamide, and morphine. Their action was abolished by naloxone.

In the aminergic regulation of somatostatin, it may be concluded that dopamine and probably noradrenaline stimulate somatostatin release. The role of 5-HT may be inhibitory. Since somatostatin definitely has a general inhibitory action on the secretion of several anterior pituitary hormones, the interpretation of the net action of various aminergic agonists and antagonists is very complicated. However, the aminergic influences on somatostatin itself may help explain the varying results in literature of the actual net effect of each particular transmitter system.

D. Adrenocorticotrophic Hormone (ACTH)

1. General aspects. ACTH secretion is affected by several interfering factors, which renders it difficult to get a uniform picture of the regulation system. (*a*). There is a strong and evidently multiphasic negative feedback by the peripheral hormones, corticosteroids (729). Under basal nonstress conditions, this constantly stabilizes the rate of ACTH secretion. There is some evidence against a significant ultrashort feedback mechanism for ACTH in rats (424) and man (453). (*b*) Many external stimuli, notably stress factors, may modify nearly any part of the feedback loop (148, 730, 923). (*c*) There is a definite circadian or diurnal rhythm in the secretion of corticosteroids, evidently in the release of ACTH as well (23), also in vitro (701). (*d*) ACTH, like several other anterior pituitary hormones, is secreted periodically in short pulses (484). (*e*) It must be pointed out that there have been a number of analytical problems with biosassays as well as with chemical extractions and assays of ACTH and corticotropin releasing hormone (CRH). Most of the data available so far have been derived by either indirect methods or bioassays, not by radioimmunoassays. Although the chemical structure of CRH has finally been determined, and the peptide has been synthetized (540, 642, 1189, 1414), not much has been done to establish directly the factors governing its release in vitro. A significant production of CRH involved in both the circadian rhythm and ether stress responsiveness clearly originates from the area of paraventricular nucleus (662, 883, 888). It is apparent, however, that the rhythm and response to stress can be dissociated (1164).

This review focuses on the aminergic regulation of ACTH secretion at the pituitary level or at a higher level. The emphasis is on studies where well-defined designs aim at solving isolated problems of the different parts of the brain-hypothalamus-anterior-pituitary-adrenal cortex axis.

2. Role of dopaminergic system in ACTH regulation. The functional role of dopamine in the regulation of the CRH-ACTH-corticosteroid axis, if any, is minor. There are, however, some findings which appear to suggest dopaminergic stimulatory or inhibitory activity, and they need to be discussed shortly.

In conscious dogs, Holland and co-workers (634) found that L-dopa slightly increased the secretion of ACTH, while clonidine did not. Pretreatment with pimozide reversed this modest stimulation to a clear inhibition. Fairly high doses of apomorphine caused a rise of ACTH secretion. These results disagree with the findings by the same group in pentobarbital-anesthetized dogs. Evidently, anesthesia is a complicating and masking factor which should be taken into account when interpreting the results. In sheep, metoclopramide elevated cortisol as well as other adrenocortical hormones. This action was blocked by dexamethasone and was interpreted to be caused by a nonspecific stress effect (1318). In the rat, the results are conflicting. Both high doses of DA given s.c. (734) and DA antagonists like haloperidol i.p. (514) and dehydrobenzperidol (305) have increased corticosterone or ACTH secretion. Smythe and Bradshaw (1304) have shown that α-methyl-*p*-tyrosine may also enhance ACTH levels, but this action was evidently not caused by DA depletion alone, since a similar depletion by monoiodotyrosine did not alter ACTH levels at all.

Bromocriptine, a dopamine receptor agonist, decreased ACTH secretion in a number of patients with Cushing's disease (799). Metoclopramide increased cortisol secretion in children with short stature, while GH levels did not change (648). Considering the ability of dopamine to decrease ACTH release from human pituitary adenoma cells in culture, this finding is in agreement with in vitro data (9, 654). Evidently, pituitary adenoma cells react abnormally in a variety of diseases such as Cushing's disease and acromegaly (see growth hormone and dopamine, section II C).

On the other hand, bromocriptine was completely ineffective in normal subjects (799) as were other dopaminergic stimulants in monkeys, dogs, and rats (see above; 489). There is further evidence strongly in favor of dopamine having no role in normal ACTH secretion. Dopamine and apomorphine injections into the third ventricle were ineffective (212, 488, 489). In vitro studies in hypothalamic preparations demonstrated no role for dopamine in CRH release either (151, 681). Finally, stress did not alter the dopamine turnover rate in the hypothalamus (473).

3. In vitro studies on the release of ACTH from anterior pituitary preparations. In their large review in 1978

(1474), Weiner and Ganong were able to conclude that catecholamines do not function as ACTH-releasing factors. There are, however, several thorough in vitro studies where relatively small concentrations of neurotransmitters have caused alterations in ACTH release. The question of the relevant concentrations is important because, for example, high concentrations of DA and noradrenaline are known to destroy ACTH (765, 1268, 1423).

The results with normal rat anterior pituitaries are confusing. In two studies, a number of neurotransmitters were completely ineffective (133, 592, 593), while in other studies, 5-HT (1332) and dopamine (1151) enhanced ACTH release. The most recent studies do not lessen the controversy, since there seems to occur some kind of regulatory adaptation in tumor cell lines (1172, 1173), possibly within a few days, even in cell cultures of normal pituitary cells (507–509). In the latter cultures, α-adrenergic activation undoubtedly enchanced ACTH release (507–509). In the mouse AtT-20 tumor cell cultures, on the other hand, β-adrenergic activation was reported to stimulate cAMP formation and ACTH release (1172, 1173). Forskolin-stimulated ACTH secretion was inhibited by carbacholine through activation of nicotinic acetylcholine receptors (610).

In human pituitary adenoma preparations, the situation is different. Five studies deny the role of 5-HT (9, 513, 654, 810, 922), while dopamine was inhibitory at 10^{-5} M (9). Inversely, Gillies et al. (513) found dopamine to be inactive up to 10^{-5}M.

While the physiological significance is not known, ACTH can also be released from the neurointermediate lobe of the rat. In the intermediate lobe, 5-HT has to some extent stimulated ACTH release in several studies (446, 763, 800) but not in all (1156). The results with catecholamines have been quite varying, but dopamine and β-adrenergic activation have sometimes been stimulatory (133, 446, 763, 1394, 1474). In another study (1394), dopamine was inhibitory and inactive in a third study (1157). Hence, the behavior of the intermediate lobe differs from both normal and adenomatous anterior pituitary preparations.

It can be concluded that, in Cushing's disease, like in acromegaly, the dopamine receptors in the adenomatous anterior pituitary cells seem to be important in inhibiting ACTH as well as GH release, respectively.

III. Noradrenergic and Adrenergic Regulation of Pituitary Hormone Secretion

A. Thyrotropin

Noradrenaline is probably the most extensively documented transmitter in the regulation of rat TSH. It has been known for a long time that reserpine, α-methyldopa, and other drugs that decrease adrenergic tone also reduce thyroid secretion (cf. 361). However, direct peripheral effects on the thyroid rendered it impossible to draw final conclusions as to the role of noradrenaline in the central regulation of TSH secretion before radioimmunoassay for TSH was available. Before that, studies utilizing the appearance of colloid droplets in the thyroid after cold exposure suggested that drugs inhibiting adrenergic neurotransmission also inhibit the release of TSH (757).

Cold response has been utilized in many studies on the rat. Acute exposure to cold leads to a stimulation of thyroid secretion in many species (140, 141, 695, 740, 757, 949), obviously via an increase in TSH secretion (612, 659, 672, 895, 1220, 1408). Within 30 min, there is a 2 to 10-fold increase in immunoassayable TSH (900, 1407, 1408).

The existence of a noradrenergic link in the cold response is practically certain. The cold response is inhibited by disulfiram, reserpine, and phentolamine (1408), i.e., inhibition of noradrenaline synthesis or storage, or α-receptor blockade. This finding has been replicated and extended in many studies, and the compounds tested include high doses of α-methyl-*p*-tyrosine, diethyldithiocarbamate, or fusarate (45, 46, 778, 901, 993, 998, 1070, 1407), all inhibitors of noradrenaline synthesis, and 6-hydroxydopamine which produces degeneration of noradrenergic nerve endings (1239). Phentolamine and phenoxybenzamine, but not propranolol, also inhibited the cold response (778, 901, 1407); hence, α- rather than β-receptors seem to be involved.

It seems that the cold response is mediated through TRH release (55, 606, 747, 1361). It is plausible that noradrenaline releases TRH and that its site of action is in the brain, possibly in the hypothalamus. The hypothalamic site of action is supported by a synergistic effect of 6-hydroxydopamine injected into the third ventricle and a small dose of α-methyl-*p*-tyrosine after 30 days (1239, 1263).

In several cases, inhibition of noradrenergic transmission was also seen to decrease basal TSH levels (46, 778, 1407, 1408). This is best demonstrated by Krulich et al. (778). Hence, it is not only the cold response which is regulated by noradrenergic systems; the basal level seems to be maintained by noradrenaline as well.

However, there are also some conspicuous discrepancies. Phenoxybenzamine decreased TSH levels (778) and blunted the cold response (778, 901, 1407), but a low dose of phentolamine rather tended to increase TSH, even though at a higher dose it tended to decrease the basal level and significantly blunted the cold response (1407). Adrenergic agonists have yielded controversial results. Krulich et al. (778) observed that clonidine increased TSH levels when used at doses with mainly α_1-receptor activity. However, another α-agonist, methoxamine, which does not readily cross the blood-brain barrier, decreased TSH levels (778). Also, high doses of clonidine and noradrenaline have been reported to decrease TSH cold response (901). Dihydroxyphenylserine, which is assumed to circumvent tyrosine hydroxylase and to en-

hance noradrenaline synthesis even when the normal route of synthesis is inhibited, consistently potentiated rather than antagonized the TSH-lowering effects of α-methyl-*p*-tyrosine or fusarate (897, 1070), and, when given alone, blunted the cold response (901). L-Dopa has been reported to abolish the α-methyl-*p*-tyrosine-induced decrease (1070), but this, too, has been disputed (897). The time course of the inhibition of TSH response did not follow the noradrenaline levels but returned to normal when noradrenaline was still low (897).

The discrepancies above cannot be explained by only assuming a central stimulatory role for noradrenaline and an inhibitory role for dopamine. Most of them can, however, be explained by assuming an additional inhibitory effect for noradrenaline outside the blood-brain barrier (897, 901). There is no firm evidence of the precise site, but since infusions of noradrenaline directly into the median eminence decreased both basal TSH and cold response, this could be the site of action (897).

Also, i.c.v. injections of noradrenaline and adrenergic agonists have yielded contradictory results. Clonidine i.c.v. has been found to increase TSH (46, 1239) and so has noradrenaline (632, 1447), but also no change or a decrease has been reported (897).

Krulich et al. (780) recently suggested that the inhibitory component of noradrenergic influence on TSH secretion is mediated by α_1-receptors, since a decrease followed i.c.v. administration of methoxamine and phenylephrine, both α_1-agonists, and was partially reversed by prazosin, an α_1-antagonist. The stimulatory input on TSH was attributed to α_2-receptors, since small doses of clonidine induced large secretory responses which could be inhibited by yohimbine, an α_2-antagonist. We agree with this interpretation in part. In our conditions, noradrenaline i.v., i.c.v., and infused into the median eminence, decreased cold response (897, 901), and after administration to the median eminence, basal TSH level also decreased (987). In our experiments, large doses of clonidine, mainly affecting α_1-receptors, consistently inhibited TSH secretion (901). Since other pressor substances also inhibited TSH secretion, Krulich et al. (780) favor the view that the inhibition is secondary to an increase in blood pressure. This we find hard to accept, since small amounts of noradrenaline into the median eminence also inhibited TSH secretion (897), and we have not found any correlation with blood pressure (894). In fact, the results of Krulich et al. (780) with clonidine derivatives not penetrating the blood-brain barrier agree with a site of action in the median eminence. The existence of α_1- and α_2-receptors in steer stalk-median eminence has been demonstrated by binding studies (222).

The role of α_2-receptors in the stimulatory input is difficult to prove or disprove, since the pharmacological tools are not very specific. This suggestion is complicated by the present concept that a great number of α_2-receptors in the CNS are presynaptic, inhibitory autoreceptors. However, inhibition by i.v. yohimbine of the TSH release, which was induced by a small dose of clonidine, as well as potentiation of clonidine-induced release by prazosin and phenoxybenzamine (780) suggest that clonidine stimulates TSH release through α_2-receptors and inhibits through α_1-receptors. In any case, it seems to be very important to study different concentrations and also the time course of the effects of the pharmacological tools used, since most of them are not specific, at least not at high concentrations.

Because it was suspected that peripheral negative feedback may prevent the measurable increase of TSH, experiments were also performed on rats made slightly hypothyroid with propylthiouracil (899). In these animals, clonidine increased TSH levels even at a dose as high as 1 mg/kg i.p. Other compounds confirmed the noradrenergic stimulation and dopaminergic inhibition found in intact rats (899). Hence, variable levels of peripheral feedback may explain at least part of the discrepant results obtained with adrenergic agonists.

Several groups have tried to delineate the possible area of hypothalamus which would control TRH secretion in the rat (18, 605a, 605b, 1105). The crucial site seems to be the paraventricular nucleus. Lesions of this nucleus abolished the TSH response to cold and also to small doses of clonidine (656). Antiserum to TRH abolished the clonidine-induced increase of TSH (656). Hence, it appears likely that cold response is mediated by noradrenaline to TRH neurons located in the paraventricular nucleus. These findings are supported by immunohistochemical studies in which a dense population of TRH cell bodies was found in the paraventricular nucleus (824). The axons of these neurons may terminate in the median eminence (605a, b).

After completion of the major part of this manuscript, a series of interesting turnover studies was published (32a). TSH given to rats 2 h before decapitation caused a significant increase of catecholamine turnover (measured by α-methyl-*p*-tyrosine induced disappearance of catecholamine fluorescence) in medial and lateral palisade zones of the median eminence, and a significant decrease of noradrenaline turnover within parvo- and magnocellular parts of the paraventricular nucleus (32d). TRH i.v. caused similar changes in catecholamine turnover: increase in medial and lateral palisade zones and decrease in the paraventricular nucleus. These results suggest the existence of ultrashort and short feedback mechanisms for TRH and TSH and agree with the concepts that noradrenaline neurons stimulate TRH nerve cell bodies located in paraventricular nucleus, and that dopamine neurons inhibit TRH nerve endings in the median eminence. Results in thyroidectomized animals also support these concepts: thyroidectomy decreased dopamine activity in the median eminence and increased noradrenaline activity in the paraventricular nucleus; these effects were reversed by restitution ther-

apy with T_3 or T_4 (32b). Since no synaptic structures are apparent in the medial and lateral palisade zones, dopamine terminals may establish axo-axonic contacts with TRH nerve terminals. Hence, the hypothetical catecholamine regulatory system can be depicted as in fig. 4.

Noradrenaline regulation of TSH secretion at the anterior pituitary level does not seem likely since the TSH response to exogenous TRH was not modified by drugs affecting adrenergic activity (780, 897, 901, 1407). Recently, however, adrenaline and noradrenaline were suggested to exert a stimulation and a synergistic effect with TRH in anterior pituitary cells (367, 739, 1104). The relevance of these findings remains to be established.

There is little information on the role of adrenergic control of TSH secretion in humans. However, fusaric acid, a dopamine-β-hydroxylase inhibitor, was demonstrated quite early to suppress the elevated TSH levels in hypothyroidism (1505). This clearly suggests the participation of noradrenaline in the secretion of TSH. In one study, phentolamine but not propranolol decreased TSH levels, which would support the role of α-adrenergic stimulation (1513). Cold environment was shown to simultaneously increase circulating noradrenaline and serum TSH levels (1067). Noradrenaline was suggested to have been responsible for the observed TSH rise via TRH release, or by direct stimulation, or by both mechanisms (1067). TRH-stimulated TSH release has been studied, and drugs affecting α- or β-receptors have been found without effect (105, 408, 1057, 1197, 1494). However, this obviously gives no information as to what takes place above the TRH level in the central nervous system.

In conclusion, it is virtually certain that noradrenaline participates in the stimulation of TSH, associated with a cold exposure, and it probably also has a positive effect on basal TSH secretion in rats. There is some evidence that this effect is mediated through central α_2-receptors. Noradrenaline also inhibits TSH secretion, probably outside the blood-brain barrier; possibly through α_1-receptors. The exact mechanisms and interrelations of these effects are not clear. There is little information on noradrenaline in the regulation of human TSH, but the existence of an α-adrenergic stimulation is possible.

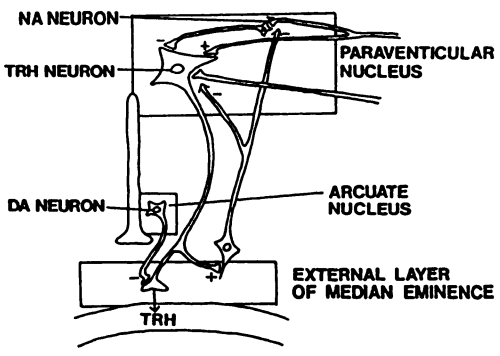

FIG. 4. Hypothetical interplay of dopamine and noradrenaline neurons in the regulation of TRH release. Modified after Andersson (32a).

B. Prolactin

Early studies indicated that noradrenaline can directly inhibit prolactin release from the anterior pituitary in vitro and also when injected into a portal vessel (cf. 1474). However, the doses of noradrenaline required are considerably higher than those of dopamine (624) and higher than noradrenaline levels found in hypophyseal portal blood (85, 267). This, together with the reversal of inhibition by both α- and β-adrenergic receptor antagonists (624), suggests a nonspecific effect.

On the other hand, when dopamine receptors were blocked with domperidone, a stimulating effect of noradrenaline, adrenaline, or isoprenaline was seen (351). Receptor antagonist studies suggested that this is a β_2-receptor stimulatory effect (64). Since adrenaline concentrations are higher in hypophyseal portal plasma than in peripheral plasma, this catecholamine may have a physiological role in the control of prolactin release (676). The latter alternative also introduces the most intriguing possibility of a hypothalamic-adrenal interaction in the regulation of pituitary hormone secretion, since about one-half of the adrenaline appeared to be of adrenal origin, and the other half of central origin (676). In humans, however, adrenaline infusion was reported to decrease prolactin levels (1054).

There is also early information of possible central facilitatory effect of adrenergic systems in the regulation of prolactin secretion, notably periodic secretion related to estrogens and stress (cf. 1474). During the past few years, this concept has gained some support. It was reported that elevated plasma prolactin levels in proestrous and ovariectomized steroid-primed rats coincide with increased noradrenaline turnover in the medial basal hypothalamus (637). Inhibition of dopamine-β-hydroxylase resulted in supression of prolactin release in ovariectomized rats (1043) but not in male rats (1387). Clonidine increased prolactin secretion (388, 819, 1387), and α-receptor antagonists have yielded contradictory results (819, 915, 1347, 1484).

Injections of catecholamines, notably adrenaline, into medial basal hypothalamus stimulated prolactin secretion (302). On the other hand, 6-hydroxydopamine was not found to have much effect on the basal hormone profile (302, 432). These findings could be interpreted as supporting the stimulatory role of adrenaline in prolactin secretion, but participation in the regulation of basal levels does not seem likely.

There is also indirect histochemical evidence that noradrenaline may stimulate prolactin release. Single doses of nicotine increased noradrenaline turnover in several hypothalamic areas and increased prolactin secretion (32c). Also, toluene exposure increased noradrenaline turnover and enhanced prolactin secretion (40).

In human studies, adrenaline infusion was shown to decrease the prolactin levels raised by α-methyl-*p*-tyrosine pretreatment (1054). Synthetic α-adrenergic com-

pounds had little effect per os (811). Tolamolol but not propranolol dose dependently increased plasma prolactin (297, 1229). The reason for the effect of tolamolol is not known, but it may be associated with other than β-receptor blocking effects (1229). Also, i.v. labetalol, an α-and β-receptor blocking drug, increased prolactin (72).

Finally, it should be noted that TRH releases prolactin, and TRH seems to be released by noradrenaline (see above). The role of TRH has been advocated in suckling-induced prolactin release (542). This has also been disputed on the basis that TSH does not markedly increase during suckling (1187). This objection may not hold, however, since prolactin release may be controlled by a delicate interplay of at least 5-HT and dopamine in addition to TRH (416, 1121), and they are not synergistic for TSH.

C. Growth Hormone

1. Primates and dogs. Most of the stimuli that cause GH release in primates and dogs appear to act through central α-adrenergic receptors. Hence, in man, GH secretion induced by insulin (108, 1376), arginine (154), vasopressin (607), and even L-dopa (705) can be prevented by phentolamine and in some cases also by reserpine pretreatment (for review, cf. 1018). Finally, yohimbine, an α_2-antagonist, antagonized the GH response to insulin-induced hypoglycemia (1376). A notable exception to this rule may be the nocturnal GH elevation (870). Moreover, chronic treatment of hypertensive patients with α-methyl-dopa did not affect the result of the insulin test (1357).

Studies with adrenergic agonists have also shown that intracerebral (1396, 1397) or a high i.v. dose of noradrenaline and adrenaline (1370) as well as dihydroxyphenylserine (DOPS), a direct precursor of noradrenaline (212), increased GH levels. Negative results have been obtained with peripheral administration of catecholamines (867). In some studies, i.v. adrenaline enhanced GH levels in man only when given with propranolol (109, 1060). A similar combination treatment increased the GH responses to hypoglycemia and arginine (1087). However, clonidine, an α_2-adrenergic agonist, is a good stimulant of GH secretion in primates including man and dogs as well as a number of other species (13, 194, 212, 269, 409–411, 489, 634, 762, 780, 796, 867, 868, 1211, 1212). The action of clonidine was blunted in elderly subjects (510), in children with constitutional growth delay (1112), in depressed subjects (1297), in regular beer-drinkers, and in women during their menses (934). Another agonist, methoxamine, was also stimulatory in man (650). This α_1-agonist decreased GH levels in dogs and prevented the stimulatory action of arginine and an α_2-agonist clonidine when given i.v. (206). Methoxamine did not alter GRH-induced GH secretion (206). Since the stimulatory action of L-dopa has been antagonized rather with α-blockers than DA blockers, even this action may be caused by noradrenergic activation (634, 705, 867). Also, amitriptyline (1269) and desipramine (789), two inhibitors of noradrenaline uptake, increase GH levels in man. Furthermore, amphetamine can enhance GH secretion in both man (814) and monkey (904).

Since a great number of α_2-receptors are presynaptic inhibitory autoreceptors, the action of clonidine has recently been interpreted to decrease and not to increase the noradrenergic tone, at least at doses specific for presynaptic action (207). In recent studies, the action of clonidine was effectively antagonized by mianserin, a presynaptic α_2-receptor antagonist, but not by 5-HT or H_1-receptor antagonists (207). Also, the pharmacological denervation of dopamine or noradrenaline nerve terminals by reserpine (208) or 6-OH-dopamine given intracerebroventricularly to dogs (1340) abolished the action of clonidine. Finally, it was demonstrated that supersensitivity of GH elevating activity to clonidine develops during repeated administration of yohimbine, another α_2-receptor antagonist (207). Hence, the hypothalamic noradrenergic activity would be inhibitory rather than stimulatory as far as GH release is concerned.

On the other hand, in primates and dogs, a β-adrenergic blocker, propranolol, enhances both basal (25, 867, 1477, 1499) and stimulated GH secretion (108, 1166). Analogously, practolol has been shown to elevate exercise-induced GH secretion in man (1357). However, single doses of tolamolol and practolol were not effective in elevating basal GH levels (1229). The positive evidence of the direct inhibitory activity of β-adrenergic stimulants is lacking.

It is noteworthy that electrical stimulation of ascending noradrenergic pathways (subceruleus and ventral noradrenergic bundle) of dogs failed to increase GH secretion, while ACTH secretion was elevated (1205). The authors conclude that evidently separate noradrenergic systems are regulating GH and ACTH release. According to the present interpretation of the role of α_2-adrenergic receptors, inhibition of GH would have been a more appropriate result than stimulation (207).

2. Other species. Certain species-related differences exist in the GH response to pharmacological stimuli. There is no perfect animal model that precisely mimics GH control in man. Anesthesia has been a complicating factor especially in studies with rats, since various hypnotics may have opposite actions on GH (e.g., urethane causes depression, pentobarbital elevation).

Since GH is under a dual hypothalamic control by stimulating (GRH) and inhibiting (somatostatin) factors originating from separate hypothalamic loci (see above), it has been possible to exclude the actions of somatostatin by anterolateral hypothalamic deafferentation. Kakucska and Makara (696) studied the regulation of GRH alone under such conditions. Although they unfortunately used anaesthetized animals in their acute experiments, the results are interesting. Noradrenaline (2.5 μg/rat) and dopamine (5 μg/rat) given into the third

ventricle enhanced GH secretion only in deafferentiated animals. Evidently catecholamines stimulated both GRH and somatostatin release in intact animals, but only GRH release occurred in operated rats. This gives us additional information about the possible aminergic regulation of somatostatin (see above). Miki and coworkers (978) have obtained a direct proof that α_2-adrenergic activation by clonidine is mediated through GRH release, since the anti-GRH antiserum abolished the stimulatory action of clonidine in the rat.

The anatomical dualism in the control of GH secretion has been confirmed by the electrical stimulation of the ventromedial nuclei (the principal site of GRH cell bodies, see above) of the rats bearing various hypothalamic lesions (717). The same group has also found that the urethane-anesthetized rats have very low GH levels which can be restored by hypothalamic deafferentation or anterior hypothalamic cuts (719). Urethane may therefore be assumed to enhance somatostatin release.

Gammahydroxybutyrate anesthesia elevated GH levels in rats (117). Clonidine further stimulated GH release, while inhibition of the synthesis of catecholamines decreased GH (116, 1257). Under similar conditions, β-adrenergic agonists were found to inhibit GH secretion (115, 1257). These results are in good agreement with those obtained with primates and dogs.

Studies on conscious rats have given valuable information about the role of biogenic amines in episodic GH release. Depletion of hypothalamic catecholamines by 6-OH-dopamine given into the third ventricle abolished GH secretion for 7 days. On the eighth day, secretion was restored in spite of the low catecholamine concentrations. Then, the GH secretion was easily depressed by phentolamine but not by butaclamol (1484). It is noteworthy that i.v. 6-OH-dopamine increased GH levels, but it did not alter stress-induced GH decrease (303). Secretion bursts can be eliminated by α-methyl-*p*-tyrosine, diethyldithiocarbamate bis(4-methyl-1-homopiperazinyl-thiocarbonyl)disulfide (FLA-63), as well as by reserpine. In these animals, episodic GH secretion can be restored by clonidine but not by apomorphine (388, 390, 915, 1043, 1385, 1387). Similarly, phenoxybenzamine (915) and yohimbine (58) can suppress episodic GH secretion, while dopamine antagonists have minimal effects. Even the action of morphine seems to be mediated via noradrenergic (748) or adrenergic (1386) pathways. These results show quite clearly that α-adrenergic mechanisms have a facilitatory action on episodic GH secretion, possibly through α_2-receptors. This noradrenergic mechanism matures only after puberty (785). Whether this phenomenon can be generalized to include primates or not, remains to be seen. Furthermore, 5-HT may contribute to some extent to episodic GH release (see below).

Recently, the use of specific inhibitors of phenylethanolamine-N-methyltransferase (PNMT) has made it possible to study directly the role of adrenergic activity on the GH secretion. A selective adrenaline depletion eliminated episodic GH secretion in the rat (1386). The GH elevating activity of morphine (but not that of clonidine) was also attenuated by inhibiting the synthesis of adrenaline (1386). In another study, only the centrally active inhibitors of PNMT were effective as inhibitors of GH secretion bursts, while the peripheral inhibitor was not (283).

Krulich and coworkers (780) have carried out an impressive series of experiments on conscious unrestrained rats with chronic cannulation for blood sampling. They found striking similarities in the adrenergic regulation of GH and TSH secretion. Intraventricular α_1-receptor agonists, methoxamine and phenylephrine, induced a rapid and dose-related lowering of the plasma levels of both GH and TSH. This action was effectively antagonized by prazosin, an α_1-receptor antagonist. On the other hand, small doses of α_2-agonist clonidine induced a significant rise in both hormones. The rise was inhibited by yohimbine, an α_2-receptor antagonist. The action of clonidine on GH was not antagonized by inhibition of noradrenaline synthesis, while the effect on TSH was reversed. Prazosin also partially decreased the action of clonidine on GH. Yohimbine depressed both hormones, but prazosin was ineffective. As a whole, these results show that activation of the postsynaptic α_1-adrenoceptors causes attenuation of both GH and TSH secretion, whereas the α_2-adrenoceptors mediate the stimulatory action of both hormones. The authors have interpreted the differences between the regulation of GH and TSH as follows: the α_2-action on GH is mediated mainly through postsynaptic mechanisms, and that of TSH, through presynaptic mechanisms. In the case of GH, the activation of postsynaptic receptors inevitably causes activation of noradrenergic neurons. As far as TSH is concerned, it remains to be established whether the activation of the presynaptic receptors actually means an inhibition of the noradrenergic tone (cf. clonidine and GH in dogs; 207).

Ishikawa and coworkers (657) observed that, after α-methyl-*p*-tyrosine pretreatment, intracerebral clonidine was able to enhance GH levels only when given into preoptic or anterior hypothalamic regions but not when given into periventricular or ventromedial regions. They conclude that the section of somatostatin is reduced rather than that of GRH enhanced. Miki and coworkers (978), however, obtained an opposite result. The stimulating action of clonidine was abolished by passive immunization by anti-GRH antiserum. Hence, GRH seemed to mediate the action of clonidine.

Using injections into the third ventricle, Vijayan and coworkers (1447) found that both noradrenaline and adrenaline produced a significant rise of GH secretion in ovariectomized rats. Similar results have been obtained after infusion of noradrenaline into the lateral ventricles

of rats (1016). Isoprenaline has been shown to reduce and beta-blockers to enhance GH levels after intracerebroventricular administration into conscious ovariectomized rats (644). When studying the GH response to exogenous GRH, it was found that the GH elevation was affected neither by lesions in the ventromedial or arcuate regions nor by α-methyl-*p*-tyrosine treatment, but that reserpine blocked the GH response to GRH, presumably by stimulating somatostatin secretion (1469). In freely moving rabbits, phenoxybenzamine evidently decreased GRH release and enhanced somatostatin liberation. Propranolol, on the other hand, decreased somatostatin release. These results support the α-adrenergic stimulation and β-adrenergic inhibition of GH secretion (233).

In birds and sheep, the situation is reversed. In domestic fowl, i.v. adrenaline decreased TRH-induced GH release (1231). In a comprehensive study on young domestic fowl, Buonomo and coworkers (159) obtained evidence of a dual action of catecholamines in the control of GH secretion. The stimulatory component seems to be acting at the hypothalamic level, being possibly adrenergic rather than noradrenergic. The inhibitory component is acting outside the brain and may be beta-adrenergic and adrenergic rather than noradrenergic.

In immature cockerels, i.v. adrenaline, noradrenaline, and isoprenaline depressed GH secretion, while phentolamine and propranolol had a stimulating effect on GH (590). In sheep, however, catecholamines did not have any effect on GH secretion when given into the lateral ventricle (382). However, i.v. adrenaline infusions definitely decreased basal and arginine-stimulated GH secretion in the sheep. The action of adrenaline was counteracted by an acute (613) or chronic treatment (614) with phentolamine but not with propranolol.

3. In vitro experiments. Studies with isolated anterior pituitaries or isolated cells have yielded rather conflicting results. Noradrenaline but not adrenaline inhibited GH and prolactin release from cultured normal anterior pituitary cells isolated from human gland (1371).

Noradrenaline had no effect on basal GH secretion but inhibited the TRH-stimulated GH release in isolated sheep pituitaries (1366). In the dispersed rat anterior pituitary cells, both adrenaline and isoprenaline (10^{-9} to 10^{-6} M) enhanced GH release. This action was effectively antagonized by propranolol but not by phentolamine. Dopamine and noradrenaline were ineffective. The secretory bursts lasted only a few minutes. Desensitization to the stimulatory action of isoprenaline developed in 20 min (1102). A similar stimulation was reported by slightly higher concentrations of adrenaline and isoprenaline (10 to 50 μg/ml) in whole rat anterior pituitaries (cf. 1488). However, in another similar study, an inhibition of GH release by adrenaline was observed (615), and in two other studies, no effect whatsoever was detected by adrenaline and noradrenaline (104, 874). Finally, caffeine enhanced GH release from dispersed rat anterior pituitary cells (622).

It is difficult to draw definite conclusions. It seems, however, quite possible that a short-lived β-adrenergic stimulation of GH release may occur at least in dispersed rat anterior pituitary cells. In human tissues, just an opposite effect, if anything, may occur.

D. ACTH

Noradrenergic activation has been reported to cause no change, inhibition or stimulation of ACTH secretion, or adrenocortical activation (for reviews, cf. 490, 1018, 1474). A contributing factor to this controversy is evidently the opposite actions of the noradrenergic system on ACTH release at different levels of the hypothalamo-anterior pituitary-adrenal cortex axis (cf. fig. 1). Another point of uncertainty arises from neglect of the usually opposite actions of presynaptic and postsynaptic receptors, which, however, can be activated (or inhibited) by the same compounds. It seems possible, however, to draw some conclusions on the basis of a great number of reports available on a variety of animal species, including some in vitro studies. The bulk of the available data suggest that the central action of noradrenaline is to reduce CRH and ACTH secretion, probably though α_1-type receptors and also through enhanced somatostatin release. However, stimulation of α_2-type receptors seems to cause increased ACTH release by decreasing the noradrenergic tone.

The net influence of the CNS on ACTH secretion is inhibitory, since complete hypothalamic deafferentation (572) or removal of the whole brain, leaving an isolated hypothalamus (393), was associated with elevated plasma corticosterone levels. There are many well and carefully conducted experiments which demonstrate that the activation of the noradrenergic nervous system mediates this inhibition, no matter whether a tonic ACTH release or an influence on various stimuli is concerned. We will consider the inhibitory activity of brain and hypothalamic noradrenergic neurons and then discuss the importance of and the explanations for the opposite results.

1. Inhibition of basal ACTH-corticosteroid secretion. As to tonic or basal CRH-ACTH-corticosteroid secretion, the easiest way of studying the possible inhibitory role of noradrenergic neurons is to abolish or decrease the brain neuronal activity by a variety of antagonists and monitor the expected increase in ACTH-corticosteroid secretion. Starting from the very basic situation, reserpine (cf. 1018) and its derivatives (1479) enhanced ACTH secretion, as analyzed by measuring plasma corticosteroids or by other indirect methods. The prerequisite was, however, that the brain noradrenaline and 5-HT levels were decreased by more than 50% (1479). Reserpine has been active in the rat, dog, monkey, and man (cf. 1018). The importance of the central depletion of catecholamines is supported by the fact that guanethidine, which

does not penetrate the blood-brain barrier, was not active in elevating corticosterone levels after systemic administration (395, 1249), while after intracerebroventricular injection, it depleted hypothalamic noradrenaline and dopamine and elevated plasma corticosterone levels (1245, 1249). Basal corticosterone levels were high in starved rats which exhibited decreased catecholamine turnover in the preoptic area in the median eminence (1113).

A further approach has been to use inhibitors of catecholamine synthesis, like α-methyl-*p*-tyrosine or a less irritating water-soluble methylester. Both peripheral administration (707, 943, 1243, 1248, 1304, 1305, 1417) and infusion into the third ventricle (1425) enhanced plasma corticosterone or ACTH levels in the rats, if only a large single dose was given. In chronic treatment, no effect was seen, although the brain catecholamine content remained low (707). α-Methyl-*p*-tyrosine did not elevate corticosterone in hypophysectomized rats, which excludes the direct adrenal action (1417). It was also demonstrated rather early that the inhibitory catecholamine is noradrenaline rather than dopamine. Scapagnini and coworkers showed that an inhibitor of dopamine-β-hydroxylase, which decreased only noradrenaline but not dopamine levels in the brain, caused adrenocortical activation (1246, 1249). Other evidence was obtained using α-methyl-*p*-tyrosine together with dihydroxyphenylserine, a direct precursor of noradrenaline. Now plasma corticosterone levels elevated by the synthesis inhibitor were rapidly depressed through the replenishment of noradrenaline stores by dihydroxyphenylserine (286, 1245).

Interesting new findings have been obtained with a specific inhibitor of phenylethanolamine-N-methyltransferase (8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine (LY134046)) which causes depletion of the hypothalamic adrenaline. After this kind of treatment, CRH staining was greatly increased in the rat paraventricular nucleus neurons. This has been regarded as an indication of the inhibitory activity of adrenergic activity on CRH and subsequently ACTH release (976).

Studies with a neurotoxic compound, 6-OH-dopamine, further support, although not quite unanimously, the importance of the central noradrenergic activity in the adrenocortical depression. In rats, 6-OH-dopamine lesion after intraventricular administration caused significant corticosterone secretion only shortly after the drug infusion. No effect was apparent after 3 to 30 days, although the hypothalamic noradrenaline levels remained low (287a, 708, 709, 787, 846, 1246). The same was true with reserpine (997). Ulrich and Yuwiler (1410) did not find 6-OH-dopamine to alter the circadian corticosterone rhythm. In the dog, Ganong et al. (495) reported a triphasic response to intraventricular 6-OH-dopamine. The initial inhibition of the adrenocortical function was evidently caused by the release of noradrenaline from injured neurons. The real toxic effect prevailed next, enhancing adrenocortical activity. Thereafter, the stimulation faded again, although the brain noradrenaline levels were still very low. This dissociation has been explained by a so-called functional or fully active catecholamine pool which recovers rapidly and is marginally capable of maintaining the normal adrenergic tonus. If this small functional pool is further disturbed by an inhibitor of catecholamine synthesis, even very small doses of α-methyl-*p*-tyrosine will eliminate the active pool, leading to adrenocortical activation (1246). Another, or more probably, an auxiliary explanation is the development of the supersensitivity of the surviving postsynaptic adrenergic receptors (1413).

The injection of 6-OH-dopamine into the medial forebrain bundle depleted the noradrenaline content of the mediobasal hypothalamus and elevated significantly the basal levels of serum ACTH and corticosterone in nonstressed rats (430). However, similar treatment inhibited the rise of both hormones normally following photic stimulation (430). Hence, the hypothalamic noradrenaline system has an inhibitory effect on basal ACTH and corticosterone secretion, but photic stimulation of both hormones is also mediated by the hypothalamic noradrenaline system.

Finally, the experiments with central adrenergic antagonists have to some extent added to our knowledge of the adrenergic inhibitory tone of ACTH secretion. Nonspecific blockers such as chlorpromazine (360, 882), perphenazine (218, 1303), and butyrophenones (305) generally activated the adrenal cortex in the rat. More specific α-blockers, phentolamine and phenoxybenzamine, were mostly similarly active both after systemic (561, 1247) and particularly after intracerebroventricular administration to rats or cats (395, 1347).

Usually it has not been possible to decrease basal ACTH or corticosterone levels by adrenergic agonists or precursors. Some of the few positive examples, however, include the ACTH-depressing activity of amphetamine in unstressed monkeys (904) and that of clonidine in retarded children (938) as well as the decrease of basal corticosterone levels after intracerebroventricular injection of various catecholamines (491, 1265) and clonidine (491). Methoxamine and phenylephrine were not effective (491). The lack of effect of agonists is evidently due to rather low basal corticoid secretion which is hard to decrease further. The inhibitory effect of clonidine in anesthetized dogs was interpreted to be postsynaptic, as judged from the results with the 6-hydroxydopamine lesions (1340). The stimulatory action to GH secretion was rather presynaptic.

2. Inhibition of stress-induced ACTH-corticosteroid secretion in animals. The possible inhibitory function of the central adrenergic activation can best be examined under stressful conditions when the hormone secretion is abundant. Hedge and coworkers (603) have found a

correlation between the catecholamine synthesis in the arcuate nucleus area and the ether-induced corticosterone secretion in the rat. Systemic L-dopa which reaches the brain (but not even high doses of either noradrenaline or dopamine) has been able to inhibit adrenocortical activation to laparotomy-induced stress in the rat (1421). Similarly, a central α_2-adrenergic agonist, clonidine, prevented corticosterone liberation due to laparotomy in dogs (492, 493). The actions of both L-dopa and clonidine were effectively counteracted by intracerebroventricular phenoxybenzamine but not by propranolol (492, 493). In anesthetized dogs, the effect of L-dopa was not abolished by dopamine receptor antagonists, pimozide and butaclamol (488, 489), which excluded the significance of dopamine in this animal model.

In conscious, nonstressed rats, intracerebroventricular clonidine (10 μg) increased corticosterone levels in serum. This action was prevented by yohimbine, an α_2-antagonist, but not by phenoxybenzamine. However, high intracerebroventricular doses of yohimbine and phenoxybenzamine also increased corticosterone secretion (1509). A depletion of brain catecholamines by α-methyl-*p*-tyrosine increased corticosterone levels, and now clonidine suppressed the rise. The action of clonidine was again antagonized in part by yohimbine (1509). These results are interpreted as follows. Under basal conditions, clonidine stimulates presynaptic α_2-receptors and inhibits noradrenaline release. Since the noradrenergic system is inhibitory regarding ACTH release, clonidine elevates ACTH and corticosterone secretion. After α-methyl-*p*-tyrosine, the action of clonidine is rather postsynaptic, mimicing the inhibitory noradrenaline.

Also, amphetamine, an indirectly acting sympathomimetic compound which releases both dopamine and noradrenaline, has prevented in part the increase of ACTH or corticosteroid discharge due to various stimuli in rats (101, 619), dogs (1426), and monkeys (1217, 1397). The action of amphetamine was not modified by pimozide (1217).

In some studies, the central adrenergic (and also serotoninergic) tone has been activated in mice and rats by using inhibitors of monoamine oxidase, e.g., iproniazide (354, 619), pheniprazine (619), and pargyline (101). These drugs were, as a rule, effective only in preventing the corticosterone response to rather mild stimuli like formalin stress or reserpine administration (354), but they also potentiated the inhibitory action of dexamethasone. This combined inhibition of the adrenocortical activation was rather well antagonized by phentolamine but not by β-blockers, suggesting the involvement of α-adrenergic pathways (1245, 1247, 1249).

On the basis of the reports referred to so far, it can be concluded that central, α-adrenergic but not β-adrenergic or dopaminergic, pathways inhibit ACTH-corticosteroid secretion caused by various stimuli in a variety of animal species. The central action is quite evident, since in the several studies cited above, the biogenic amines were inactive after systemic administration when they remained outside the brain. There are some studies where the compounds were given directly into the third ventricle, further supporting the inhibitory role of the central adrenergic system in the stressed dogs (1426) and in the reserpine-treated rats (574, 592, 907). A direct support for the significant inhibitory role of the noradrenaline released from the hypothalamic neurons has been derived from the stimulation studies in the dog (1204). Electric stimulation of the points near the ventral ascending noradrenergic bundle and the subceruleus area inhibited the ACTH response to surgical stress. Stimulations outside these loci were ineffective. In vitro studies on isolated hypothalamic preparations (see below) will further support this reasoning.

The action of noradrenaline on the anterior pituitary seems unlikely as well, since the peripheral amines which can easily reach the pituitary gland were not inhibitory. Neither do the results of the in vitro studies with anterior pituitary preparations support any significant inhibitory role for α-adrenergic activity at this level (153). See, however, section II D 3 for further discussion.

In primates, including man, the situation is evidently quite different, although rather few studies have been carried out. In conscious rhesus monkeys, neither dopaminergic nor adrenergic drugs given systemically altered resting plasma cortisol levels (212). Chronic L-dopa treatment of Parkinsonian patients somewhat decreased 17-hydroxycorticoid response to insulin-hypoglycemia (1454), while Hsu et al. (641) rather found enhancement by L-dopa of plasma ACTH response to metyrapone.

3. Apparent stimulation of the CRH-ACTH-adrenocortical axis by noradrenergic activation. It has been known for more than 30 yr that peripheral catecholamines and their precursors cause adrenocortical activation in situations where the corticosteroid output is low (cf. 1018 for review). This stimulation has been particularly well defined in rats (1191, 1290, 1305, 1311) but has been reported also in dogs (1018), sheep (682), and even in man (1034). Also, stimulation of the sympathetic ganglion may cause adrenocortical activation (22). Although this reaction is in most cases a typical stress response to noxious stimuli (cf. 710, 975), it is, however, quite certain that this action is centrally mediated. (*a*) Fuxe et al. (473) reported enhanced noradrenaline turnover in the hypothalamus during stress or after adrenalectomy. (*b*) Adrenaline does not liberate corticosteroids from the adrenal glands in vitro (600, 1452). Adrenaline also lost its activity in hypophysectomized animals (502). Neither is the adrenergic activation of the anterior pituitary probably on the basis of a number of studies (153, 521, 563, 591, 1423). Only a high dose of adrenaline (10 μg), but not noradrenaline, given into the anterior pituitary caused ACTH release (618). Proulx-Ferland and cowork-

ers (1139), however, reached an opposite conclusion using anterior pituitary cells in culture. They claim that there is a strong α_1-adrenergic stimulation of ACTH release in the rat anterior pituitary gland. In the mouse AtT-20 tumor cell lines, β-adrenergic activation increased ACTH release (1172, 1173). This controversy has been discussed in section II D 3. The most likely explanation might be the activation of the peripheral ascending adrenergic pathways which stimulate CRH release in the hypothalamus (see below). In fact, it has been demonstrated that there are indeed both stimulatory and inhibitory adrenergic pathways in the brain stem and hypothalamus affecting ACTH release (1462, 1463). In one study, i.v. isoprenaline injections elevated ACTH levels in intact rats but not in the rats with hypothalamic lesions (1139). Further, i.v. isoprenaline and adrenaline increased ACTH and corticosterone levels in rats. This action was not mediated through vasopressin (95). Shimizu (1290) has recently characterized the role of adrenergic activation in the secretion of bioassayable ACTH in rats. Both peripheral α_1- and α_2-adrenoceptors are involved in ACTH secretion induced by systemically injected adrenergic drugs in rats. However, intact neuronal pathways entering the mediobasal hypothalamus are necessary.

To our knowledge, there are very few studies where adrenergic antagonists have been used. In pigs, however, phentolamine did not affect the ACTH levels elevated by insulin, while GH levels were decreased (1328). Chronic reserpinization did not alter basal ACTH levels, while the stress-induced ACTH elevation was blocked (cf. 623, 1435). Depletion of the mediobasal hypothalamic noradrenaline by 6-OH-dopamine prevented the rise of ACTH and corticosterone normally induced by photic stimulation (430).

Direct evidence of the central stimulatory component of catecholamines has been obtained by injecting the amines directly into the brain. For example, injections of adrenaline, noradrenaline, and ephedrine into the posterior hypothalamus or ventral tegmentum increased corticosteroid secretion in cats (401). Noradrenaline implants at various sites of the diencephalon of cats were also stimulatory (774). Further, in guinea pigs, applications of noradrenaline into the posterior hypothalamus or rostral mid-brain resulted in enhanced corticosteroid output (1040, 1041). Both noradrenaline and dopamine injections into the lateral ventricle of anesthetized and conscious rats (6) seemed to liberate ACTH but did not further augment the effect of stress. It is quite interesting, indeed, that the mid-brain transection prevents the stimulatory action of noradrenaline given either systemically (918) or into the hypothalamus (1041). Some interesting results have been obtained in newborn rats. Subcutaneous noradrenaline (0.5 to 5 mg/kg) elicited a sharp rise in basal ACTH levels in serum, and even 0.2 mg/kg augmented the ACTH response to ether stress. The action of noradrenaline was significantly reduced by phenoxybenzamine but not by propranolol. The destruction of the arcuate nucleus did not affect basal or CRH-stimulated ACTH secretion (591).

These findings may be explained as follows. In order to be functional, the stimulatory impulses must be mediated through the peripheral pathways, even if the initial stimulus arises in the brain. In the latter case, the efferent pathways first convey the information to the spinal cord, and only then, the afferent pathways mediate the message back to the brain. It must be pointed out, however, that intracerebroventricular injection of saline or any biogenic amine may be stressful and therefore stimulates ACTH and corticosteroid secretion.

4. Effect of noradrenergic system on corticotrophic releasing hormone release from hypothalamic preparation in vitro. After it was discovered that isolated hypothalami or synaptosomes retain their viability in vitro and respond to hyperpolarizing stimuli by releasing CRH (124, 392), it has become possible to study directly the effect of various neurotransmitters on hypothalamus. Basal CRH release was not modified by noradrenaline in several studies (392, 617, 1377). A minor decrease was found by Buckingham and Hodges (151) and an increase by Fehm et al. (425). However, the CRH release induced by acetylcholine and 5-HT (151, 161, 617) as well as that induced by electric stimulation of the synaptosomes (392) have been antagonized by noradrenaline. However, phentolamine, but not haloperidol or propranolol, slightly decreased CRH release from the microdissected, electrically stimulated rat median eminences (90).

As a whole, these in vitro studies add to the confusion concerning the role of noradrenaline suggested by animal studies in vivo (see above). However, analogously to the in vivo results, the in vitro studies are also rather in favour of the inhibitory rather than stimulatory role of noradrenaline in CRH release.

IV. Serotonergic Systems in the Regulation of Pituitary Hormone Secretion

A. Stimulation of Prolactin Surges

Serotonergic modulation of prolactin secretion seems to supplement the dominating dopaminergic control. In mammals, the stimulatory role of 5-hydroxytryptamine (5-HT, serotonin) is well documented during lactation-induced prolactin surges. There is also evidence that afternoon surges of prolactin in rats correlate with 5-HT as is the case with prolactin during sleep in humans. The serotonergic tonus may be minimal in resting conditions (252, 775). Early literature has been well covered in previous reviews (1018, 1406, 1474). The problems in solving the role of this regulation were reviewed in a recent essay (1136).

1. Neurochemistry of serotonergic prolactin regulation. There is no firm evidence that 5-HT has any effect at the pituitary level (104, 332, 482, 699, 804, 869), although

in some studies an increase of prolactin secretion was seen after systemic injections of large doses of 5-HT (819, 821, 1110, 1341, 1471). Males are more sensitive to 5-HT-induced prolactin release than females (80). 5-HT even stimulated prolactin release from stalk-sectioned or ectopic pituitaries, at least in some conditions (1341, 1471).

Injection i.c.v. of 5-HT increased prolactin levels (699, 783, 1111). This increase was abolished by methysergide (783).

The increase is also achieved in various species, including man, with the 5-HT precursors, tryptophan and 5-hydroxytryptophan (5-HTP) (216, 220, 252, 511, 722, 804, 812, 816, 869, 872, 1012, 1061, 1493). Tryptophan-free diet rendered rats supersensitive to 5-HTP (244). As expected, tryptophan is less reliable in increasing prolactin than 5-HTP, and negative results have been obtained in both animal (869) and human studies (456, 1480). 5-HT receptor blocking drugs inhibit the 5-HTP-induced prolactin response (722, 821). The effect of 5-HTP was clearly potentiated by 5-HT uptake inhibitors such as fluoxetine (248, 252, 775, 821). Potentiation by neuronal uptake inhibitors renders it unlikely that 5-HT would stimulate lactotrophs directly after being released to portal veins.

Conversely, inhibition of 5-HT synthesis by *p*-chlorophenylalanine (pCPA) reduced baseline prolactin levels (12, 220, 511, 1496) and blocked the suckling-induced prolactin rise (756). These effects were not seen in all conditions (485, 756, 954).

Destruction of 5-HT nerve terminals with 5,7-dihydroxytryptamine caused a decrease in prolactin levels in male rats (511, 915, 1496). These animals are supersensitive to 5-HTP (130, 243). This potentiation was explained by receptor supersensitivity, since the effect of postsynaptic 5-HT agonists, too, was potentiated (786). Secretory episodes continue to occur after 5,7-dihydroxytryptamine treatment (1486). Since prolactin responses induced by fenfluramine are qualitatively normal a few days after 5,7-dihydroxytryptamine or *p*-chlorophenylalanine treatment (1486), it appears that the supersensitivity of 5-HT receptors is strong enough to help the remaining or regrowing terminals function.

In most studies on the role of serotonergic systems on prolactin secretion, 5-HT receptor agonists or antagonists have been used. These are by no means specific, which complicates the interpretation (1136). Compounds which exhibit dopamine receptor blocking properties in addition to serotonergic agonist or antagonistic properties involve special difficulties for interpretation.

Serotonergic agonists generally cause similar increases of prolactin secretion as 5-HT i.c.v. and 5-HTP i.v. These compounds include quipazine, both i.v. and i.c.v. (248, 451, 783, 821, 954, 1141, 1264), which mainly acts as a direct 5-HT receptor agonist; and fenfluramine, norfenfluramine, and *p*-chloroamphetamine (465, 466, 1141, 1264, 1415, 1486), which cause a rapid release of 5-HT. This release is prevented by *p*-chlorophenylalanine pretreatment. On the other hand, a presynaptic 5-HT agonist, 5-methoxy-N,N-dimethyltryptamine, inhibited prolactin release which depends on serotonergic neurotransmission (e.g., that induced by 5-HTP) (245). Several indoleamine derivatives have been reported to increase prolactin secretion possibly due to their postsynaptic serotonergic activity (147, 420, 699, 956, 957). In most cases, the prolactin release induced by serotonergic agonists could be blocked by 5-HT receptor blocking drugs.

In man, quipazine proved a very poor prolactin stimulator (1085).

Previous treatment with *p*-chlorophenylalanine slightly augmented the prolactin- releasing effect of quipazine, which may be a supersensitivity effect (783, 954). Similar potentiation of quipazine effect was seen after the destruction of 5-HT neurons with 5,7-dihydroxytryptamine (786). Another 5-HT receptor agonist, *m*-chlorophenylpiperazine, was similarly potentiated by 5,7-dihydroxytryptamine (1142).

Blockade of serotonergic neurotransmission has yielded conflicting data probably due to the nonspecificity of drugs used. Inhibition of 5-HT synthesis generally lowers prolactin and blocks prolactin surges (see above). Also, 5-HT receptor antagonists generally inhibit prolactin release, and the most extensively used compounds are methysergide and metergoline. They inhibited 5-HTP-induced prolactin release (248, 252), that induced by suckling (485, 756), estrogen injection (170), or stress (906) as well as the afternoon surge of prolactin in estrogen-treated, ovariectomized rats (1347).

Oral methysergide has also been demonstrated to inhibit sleep-induced prolactin release in man (964). Ergot alkaloids with 5-HT receptor blocking properties have also been shown to decrease prolactin in a variety of pathological conditions as well as in normal puerperium (241, 289, 328, 330, 419, 436, 438, 1075).

Paradoxically, 5-HT receptor antagonists have also been reported to cause prolactin release in some conditions (481, 483, 485, 820, 821, 962). These effects may be explained by the nonspecificity of these drugs. Evidence of the 5-HT receptor blocking activity of these drugs is mainly derived from experiments on peripheral tissues, while central activity has been questioned (570, 665). These compounds may also be mixed agonist-antagonists of dopamine receptors (270) and their effects on prolactin secretion partially unrelated to 5-HT receptor antagonism (98, 253, 777, 804–806). Indeed, Krulich et al. (781) demonstrated quite clearly in animals with lesions in the median eminence-mediobasal hypothalamus that metergoline and methysergide had direct profound effects on the pituitary, and these prolactin-decreasing effects could be completely prevented by spiroperidol or flupentixol. The dopaminergic potency was roughly equivalent to the dopamine receptor agonist, piribedil. However,

these compounds were also potent blockers of central serotonergic receptors as shown by the antagonism of prolactin releasing activity of 5-HTP or 5-HTP plus fluoxetine. Due to this lack of specificity, interpretation of the results with 5-HT receptor antagonists should be treated with great caution (781, 1136).

5-HT uptake inhibitors do not generally release prolactin when given alone (775, 821), but they potentiate the prolactin releasing effects of 5-HTP and tryptophan as well as stress-induced prolactin release (775). In clinical studies, there are also no effects on the resting level of prolactin in most cases (961, 1068, 1359). In a recent study, however, a single i.v. dose of clomipramine but not desipramine caused a significant but short-lived increase of prolactin in healthy male volunteers (789). Initially and perhaps in a somewhat stressful situation, 5-HT uptake inhibition will probably induce prolactin secretion.

2. Neuroanatomical considerations. The majority of central serotonergic neurons innervating different forebrain structures originate in the dorsal and median raphe nuclei in the hindbrain (290) and project rostrally innervating, for example, cortex, hippocampus, caudate-putamen, and hypothalamic areas (1079, 1416).

Several recent studies indicate that electrolytically, electrically, or chemically induced lesioning of dorsal and/or median raphe nuclei decreases basal prolactin secretion (12) or inhibits prolactin surges induced by fenfluramine (1143, 1264), *p*-chloroamphetamine (1415), or 5-HTP combined with 5-HT uptake inhibitors, fluoxetine, or citalopram (440). Stimulation of raphe nuclei was reported to cause a prolactin surge (12). There is some uncertainty about whether both nuclei are involved. Van de Kar and Bethea (1415) demonstrated that chemically induced lesions of the dorsal raphe nucleus prevented the prolactin response to *p*-chloroamphetamine, whereas lesions of the median raphe did not. In other studies, electrically induced lesions of the median raphe had an effect as well, but as pointed out by Fessler et al. (440), these lesions might also destroy fibers originating from the dorsal raphe nucleus. The latter authors also found a near correlation between the prolactin response and median eminence 5-HT. Barofsky and coworkers (76) found a decrement in suckling-induced prolactin release in dorsal raphe-lesioned animals. The influence of median raphe lesions may be indirect and due to behavioural factors (76).

Studies on raphe destruction are supported by another kind of lesioning experiment: transection of medial forebrain bundle, which conveys most of the 5-HT fibers to the diencephalon, blocks the suckling-induced prolactin response (62).

5-HT turnover studies of discrete hypothalamic nuclei may give some information on the important sites of serotonergic activity. As yet, only a few studies have been carried out, and changes in several hormones complicate the interpretation. Turnover changes in the median eminence and medial preoptic nucleus are of interest, however (675).

In another approach, electrical stimulation of medial basal hypothalamus was found to cause a prompt increase in serum prolactin in Rhesus-monkeys, and this response could be inhibited by methysergide as well as by bromocriptine (1090). Inhibition by bromocriptine obviously took place in the pituitary, and it also inhibited TRH-induced increase, whereas methysergide did not. This suggests a hypothalamic involvement of 5-HT in releasing prolactin.

3. Conclusions: existence of serotonergic prolactin stimulation and interactions with dopaminergic inhibition. Both the neurochemical and neuroanatomical evidence presented above clearly substantiates the hypothesis that 5-HT is a stimulatory transmitter in prolactin regulation. The serotonergic neurons involved seem to project from the dorsal raphe nucleus to medial basal hypothalamus. The influence on basal levels is not outstanding. 5-HT rather seems to participate in the regulation of prolactin surges such as occur during suckling in lactating animals.

The statement that 5-HT stimulates prolactin release still leaves us with a least three possibilities: (*a*) 5-HT could be a prolactin-releasing factor (PRF); (*b*) it could stimulate the release of a prolactin-releasing factor; or (*c*) it could inhibit the release of dopamine to pituitary portal vessels. The first possibility has been reasonably well ruled out, although not all researchers agree; 5-HT probably does not stimulate pituitary lactotrophs directly and is not a PRF. A number of researchers have indirectly tried to differentiate between the remaining possibilities (871, 1136), but there is very little firm evidence.

Probably the best piece of evidence to indicate that 5-HT inhibits TIDA neurons is derived from direct assays of dopamine in pituitary portal plasma after i.c.v. injection of 5-HT (1111). Marked and dose-dependent decreases in dopamine concentration and secretion rates in pituitary portal plasma were found after i.c.v. injection of 0.5 to 5.0 μg 5-HT. A simultaneous increase of prolactin in plasma was seen. To establish whether the inhibition of dopamine release was the sole cause of prolactin increase, peripheral dopamine infusion was tested. In spite of a reasonable dopamine concentration in arterial plasma, 5-HT i.c.v. caused a rapid prolactin increase (1111). These results suggest that 5-HT inhibits the dopamine release from TIDA neurons, but this is not the sole cause and probably not the main cause of the prolactin surge. This hypothesis is supported by the indirect evidence obtained by using agonists and antagonists of serotonergic and dopaminergic systems (246, 821). Hence, the best guess at the moment could be the hypothesis depicted in fig. 5. It is of interest that estradiol increases the density of 5-HT_1-receptors in the arcuate nucleus (103), i.e., at the site of TIDA neurons.

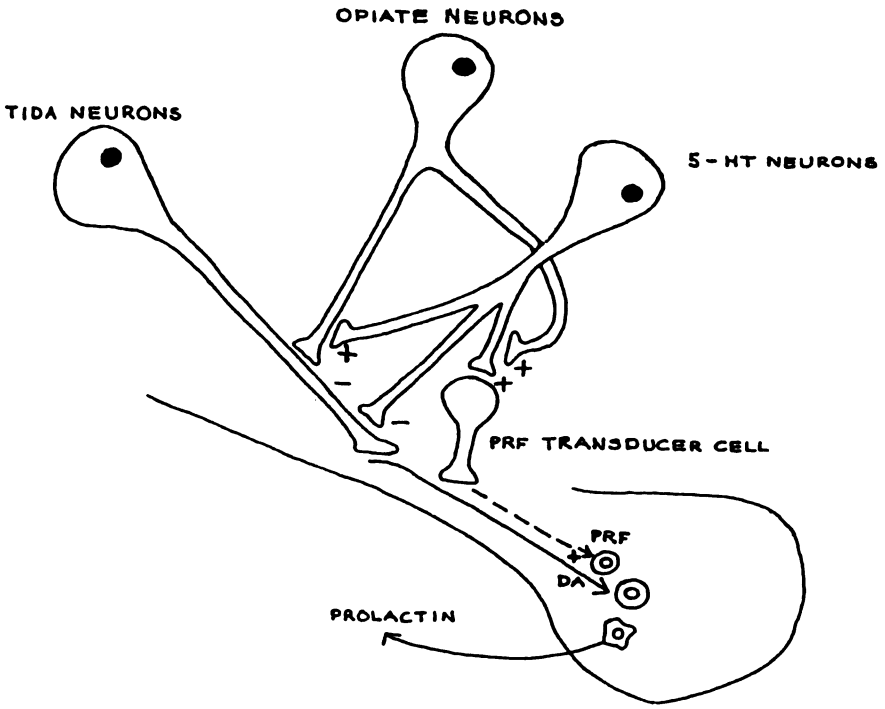

FIG. 5. Hypothetical interplay between 5-HT, opiate, and dopamine neurons in the control of prolactin secretion. Modified after Preziosi (1136).

B. Growth Hormone

The importance of 5-HT in the regulation of GH secretion is far from clear. There are at least two basic reasons for the discrepancies. (*a*) The drugs used as tools are not very specific, and their actions are not limited to 5-HT neurons. (*b*) 5-HT is one of the few transmitters which inhibit the release of somatostatin (see above). The apparent inhibitory actions of tryptaminergic agonists may be masked to varying degrees, and the net result measured as peripheral GH concentration is hard to predict. In spite of the above factors of uncertainty and several important exceptions, most reports available support the stimulatory role of 5-HT in the release of GH in a variety of species.

1. Primates. In acromegalic and normal man, the 5-HT precursors, L-tryptophan and 5-hydroxytryptophan, enhanced basal GH secretion (217, 645, 758, 812, 1031, 1507). This has not been the case in all studies (586). Anecdotically, GH levels have been high in patients with carcinoid syndrome (429).

In support of these findings, the more or less selective 5-HT antagonists such as cyproheptadine (571) and metergoline (241, 329, 428) decreased basal or stimulated GH levels, not in all cases, however (583, 1094). In acromegalic patients, metergoline even decreased GH levels (437). There are also quite a number of studies where cyproheptadine inhibited GH levels stimulated by sleep (231), exercise (262), hypoglycemia (106), L-dopa (325, 1032), arginine (1033, 1313), and 5-HPT (1307). Pizotifen, another antiserotonergic drug, induced inhibition of the GH-stimulating activity of metoclopramide in normal women (237). A fairly specific 5-HT_2 receptor antagonist, ketanserin, did not influence the GH response to insulin (1134). Casanueva and coworkers (192) found that the central serotonergic activation by fenfluramine blocked the GH response to L-dopa but had no effect on the arginine response. No sign of serotonergic stimulation was detected. Finally, 5-HT antagonists have not yielded too impressive results in the treatment of acromegaly (106, 241, 329, 428). In conscious Rhesus monkeys, 5-HTP increased basal GH levels (212, 664), while it was not active in man (86).

2. Dogs. In conscious dogs, basal GH levels have rather uniformly been stimulated by 5-HT precursors (381, 980, 1178, 1514), while the stimulated GH was clearly inhibited by various 5-HT uptake inhibitors and fenfluramine (852); of the serotonin antagonists, only metergoline enhanced the action of insulin, while cyproheptadine and methysergide did not (852). Müller et al. (1021), also found increased response to insulin by *p*-chlorophenylalanine. This action was reversed by 5-HTP. It must be pointed out, however, that it has not always been possible to antagonize the actions of 5-HPT by 5-HT antagonists (980, 1178). The unspecificity of 5-HTP, but not L-tryptophan, is caused by an unselective 5-HTP uptake also into other than 5-HT neurons. Therefore, 5-HTP may release noradrenaline and DA (435, 1514). In fact, it has been observed that, in some cases, the action of 5-HTP can be antagonized by phentolamine (252, 980, 1031) or phenoxybenzamine but not by metergoline (1514).

3. Rats. Studies in rats also tend to support the stim-

ulatory action of 5-HT on GH secretion (1310). In conscious rats, both 5-HT and quipazine, 5-HT agonists, enhanced GH levels when given into the third ventricle. As expected, this action was counteracted by methysergide (1445). A similar result was obtained by i.p. L-tryptophan and a 5-HT agonist, MK 212 (6-Cl-2[1-piperazinyl]-pyrazine). The stimulatory actions were antagonized by metergoline (59). 5-HTP enhanced basal GH levels in adult rats. This effect was counteracted by cyproheptadine and also by melatonin (1312). In 10-day-old rats, 5-HTP stimulated GH secretion, but this action was not attenuated by 5-HT antagonists. Phentolamine and pimozide, on the other hand, both reversed the stimulation (252). Surprisingly, two 5-HT uptake inhibitors also attenuated the effect of 5-HTP. In urethane-anesthetized rats, intracerebroventricular 5-HT elevated GH levels. Phenoxybenzamine was an effective antagonist (259). These studies emphasize the lack of specificity of the tools used.

p-Chlorophenylalanine, an inhibitor of 5-HT synthesis, usually decreased basal GH levels (116, 915, 1486) but not always (390). Also, 5-HT receptor antagonists, methylsergide, cyproheptadine, and metergoline, decreased GH levels in adult (58, 808, 1389, 1486) and neonatal rats (1344, 1389). The study of Arnold and Fernström (58) is of special interest, since the action of metergoline was abolished by somatostatin antiserum. The latter authors conclude that metergoline stimulated somatostatin secretion, but it inhibited diurnal GH peaks. This view is in accordance with the serotonergic inhibition of somatostatin release (228).

The results with the neurotoxic compounds, 5,7-dihydroxytryptamine and *p*-chloroamphetamine, are not uniform. The former inhibited GH secretion (1486), but the latter did not (243). In 2-day-old rats, 5,7-dihydroxytryptamine even increased GH secretion (1014).

4. Other species. 5-HTP was stimulatory in cats (1212) and ovine fetuses (909). In adult sheep, 5-HT infusions into the lateral brain ventricle had no clear effect (382). Finally, there are several studies in domestic fowl. Quipazine and 5-HTP depressed basal GH levels, while *p*-chlorophenylalanine and several 5-HT antagonists enhanced GH secretion (1148). In other studies, an increase in the brain 5-HT levels or activity by MAO inhibitors, imipramine, L-tryptophan, or quipazine, decreased GH levels (578, 579).

5. In vitro experiments. In vitro studies with 5-HT and compounds affecting serotonergic activity are not numerous. In rat hemipituitaries, cyproheptadine did not alter GH release, while in tumor cell cultures, GH release seemed to be inhibited by cyproheptadine (807). Two studies on domestic fowl hemipituitaries supported the central inhibitory action of 5-HT in this species. 5-HT and quipazine decreased GH release from hemipituitaries only in the presence of hypothalamic fragments. This action was reversed by methysergide (575, 580). In another study, the pigeons were first treated with pargyline and imipramine to elevate hypothalamic 5-HT levels. Then, the hypothalamic fragments were added to the incubation containing intact hemipituitaries; as a result, GH release was inhibited (579, 582).

C. Thyrotropin

The lack of specific pharmacological tools has hampered studies of the effects of 5-HT on thyrotropin. A clear picture of the serotonergic regulation of TSH secretion has thus far failed to emerge. The problems encountered may not only be methodological; 5-HT may have a complex role in the regulation of TSH release.

In early studies, 5-HT was shown to inhibit the release of radioactivity believed to represent TRH from mouse hypothalamic slices (538) or of immunoreactive TRH from hypothalamic synaptosomes (87). In our in vivo studies, 5-HTP inhibited the cold response of TSH (1408). These findings suggested an inhibitory action of 5-HT on TSH and probably also on TRH secretion. However, a stimulation of TRH release was reported in superfusion experiments in vitro (221).

Intracerebroventricular injections yielded totally contradictory results. Large (632) and small doses (0.5 to 10 μg) (685) of 5-HT injected i.c.v. to anesthetized rats increased TSH levels. On the other hand, a clear dose-dependent decrease of 5-HT was demonstrated with doses of 4 to 20 μg through permanent silastic cannulas in unanesthetized rats (783). The 5-HT receptor antagonist, methysergide, blocked the effect. Further studies demonstrated an enhancement of the TSH cold response after 10 μg of 5-HT into the third ventricle but no effect when injected into medial basal hypothalamus of conscious rats (932). The 5-HT receptor agonist, quipazine, was demonstrated to decrease basal TSH levels both i.c.v. and i.p. (783) and also to blunt the cold response of TSH (932). It is curious that the inhibition by the i.c.v. route did not exhibit dose dependency, but 4 μg inhibited more effectively than 20 μg in contrast to prolactin increase, which was dose dependent in the same study (783). Similarly, the stimulation of the TSH cold response by 5-HT was obtained only by 10 μg i.c.v. but neither by 5 μg nor 50 μg (932).

Quipazine, fenfluramine, *p*-chloroamphetamine, and even systemic 5-HT were demonstrated to inhibit TSH basal secretion (220, 370, 371) and to block cold response (370, 932). The effect of fenfluramine, an indirect agonist, was blocked by methergoline, a 5-HT receptor antagonist (370); 5,6-dihydroxytryptamine, a neurotoxic agent destroying 5-HT nerve terminals; and electrolytic lesioning of the median raphe nuclei (371). On the other hand, 3 wk after 5,6-dihydroxytryptamine treatment, supersensitivity to quipazine, a postsynaptic agonist, was noted (47).

In another study (971, 1215), mesencephalic transection with Halasz knife increased serum TSH at 3 wk.

These findings might suggest an inhibitory serotonergic output from raphe-derived neurons.

The results with 5-HTP are controversial; an increase (220, 1220), a decrease (991), and no change (932, 1012, 1407) in basal TSH levels have been reported. Tryptophan either caused no change (932, 1008) or a decrease (991, 1012). High concentrations in the diet for 2 wk decreased TSH (1008). The cold response seems to be blocked by these precursor amino acids, although the doses required vary (932, 991, 1070, 1407).

Inhibition of 5-HT synthesis has also given equivocal results. pCPA decreased the basal TSH level (1407), caused no change (932, 1008), or increased it at one time point (991). Repeated injections for 1 wk also increased serum TSH (1215). The cold response was blocked dose dependently by pCPA (932) or remained unchanged (991, 1407).

There is little information on the effect of 5-HT uptake inhibitors on TSH release. In one study, an acute increase of TSH was seen after acute fluoxetine administration (523). In chronically treated rats, both basal and TRH-induced TSH levels were increased. In another study, zimeldine (2 wk) decreased TSH (1008). In man, no changes were seen in either basal or TRH stimulated TSH after zimeldine (1068).

The results referred to mostly seem to favor an inhibitory role for 5-HT in the regulation of TSH secretion. In addition to the nonspecificity of the tools available, the serotonergic system per se is complex and difficult to approach. One of the sources of discrepancies may be the circadian rhythm. Jordan et al. (684) demonstrated that the daily rhythm in TSH with a peak late in the morning (462, 830, 898) can be abolished by lesioning the dorsal and central raphe nuclei as well as by pCPA and 5,6-dihydroxytryptamine. After these drug treatments, TSH remained close to the daily low level; after raphe lesioning, a low-amplitude rhythm remained but was slightly delayed. The timing of drug administration may be crucial. Since most experiments have been done around the time of the daily peak, this may have affected the variability.

Another explanation for the inconsistent results is the involvement of 5-HT in at least two different sites in the regulation of TSH release. The persistence of a residual rhythm after raphe lesions but not after pCPA suggests the involvement of other 5-HT neurons as well (684). Since 5-HT in addition to quipazine systemically decreased TSH responses, Mattila and Männistö (893, 932) suggested that an inhibitory serotonergic site in the TSH regulation would be outside the blood-brain barrier.

A significant action of 5-HT on TSH release at the anterior pituitary level does not seem probable (685, 783, 932, 1407).

Hence, the information is conflicting, but there may be a stimulatory neuronal connection from the dorsal and/or central raphe nuclei to the hypothalamus (684) involved with the circadian rhythm, and another, inhibitory serotonergic neuronal system either from the median raphe nucleus to hypothalamus (371) or within the hypothalamus. The blockade of the dorsal-central raphe-derived system would influence TSH levels variably, depending on the circadian phase. The existence of two opposite systems may also explain why pCPA augmented the TSH inhibiting effects of quipazine (783). Another explanation would be receptor supersensitivity. The inconsistent i.c.v. results remain puzzling, but the approach is rather sensitive to slight technical differences. Anesthesia (903), stress factors, and the relative sensitivity of pre- and postsynaptic 5-HT receptors should be taken into account. Finally, as discussed separately, 5-HT is one of the neurotransmitters inhibiting the release of somatostatin (section II C 7). This may contribute to the TSH-enhancing effect of 5-HT.

With the present knowledge, it may be concluded that there are several possibilities, and slight differences in conditions may be expected to lead to variable results. These questions warrant further studies in rigidly standardized conditions.

D. ACTH

The role of 5-HT in ACTH regulation seems to be a dual one. 5-HT is important both in the circadian or diurnal regulation of CRH-ACTH secretion and in mediating or modifying the acute stress response. The overall effect of serotonergic pathways on the CRH-ACTH-adrenocortical axis is, however, complicated, since both stimulatory and inhibitory actions have been described (cf. 766, 768).

1. Inconsistency of effect at the anterior pituitary level. The action of 5-HT is evidently located in the central nervous system, although 5-HT clearly seems to release ACTH from the neurointermediate lobes in vitro (446, 763, 765, 798). However, 5-HT definitely plays no role in human anterior pituitary adenoma cells. In normal rat anterior pituitary preparations, the results have not been conclusive (1204), although in one study 5-HT and quipazine elicited small but significant release of ACTH from dispersed rat anterior pituitary cells (1332). Cyproheptadine seems to inhibit ACTH release directly at the anterior pituitary level, probably via α-adrenergic receptors (1489).

2. Effect of 5-hydroxytryptamine on diurnal rhythm of ACTH and corticosteroid secretion. Corticosteroid and evidently also ACTH secretion have a diurnal rhythm with a nadir in the light period and peak secretion during the dark period (23, 96, 1483). Several studies in mice, rats, hamsters, and cats have demonstrated a corresponding fluctuation of 5-HT levels in the whole brain (1018, 1474) as well as in the limbic system (1244, 1298). However, many studies have failed to show any 5-HT rhythm in the brain (1018, 1474). Although the reduction in 5-HT stores by systemic *p*-chlorophenylalanine or other chemicals has generally eliminated the diurnal

rhythm of corticosteroid secretion in birds, rats, and cats (772, 1018, 1363), this action is evidently transient: the rhythm reappears in a couple of days in spite of the very low 5-HT levels (1442). It is also interesting that *p*-chlorophenylalanine eliminates the rhythm by elevating the low morning values and decreasing the high nocturnal values of corticosterone (772, 1210, 1244, 1442). Similar findings have been described after intracerebral administration of a neurotoxic compound, 5,6-dihydroxytryptamine (475, 1240). Lesions of the raphe nuclei (588, 1240) and septum (588) or sectioning of the fornix (828, 923, 993) abolished the diurnal corticosterone rhythm, or they were associated with a flattened fluctuation. Even the effect of fornix transection was transient (828). Finally, a complete or frontal deafferentation of the hypothalamus can block the diurnal ACTH cycle (572, 1077), but they also decrease the ACTH stress response (1440). Destruction of the suprachiasmatic nuclei, too, abolishes the variation in ACTH secretion (1000, 1363).

These results may be concluded to show that the normal diurnal fluctuation of the function of adrenal cortex is at least acutely dependent on the intact serotonergic system of the brain. Apparently, both the limbic system and the anterior hypothalamus, particularly the suprachiasmatic nuclei, are important. The rhythm can, however, be restored in a few days even before complete recovery of the 5-HT system.

3. Role of 5-HT in basal and stimulated ACTH and corticosteroid secretion. Acute stress seems to alter the 5-HT activity in the brain (1206, 1390), although the changes are not too consistent (494) and seem to vary from one animal species or type of stress to another (1018, 1474). Insulin hypoglycemia increased 5-HT turnover in the rat hypothalamus (1500). Acute immobilization of rats for 1 to 3 h, but not repeated immobilization, elevated both plasma corticosterone and 5-HT levels in all brain parts studied. Forebrain dopamine concentrations were decreased only after 1 h of immobilization but gradually increased with prolonged stress (1179). Destruction of 5-HT nerve terminals by 5,6-dihydroxytryptamine potentiated the rise in plasma corticosterone, while 6-hydroxydopamine treatment had no effect. These data support the hypothesis that ACTH release during immobilization stress is stimulated by serotonergic neural activity.

The majority of the results with 5-HT agonists and antagonists are in favor of a stimulatory action for 5-HT in basal and stress-induced ACTH-corticosteroid secretion. Intracerebral or i.c.v. infusions of 5-HT caused adrenocortical activation (6, 771, 774, 1041, 1042, 1204, 1446) in rats with mid-brain transections (1041). Intracerebral 5-HT retained its activity after anterolateral deafferentation of the hypothalamus (1130), although the ACTH response to unilateral adrenalectomy was prevented (712). A systemic administration of a 5-HT precursor, 5-hydroxytryptophan, was stimulatory in man (651), in conscious monkeys (212), and in normal rats (467, 468, 974, 1130, 1137, 1442). In the rat, the serotonergic system was functional during the first postnatal week (785). Another precursor, L-tryptophan, enhanced basal ACTH levels in man (994) and potentiated the ACTH response to hypoglycemia in rats (1500). Further, the stimulatory action of 5-hydroxytryptophan was clearly visible in the rats fed a L-tryptophan-deficient diet (244). It was also potentiated by fluoxetine (467, 468).

5-HT uptake inhibitors, fluoxetine (142, 467, 746) and 3-(*p*-trifluoromethyl phenoxy)-N-methyl-3-phenyl propylamine (908), a 5-HT releasing drug, fenfluramine (940, 974), or 5-HT receptor agonists, quipazine (142, 974) and 1-(trifluoromethylphenyl)piperazine (594), exhibited stimulatory results in rats under basal conditions or in response to various stimuli. Fluoxetine was active also in cats (1212) and elevated CRH levels in the rat pituitary portal blood as well as ACTH levels in the peripheral blood (506). In conscious dogs, i.v. and i.c.v. fenfluramine and i.v. quipazine elevated serum cortisol levels. Their action was reversed by ketanserin, a 5-HT_2 receptor antagonist (73). The actions of fluoxetine and quipazine in rats have been blocked by 5-HT receptor antagonists (142) or mediobasal lesions (974). Zimeldine, a 5-HT uptake inhibitor, potentiated the ACTH response to metyrapone (636). Recently, it was made clear that serotonergic drugs may act at multiple sites both centrally and peripherally to evoke an activation of the anterior pituitary-adrenal cortex-axis (940, 974).

Several studies with more or less specific 5-HT antagonists tend to support the stimulatory action of 5-HT on CRH-ACTH secretion. Metergoline prevented the ACTH burst caused by metyrapone (200), arginine, L-dopa (1128), or hypoglycemia (204). Also, cyproheptadine and methysergide were active in preventing the ACTH-elevating actions of hypoglycemia (1117, 1500), metyrapone (1116), and L-dopa (325). Further, they decreased resting ACTH levels (325) and prevented the morning rise of cortisol secretion (231). Brain 5-HT depletion by intracerebroventricular 5,7-dihydroxytryptamine or 5,6-dihydroxytryptamine attenuated the corticosterone response to stress or to insulin (28, 1500). The same was true with *p*-chlorophenylalanine (28). However, in adrenalectomized rats, neither cyproheptadine, destruction of the raphe nuclei, nor intracerebroventricular 5,6-dihydroxytryptamine was able to alter the ether-stimulated ACTH secretion (712).

Studies with human patients have not given uniform results. In healthy man, fenfluramine elevated ACTH and cortisol levels. These actions were blunted by cyproheptadine (832). Cyproheptadine has shown some activity in Cushing's disease (669, 756, 767, 769, 860, 977). The efficacy of cyproheptadine in Nelson's syndrome has not been uniform (193, 589, 767, 860). Chronic ketanserin

treatment had no effect on ACTH concentrations in six patients with Nelson's syndrome (1135). In normal subjects, acute ketanserin even enhanced ACTH secretion (1134). Finally, in carcinoid tumors secreting large amounts of 5-HT, cyproheptadine decreased basal 17-hydroxycorticoid secretion and blunted the exaggerated response to metyrapone (1115). Cyproheptadine was not able to inhibit ACTH secretion induced by vasopressin (204, 501). Similarly, methergoline did not affect the naloxone-induced ACTH secretion (236). Since vasopressin liberates ACTH at the anterior pituitary level like CRH, these results suggest that cyproheptadine acts in fact above the pituitary gland.

4. In vitro studies on isolated hypothalami. The in vitro studies with isolated hypothalami rather uniformly support the stimulatory role of 5-HT in the release of CRH. Buckingham and Hodges (151, 152) found that both CRH release and CRH content of the hypothalamus increased after addition of 5-HT in concentrations of 1 to 100 ng/ml. This suggests that 5-HT may enhance CRH synthesis. It must be pointed out, however, that 5-HT was a much less potent stimulant than acetylcholine. Holmes et al. (635) and Jones et al. (678, 681) have obtained similar results. Both 5-HT (100 pg/ml to 10 ng/ml) as well as chlorimipramine and *d*-fenfluramine enhanced CRH release. The action of *d*-fenfluramine was counteracted by metergoline and methysergide. Moreover, the intracerebroventricular injection of a neurotoxic drug, 5,7-dihydroxytryptamine, made the hypothalami in vitro supersensitive to 5-HT (635). The stimulatory action of 5-HT can be reversed by cyproheptadine but also by melatonin and high doses of atropine and hexamethonium. The involvement of a cholinergic interneuron mediating the action of 5-HT (678) has not been confirmed by Buckingham (148). Cyproheptadine inhibited the 5-HT stimulated CRH release and also the action of acetylcholine, possibly through its anticholinergic action (681).

Some groups have not been able to demonstrate any action by 5-HT on the CRH release from the isolated hypothalami (425, 1377). The main argument of Tate and coworkers (1377) against the studies referred to above is that these used adrenalectomized rats instead of obtaining the hypothalami from normal rats. Also, Edwardson and Bennett (392) failed to alter the stimulated CRH release from isolated sheep synaptosomes. Finally, 5-HT (10^{-7} M) even reduced the efficacy of the hypothalamic homogenate to stimulate ACTH release from isolated anterior pituitaries (1439).

It seems quite certain that 5-HT is an efficient liberator of CRH from isolated hypothalami taken from adrenalectomized rats, while its role may be less significant if the hypothalami are taken from intact animals.

5. Inhibition of ACTH secretion by 5-HT: evidence of serotonergic mediation of the negative feedback caused by adrenocortical steroids. In sharp contrast to all findings referred to above, a reciprocal relationship between adrenocortical activation and central serotonergic activity has been reported (1379–1382, 1443). In some studies, 5-HT is said to be involved in the negative feedback. Quite recently, it was reported that intracerebroventricular 5,7-dihydroxytryptamine treatment of rats prevented the corticosterone suppression normally caused by dexamethasone (941). Since the metyrapone-induced elevation of ACTH has repeatedly been blocked by 5-HT antagonists (204, 1116) and enhanced by 5-HT agonists (636), this view is hard to accept. Ulrich et al. (1411) implanted cortisol in the hypothalamus and found enhanced 5-HT levels in the hypothalamus and decreased corticosterone production in the rats. Vernikos-Danellis et al. (1442) reported that L-tryptophan and 5-hydroxytryptophan reduce the stress response, while 2 to 4 days of treatment with *p*-chlorophenylalanine enhanced the stress response and altered the diurnal corticosterone rhythm. Similar findings were reported by others (94). Implantation of 5-HT into the lateral hypothalamic area or infusion into the third ventricle blocked the stress-induced corticosterone secretion in anesthetized rats and guinea pigs (1204, 1438). At the same time, a compensatory adrenal hypertrophy was prevented (1437). A stimulation of the raphe nuclei was reported to decrease the stress response, while the raphe lesions caused enhanced activation of adrenal cortex (1441).

Also in dogs, large doses of 5-HT given intraventricularly inhibited ACTH secretion (1417). In man, L-tryptophan decreased plasma cortisol levels and reduced response to hypoglycemia (1493). In dogs, 5-HTP decreased cortisol levels, but this action was interpreted not to be mediated through 5-HT (1514). Chronic treatment with cyproheptadine did not affect pituitary-dependent hyperadrenocorticism in dogs (1342). Pavel et al. (1091) reported that small doses of arginine vasotocin infused into the third ventricle inhibited ACTH secretion in cats. This inhibition was not found in cats pretreated with *p*-chlorophenylalanine but could be restored by 5-hydroxytryptophan. In contrast to the results of other similar studies where septal lesions were made, Azmitia and Conrad (63) found that tryptophan hydroxylase activity was temporarily lost while plasma corticosterone levels were increased.

In summary, the data related to the brain serotonergic activity and ACTH secretion are inconclusive, conflicting, and defective. Part of these problems may be due to an inadequate specificity of the tools available for studying 5-HT neurons. A further explanation may lie in the modification of the diurnal rhythm. Depending on the time of the day, the same drug may increase or decrease the hormone levels. Finally, there may in fact be both stimulatory and inhibitory serotonergic elements in the brain. Why these opposite systems are activated selectively under different experimental conditions, and

whether the inhibitory system is in part responsible for the negative feedback, remain to be established.

V. Opioid Peptides as Regulators of Pituitary Secretion

A. Growth Hormone

It has been known for more than 20 yr that morphine and other opiates have an influence on pituitary hormones (360). After discovering the family of endogenous opioid peptides, it soon became evident that, apart from their pharmacological actions, their endocrine actions, too, were qualitatively similar to those of opiates. There are, however, great quantitative differences between the peptides and morphine in their actions on pituitary hormones. β-Endorphin is generally much more potent than morphine. Of the anterior pituitary hormones, GH and TSH are the most sensitive to opioid peptides, while prolactin and especially ACTH are less sensitive. On the other hand, TSH is least sensitive to naloxone, an antagonist of both opiates and opioid peptides (cf. 631, 1005).

It is well documented that morphine enhances GH secretion (257, 258, 360, 410, 840, 1188, 1279, 1329, 1330) and can even counteract the stress-induced inhibition of GH release (134). It is also quite interesting that the GH-elevating action of i.v. morphine was best antagonized by δ-receptor antagonists like naloxazone, while the prolactin burst was counteracted by a μ-receptor antagonist (750). Delitala and coworkers (321) and Spiegel and coworkers (1329, 1330) were not able to characterize the receptor subtype.

The first reports on the effects of β-endorphin indicated that this peptide stimulates GH and prolactin release after both i.v. and i.c.v. administration (288, 721, 1192), which was confirmed later (531, 714). Pretreatment with somatostatin antiserum did not abolish the action of β-endorphin which was thus interpreted to stimulate GRH, not to antagonize somatostatin (227, 1459). Naloxone was an effective antagonist in most cases. The opioid system was functional during the first postnatal week in the rat (785). Similar actions have been described for met-enkephalin and for its more active synthetic derivatives in both animals (81, 145, 189, 227, 288, 714, 715, 840, 1279, 1345) and man (308, 315, 336, 337, 541, 1097, 1345). The activity was retained after somatostatin antiserum (227). Dermorphin (564), α-endorphin, and γ-endorphin (227) did not alter GH secretion in the rats. Humoral endorphin increased basal GH levels, but its action was not reversed by naloxone (1227).

Opioid peptides seem to act primarily in the hypothalamus rather than in the anterior pituitary. This has been shown by several in vitro studies, where β-endorphin and met-enkephalin did not cause GH or prolactin release from cultured pituitary cells (1192, 1281).

Although the direct action of opioid peptides on the release of the hypothalamic GRH must be seriously considered (978), there is evidence of opioid peptides altering the activity of the well-established amine transmitter systems in the hypothalamus. Both β-endorphin and met-enkephalin decrease dopamine turnover in the median eminence (433). Moreover, like morphine, β-endorphin is known to increase 5-HT turnover in the rat brain (596, 947) and to enhance 5-HT activity in the hypothalamus (1419). Morphine decreases noradrenaline concentrations in the whole brain and hypothalamus (362, 1428). Since all these neurotransmitters and several others, too, are involved in the regulation of GH secretion (see above), their alterations by opioid peptides will cause changes in GH release. In support of this view, the action of [D-Ala^2, MePhe^4, Met(o)-ol]enkephalin (DAMME), a stable met-enkephalin analogue (FK 33-824), on GH was antagonized by reserpine, phenoxybenzamine, and fusarate (714) as well as by atropine and diphenhydramine (1097). Even bicuculline and picrotoxin reversed the action of DAMME (715). The stimulatory effect of morphine was antagonized by reserpine and yohimbine (410) and also by physostigmine and pilocarpine (1279).

Whether or not the endogenous opioid peptides have a physiological role in GH modulation is still a matter of dispute. A failure of β-endorphin antiserum to alter GH secretion disagrees with the physiological role (1374). The effectiveness of naloxone itself has been considered a supporting phenomenon. In fact, Bruni et al. (145) and Shaar and Clemens (1279) have obtained some evidence in the rat that high doses of naloxone or naltrexone actually decrease GH release. Unfortunately, this has not been supported by other reports (189, 479, 916, 1459). Intracerebroventricular naloxone has been shown to increase GH levels (644). Naloxone implants for 9 days were able to antagonize the stimulatory action of morphine on GH secretion (479).

Furthermore, naloxone modified neither basal nor stimulated GH secretion in man (119, 238, 315, 541, 1007, 1202, 1512). However, naloxone antagonized the GH elevating action of clonidine (128) or that of exercise (1001). Finally, nalorphine which does have some opiate agonist activity enhanced rather than decreased GH secretion (1201). Morphine i.v. did not alter GH levels in man (1399). Butorphanol i.m. was similarly inactive (1200).

B. Prolactin

1. Increase of prolactin by opioids. Opiate alkaloids are known to stimulate the secretion of prolactin as well as that of growth hormone (145, 247, 520, 946, 1192, 1199, 1398, 1399). The central site of action of opiates is demonstrated by the ineffectiveness of quaternary compounds (1081) and the lack of effect at the pituitary level (531, 857, 1081, 1281, 1464). Stimulation of prolactin and growth hormone secretion was one of the first reported effects of i.v., i.c.v., or intracisternal β-endorphin (227, 386, 721, 1192). This compound was at least 20 times more potent than morphine. The effect was abolished by

naloxone (145, 1192) and by β-endorphin antiserum (1154). Met-enkephalin and leu-enkephalin also increased plasma prolactin in rats, but larger doses were needed (145, 255, 288, 386, 433, 576, 841, 960, 1281). The large dose needed may be explained by the more rapid degradation of met-enkephalin (288). Also, dynorphin was found less potent than β-endorphin to release prolactin (1433). Several synthetic enkephalin analogues have been shown to slightly increase prolactin (288, 337, 526, 960, 1281, 1345, 1454). A new natural opioid peptide, dermorphin, was also found to stimulate prolactin secretion (515). These stimulatory effects of opiate alkaloids and opioid peptides have been constantly found in all species studied, including man (195, 1270, 1398, 1399, 1454), and even in prepubertal animals (647).

Based on the effectiveness of the specific μ_1-receptor antagonist, naloxazone, in decreasing morphine-induced prolactin release, the release has been suggested to be mediated through high-affinity μ_1-receptors (1329). Microinfusions into various brain nuclei suggested that β-endorphin acts at a medial hypothalamic and/or preoptic-septal site (1481).

It was early noted that met-enkephalin (433) and β-endorphin (365, 1422, 1431, 1432) decreased dopamine turnover in the median eminence. This suggested that opioid peptides might stimulate prolactin release by decreasing dopamine release into the hypophyseal portal vessels. This was also suggested by the fact that morphine was unable to increase the maximal stimulation of dopamine receptor blocking drugs, but subeffective doses were synergistic (1432) and that L-dopa or dopaminergic agonists inhibited the stimulatory effects of opioids (1064, 1398, 1432, 1472). On the other hand, opiate antagonists do not block the prolactin release induced by drugs decreasing dopaminergic stimulation (560). Experiments with α-methyl-*p*-tyrosine suggested that lack of newly synthetized dopamine potentiated the effects of β-endorphin (748, 1420), whereas pargyline, a monoamine oxidase inhibitor increasing dopamine levels, blunted the effects of β-endorphin (1420). High doses of α-methyl-*p*-tyrosine or reserpine, which probably totally abolished the dopaminergic activity, also abolished the responses to synthetic opioid peptide FK-33-824 (929). Opioids were also found to decrease the amount of dopamine in the hypophyseal portal vessels (556). This effect was seen even after iontophoretic ejection of morphine directly to the arcuate nucleus (595).

After chronic exposure to increasing doses, tolerance develops to prolactin releasing effects of morphine, and in tolerant animals also, the effect on dopamine turnover was found to be attenuated (366). This further supports the hypothesis that the opioids act via inhibition of TIDA neurons. Neonatal treatment of rats with monosodium glutamate decreased β-endorphin-like immunoreactivity in the arcuate nucleus, and subsequently prolactin response to morphine was increased (51).

ACTH treatment has been shown to inhibit prolactin increases caused by various stimuli (427, 439). The probable explanation is loss of opiate sensitivity to TIDA neurons (706). These phenomena may have important implications on the interactions of ACTH and opioids in the development of opiate tolerance.

Some data on humans indicate that opioids increase prolactin secretion via the dopaminergic system. Morphine potentiated the prolactin increase caused by a small dose of metoclopramide but not after a large dose causing a maximal release (332). Morphine did not abolish the prolactin increasing effect of benserazide, a peripheral inhibitor of decarboxylases including dopadecarboxylase. The failure of morphine to increase prolactin in conditions of decreased dopamine secretion into the pituitary portal circulation also supports the action via the dopaminergic system (318, 322).

There is some evidence that opiates or opioid peptides may activate the serotonergic system in addition to decreasing the dopaminergic tonus, thus causing an increase of prolactin. Morphine-induced elevation of prolactin was antagonized in rats by 5-HT receptor blockers, metergoline and cyproheptadine, and by a 5-HT synthesis inhibitor, *p*-chlorophenylalanine, and by 5,7-dihydroxytryptamine-induced destruction of 5-HT neurons (749, 1324). Naloxone was also observed to decrease the prolactin response to quipazine, 5-HTP, or fluoxetine, whereas morphine and fluoxetine were synergistic (947). Inversely, in monkeys, the opiate-induced prolactin increase was not influenced by methysergide or *p*-chlorophenylalanine (1472). Recently, studies with methysergide suggested that in humans the prolactin release by opioids is also mediated via the serotonergic system (693) and that the contradictory results in monkeys resulted from too high doses of methysergide also inhibiting dopamine receptors (693).

Turnover studies also suggest that 5-HT neurons are activated by opioids (673). The endogenous opioid peptide systems may also mediate the estradiol-induced activation of 5-HT neurons and so participate in the elevation of prolactin caused by estrogen (673).

Noradrenaline does not seem to be involved in the opioid effects on prolactin (748, 1279), but the cholinergic system may be inhibitory, since pilocarpine, nicotine, and physostigmine inhibited the prolactin release induced by morphine (1025, 1279, 1356). These effects were counteracted by respective antagonists (1025).

Arginine vasopressin and vasotocin have been suggested to release prolactin via the opioid-mediated systems, possibly by inhibition of dopamine release (113). This illustrates the complexity of these multistep systems.

As stated above, most researchers agree that opioids act only at the hypothalamic level. This is not a completely unanimous view, since in some conditions inter-

action with the inhibitory action of dopamine at the pituitary level has been suggested (223, 405).

2. Opioid peptides and prolactin surges. Naloxone inhibits the rapid prolactin increase caused by suckling in lactating rats (434, 979, 1026). The role of endorphins in suckling-induced prolactin release may, however, not be predominant (1186).

Stress-induced prolactin release has also been shown to be inhibited by naloxone (1152, 1207, 1430) or naltrexone (533, 560). The results with β-endorphin antiserum suggest that the endogenous opioid involved in stress-induced prolactin release is β-endorphin (115). The final stage affecting the pituitary lactotrophs may be a decrease in the dopaminergic activity (726). However, the decreased release of dopamine may not in itself be sufficient to account for the increase in the secretion of prolactin (57).

There seems to be a cross-desensitization between the effects of morphine and stress on prolactin levels after repeated morphine treatment (364), which further indicates the involvement of an endogenous opioid system in the stress-induced release of prolactin. There is as yet little evidence of the participation of opioid peptides in the regulation of proestrous prolactin surge. Naloxone being shown inhibitory, they may have a stimulatory role (646).

In humans, opioid peptides may not be important in the tonic regulation of prolactin secretion (1434). It is interesting that naloxone was reported to increase prolactin during the luteal phase, but there was no change during the follicular phase (1314).

3. Effect of prolactin on endogenous opioids. Presently, there is less information on the effect of prolactin on opioids than there is on the effect on dopamine turnover. However, some indication of feedback effects can be found, for example, a decrease of β-endorphin concentrations in the hypothalamus and some other brain areas in rats bearing prolactin secreting tumors (1084), but not in those with other hormone secreting tumors (1082).

C. TSH

1. Animal studies. The views on the action of opiate alkaloids and opioid peptides on TSH secretion in the rat are fairly unanimous. Basal TSH levels in serum (145, 498, 499, 631, 1283) and in the anterior pituitary (66) were decreased after peripheral administration of morphine. Similarly, leu-enkephalin (145, 935, 989) and β-neoendorphin (988) depressed TSH secretion. The inhibitory action of these drugs was antagonized by naloxone in several cases (145, 988, 1283).

Also, the cold-stimulated TSH release was blunted by peripheral morphine (1024, 1283), leu-enkephalin (989), and β-neoendorphin (988). The same holds true with the action of morphine on the thyroidectomy-induced elevation of TSH (1024). The report of Kotani and coworkers (757) has been the only exception. They did not find any effect by pentazocine on the cold-induced colloid droplet formation of the mouse thyroid glands. A successful antagonism of morphine (1024, 1283) and β-neoendorphin (988) effects by naloxone has repeatedly been reported. The inhibitory action of β-neoendorphin was also blocked by haloperidol and 5-hydroxytryptophan (988). Also, the effect of leu-enkephalin was reversed by pretreatment with haloperidol, 5-hydroxytryptophan, and L-dopa (989). These findings demonstrate that aminergic neurons are involved in the action of opioid peptides.

Naloxone is a well-established opioid receptor antagonist with little, if any, agonist properties. Recently, it has been shown to bind preferably to so-called μ-receptors if the doses are not too large. Therefore, a lack of naloxone antagonism may indicate that opioid peptides or some opiate alkaloids are bound to other types of opioid receptors. Naloxone has been confirmed not to affect basal (145, 688, 1283) or cold-stimulated TSH levels (902, 1024, 1283). Naloxone implants did not alter TSH levels in the rat but were able to prevent the depressing activity of morphine (479).

However, both the stress-induced lowering of basal TSH levels (688) and the TSH decrease caused by heat exposure (1283) were antagonized by naloxone. These findings are strongly in favor of a physiological role of opioid peptides in TSH regulation. The effects of opioids may involve alterations in the hypothalamic noradrenaline system (135).

The action of the opioid peptides and opiate alkaloids is evidently mediated, at least partly, through the central nervous system. The apparent effect on cold response is one indication of the central action, since this response is based on enhanced TRH activity in the hypothalamus. This has been confirmed by direct cerebral or intracerebroventricular infusions. Morphine (688) and β-endorphin (688, 858) infused into the third ventricle have clearly decreased basal TSH levels. We have corroborated the inhibitory action of intracerebroventricular morphine on the cold-induced TSH burst (902). Moreover, we have also demonstrated that a microinfusion of morphine into the median eminence depressed the TSH cold response, although higher doses were needed than when infused into the third ventricle. On the other hand, bilateral infusions of morphine into the anterior hypothalamus were not active. Interestingly enough, bilateral infusions into the posterior hypothalamus constantly enhanced cold-stimulated TSH levels in repeated experiments. Both the morphine-induced attenuation of cold response and augmentation were blunted by naloxone pretreatment (902). Judd and Hedge (688) found naloxone infusion into the posterior hypothalamus to enhance basal TSH levels. The sites of infusion in the two groups were not identical, however.

The stimulatory action of morphine in the posterior hypothalamus has been suggested quite early on the basis of the selective hypothalamic lesions (861, 862). In fact,

these authors concluded that morphine has a dual action on the net TSH release: inhibition of the stimulatory components in the rostral hypothalamus and stimulation of the inhibitory components in the caudal hypothalamus.

The effect of opiate alkaloids and opioid peptides on the TSH secretion induced by the exogenous TRH is not too uniform. Morphine has even been shown to enhance the TSH response, and this action was antagonized by naloxone (1024). Leu-enkephalin has decreased the action of the TRH injection (989), and β-endorphin had no effect whatsoever (988).

2. In vitro studies. The action of opioid peptides at the level of anterior pituitary is far from clear. Basal TSH liberation from superfused, dispersed anterior pituitary cells or fragments was enhanced by β-endorphin, met-enkephalin, leu-enkephalin, β-neoendorphin, and dynorphin. This action was not blocked by naloxone but by somatostatin (689). The same group reported enhanced TSH release after injection of β-endorphin directly into the anterior pituitary (688). However, morphine affected neither basal (121) nor TRH-stimulated (1283) TSH release from isolated anterior pituitary preparations. Leu-enkephalin blunted only slightly the TRH-induced TSH liberation from the rat hemipituitaries (935). Finally, in a recent study, β-endorphin was even shown to blunt the TRH-induced TSH release from dispersed anterior pituitary cells (1222). It is noteworthy that none of the significant changes reported was antagonized by naloxone (689, 935).

As a tentative conclusion, opioid peptides may enhance basal TSH release from the anterior pituitary, but they more likely inhibit the TRH-stimulated TSH liberation. These actions are seldom antagonized by naloxone. This can be regarded as a sign of unspecific action, or the actions are not mediated through naloxone-sensitive receptor types (321).

3. Human studies. In man, most opiates and opioid peptides do not affect basal TSH levels. This is true of morphine (1399), chronic methadone (1444), pentazocine (321), butorphanol (1200), nalorphine (1201), β-endorphin (1169), and DAMME (1345). In one comparative study, single doses of morphine, methadone, and DAMME enhanced basal TSH secretion. This activity was blunted by naloxone (321). The authors conclude that opioid receptors of the μ-type stimulate TSH release. Also dermorphin was reported to stimulate thyrotropin secretion (1208).

The action of naloxone seems to be dose dependent. Small doses (0.4 to 8 mg) did not alter TSH levels (320, 1007, 1202, 1512), while a large dose of 16 mg depressed TSH secretion (541).

TRH stimulation was augmented by DAMME (541) and by small doses of naloxone (0.4 to 0.8 mg) (1202, 1512), while 8 to 10 mg of naloxone did not affect the TRH response (320, 1007). In heroin addicts (126, 214) and during chronic methadone administration (738, 1444), TRH response seemed to be attenuated. Acute methadone did not alter the TSH response to TRH (1286).

It seems that, in contrast to animal studies, opioid peptides are of minor importance in the TSH regulation in man. Chronic use of opiates (desensitization?) may reduce the responsiveness of the anterior pituitary to TRH, while an acute blockage of opiate receptors by small doses of naloxone intensifies the action of TRH.

D. ACTH

There is not much direct evidence of the involvement of opioid peptides or opiates in CRH-ACTH-corticosteroid regulation in animals. Intracerebroventricular β-endorphin caused either no change or a slight increase in circulating corticosterone levels (631). D-Ala^2-met-enkephalinamide increased basal ACTH and corticosterone levels shortly after the intraarterial injection. Naltrexone, hypophysectomy, and dexamethasone reversed this action. Later on, however, ACTH and corticosterone concentrations were decreased (358). Studies with opiates, notably morphine, provide further positive evidence. Acute morphine injections caused ACTH or corticosteroid release in rats, mice, and dogs (150, 497, 668, 752, 1023, 1428), but tolerance to this action developed within 24 to 48 h (752). Therefore, after chronic administration, either no effect (150, 213) or even a decrease of adrenocortical function may occur (621, 1023). The action of morphine could be blocked by naloxone (752) and by lesioning of the median eminence (500, 752). Direct microinfusions of morphine into the medial basal hypothalamus (865) or into the arcuate nucleus (497) elevated ACTH or corticosterone secretion. Naloxone has also increased basal (668, 1296, 1453) as well as stress-stimulated (1296) ACTH and corticosterone levels. This was also the case with naltrexone 45 to 65 min after the intraarterial injection (357). A κ-opioid agonist, bremazocine, elevated serum corticosterone levels in the rat. Naloxone was an efficient antagonist (464). In stressed mice, 0.5 and 1 mg of naloxone per kg enhanced corticosterone levels, while 10 mg of naloxone per kg inhibited corticosterone elevation (735). A novel δ-antagonist, ICI 154129, was ineffective in stressed mice (735).

In in vitro studies on rat anterior pituitary preparations, DAMME decreased ACTH release (801, 1345), while β-endorphin (801), morphine, and enkephalins (149) were not effective. However, both morphine and enkephalins enhanced CRH release from the rat hypothalamic preparations (149, 150). CRH release was enhanced when the hypothalami were taken from the rats treated with morphine. The rats made tolerant did not release CRH in vitro (150).

On the whole, it seems quite clear that, in animals, opiates and possibly also opioid peptides increase ACTH secretion through a central action. The effects can be substantiated only by using rather high doses of drugs,

and therefore the physiological significance remains to be established.

In man, the situation is quite different, although most of the evidence is indirect. Butarphanol did not alter cortisol levels (1200). Despite some opposite reports (1202), naloxone has increased either basal (236, 315, 321, 1007, 1453) or stress-stimulated (1007) ACTH or cortisol secretion in healthy individuals. In Addison's disease, the results with naloxone have been variable (359, 1401). In Cushing's disease, naloxone has been ineffective (359) or has decreased ACTH levels (1400). In cultured anterior pituitary cells isolated from a patient with Nelson's syndrome, DAMME depressed and naloxone stimulated ACTH release (809).

Various opiates, including DAMME (320, 321, 336, 337) as well as loperamide (30), inhibited basal or stress-induced ACTH release. Morphine itself was shown to be inactive in one study (1399). The actions of opiates or DAMME on cortisol secretion were not always antagonized by naloxone, while their effects on TSH and growth hormone were reversed (321). Loperamide (30) and DAMME (480) were also inhibitory in Addison's disease, and the action was antagonized by naloxone.

In conclusion, opiates and opioid peptides seem to have a tonic inhibitory action on the CRH-ACTH-adrenal cortex axis in man. The inhibition can be blocked by naloxone. The situation is less clear in diseases affecting ACTH and cortisol secretion.

VI. Amino Acid Transmitters

The evidence available is mostly on γ-aminobutyric acid (GABA) as a neurotransmitter involved in pituitary hormone secretion. There are only occasional reports on other amino acids, such as glycine (1072) and taurine (1258, 1259), which were reported to elevate prolactin levels. Another interesting finding is the fairly specific depletion of pituitary and blood prolactin by high doses of cysteamine (981, 982, 1230). Cysteamine is also known to deplete somatostatin from rat tissues (1362) and up-regulate cerebrocortical somatostatin receptors (1335). However, conclusions can be drawn only on GABA.

A. Gamma-Aminobutyric Acid (GABA) in the Regulation of Prolactin Secretion

1. Effects of GABA at the hypophyseal level. In search for hypothalamic PIF activity, Schally and coworkers isolated GABA (1255). They also showed that high doses of GABA decreased prolactin levels in rats after previous elevation of prolactin levels by dopamine receptor blockers (1255). GABA was shown to inhibit prolactin release in vitro in several studies (404, 539, 803, 850, 1255). Also, the GABA receptor agonist, muscimol, inhibited prolactin release in vitro (534, 850), and GABA receptor antagonists, bicuculline and picrotoxin, blocked the action of GABA and muscimol (539). Bicuculline methiodide, which does not penetrate the blood-brain barrier, inhibited the effects of muscimol in vivo (534). These studies suggest that GABA acts at the pituitary level as a PIF-like substance analogously to dopamine (1150).

This possibility is supported by the demonstration of gabaergic tuberoinfundibular neuronal system (1461) and other GABAergic neuron systems in the hypothalamus (1375, 1451).

GABA receptors have been demonstrated in both rat (534) and human pituitary (530). The apparent affinity constant was 30 to 40 nM. Intracellular recordings demonstrated direct and specific effects of GABA on the electrical activity of prolactin secreting tumoral cells (658).

Benzodiazepines have also been shown to depress stress-induced prolactin surge or the release in the afternoon of proestrus (529), even if basal levels were not affected. Benzodiazepines also counteracted the prolactin-releasing effect of haloperidol (529) and inhibited both basal and stimulated prolactin release in vitro (1261).

On the other hand, several investigators doubt that GABA could be a PIF. In several studies, a direct inhibitory effect on pituitary cells could not be demonstrated (986, 1190), and, because of relatively high concentrations of GABA required in all studies (404, 539), the physiological role has been questioned (803, 1292). Mulchaney and Neill (1013) did not find the concentrations of GABA in pituitary portal plasma to exceed those in peripheral plasma, although after electrical stimulation GABA may increase remarkably (987). Hence, even if other factors may increase the sensitivity (304, 534, 539), the physiological inhibitory role cannot as yet be considered as established. A suggestion of the existence of a GABA receptor ligand (which is not GABA) in pituitary portal plasma further adds to the confusion (987). However, some authors are quite clearly in favor of the physiological role of GABA (1149). The failure of GABA alone to inhibit prolactin release in vitro could be explained by rapid metabolism, and in normal conditions, only a reduced number of receptors may be operative (52).

2. Effects of GABA at the CNS level. In early studies, systemic administration of large doses of GABA was found to decrease prolactin levels in vivo in rats (1255). Also, systemic administration of a GABA receptor agonist, muscimol, decreased prolactin levels, but the antagonists, picrotoxin and bicuculline, decreased prolactin as well and were not able to counteract the effect of muscimol (850). Administration of GABA i.c.v. (378, 986, 1072, 1088b, 1369, 1449), ethanolamine-O-sulphate (851), and muscimol (534, 798, 851) increased prolactin secretion, and this increase was blocked by bicuculline (850). This led Locatelli et al. (850) to postulate a dual action of GABA with a stimulatory component in the CNS and an inhibitory component at the pituitary level. However, GABA and aminooxyacetic acid were also reported, after i.c.v. injection of large doses, to inhibit

suckling-induced prolactin release (835). There was no obvious correlation between the circadian plasma prolactin changes and hypothalamo-pituitary gabaergic activity (186).

In most studies with variable test arrangements in humans, increases in prolatin were seen after GABAergic stimulation with baclofen (197), γ-amino-β-hydroxybutyric acid (445, 1368), muscimol (1373), or i.v. GABA (950). Even large oral doses of GABA did not stimulate prolactin release nor modify prolactin release induced by dopamine receptor blocking drugs (196), but they increased the response of prolactin to insulin hypoglycemia (198). Sodium valproate, which increases GABAergic tone, decreased prolactin concentrations in normal women and in hyperprolactinemic patients with no radiological signs of prolactinoma (952). No decrease was, however, seen in prolactinoma patients (952). It is possible that these results indicate a GABAergic inhibition on the pituitary level, especially in conditions with decreased dopaminergic control. Progabide, another GABA receptor agonist, inhibited domperidone-induced prolactin release (966), which may also be best explained by the pituitary action.

3. Localization of possibe GABA neurons and interrelationship to monoamine systems. There is some morphological basis for the possibility that hypothalamic GABAergic systems may be involved in prolactin regulation. Autoradiographic studies have demonstrated GABA-accumulating cells in the hypothalamus (884, 1375), and immunohistochemistry with antibodies to glutamic acid decarboxylase has revealed networks of immunoreactive fibers in most hypothalamic nuclei, including the median eminence (1098). In a detailed study on hypothalamic glutamate decarboxylase immunoreactivity, Vincent et al. (1451) showed a dense, essentially even distribution throughout the hypothalamus and median eminence. Immunoreactive cell bodies were found in the arcuate nucleus and other hypothalamic nuclei. It is of special interest that glutamate decarboxylase-like immunoreactivity coexists with tyrosine hydroxylase-like imunoreactivity (415). This may indicate the coexistence of GABA and dopamine in the same neurons.

Interactions of GABA and other neurotransmitters as yet have been studied only to a limited extent (1450). Casanueva et al. (185) presented evidence based on pituitary dopamine concentration that the central stimulatory action of GABA would be due to inhibition of TIDA neurons. Turnover studies indicating that muscimol clearly decreases dopamine turnover in the medial preoptic area and anterior mediobasal hypothalamus (461) support this view.

B. GABAergic System and Thyrotropin Secretion

1. Animal studies. The GABAergic system has rather uniformly decreaed basal TSH secretion in rats. This action has been repeatedly documented using peripheral administration of various GABAergic drugs like baclofen (372, 931), γ-amino-β-hydroxybutyric acid (GABOB) (537, 686), aminooxyacetic acid (AOAA) (931), as well as calcium hopantenate, a GABA derivative (990), which penetrates the blood-brain barrier. GABA itself was not effective outside the brain (1448). The inhibitory action of calcium hopantenate was abolished by bicuculline pretreatment (990). GABOB was inhibitory also in rabbits (537).

The central action of GABA has been further confirmed by studies where GABA itself (686, 939, 1448–1450) or GABOB (686) was given into the brain ventricles, and a decrease of basal TSH levels was observed. The action of GABA was blocked by both bicuculline and pimozide (939, 1449, 1450) and that of GABOB by picrotoxin (686). In one study, a high dose of GABA did not affect TSH levels when given into the lateral ventricle (632).

GABA antagonists generally did not affect TSH levels (931, 939), but picrotoxin and semicarbazide, an inhibitor of GABA synthesis, induced nocturnal TSH secretion in the rat (686).

The action of GABA on cold-stimulated TSH secretion has been studied by two groups only. GABAergic compounds, baclofen, deprakine, AOAA, and muscimol (930, 931), as well as calcium hopantenate (990) given i.p., have decreased TSH cold response which is known to be mediated through the hypothalamic TRH activation. GABA itself was only occasionally active (931). The inhibitory effect of GABAergic compounds was not antagonized by bicuculline, picrotoxin, phentolamine, pimozide, or ketanserin (930). In our experiments, GABA did not affect cold-stimulated TSH secretion when infused into the third ventricle. However, moderate doses of GABA into the medial basal hypothalamus prevented the cold response. This action was not very impressive, since it could be reproduced only with a dose of 5 μg/rat, not with 1 or 10 μg/rat (931). Since GABA did not affect the release of TRH from the hypothalamic fragments (687), the locus of the inhibitory action of GABA may rather lie in the vicinity of the median eminence.

GABA does not have any clear action at the anterior pituitary level as judged from two kinds of tests. In three separate studies, GABA had no effect on the TSH release from the anterior pituitary preparations in vitro (686, 687, 1449). In support of these findings, we observed no effect by GABA, AOAA, picrotoxin, or bicuculline on the TRH-induced TSH secretion in the rat (930, 931). Inversely, Mitsuma and Nogimori (990) reported decreased TSH response to TRH after calcium hopantenate.

2. Human studies. There are only a few human studies available. Baclofen has been reported either to decrease basal TSH levels (537) or not to affect them (398), while GABOB was slightly inhibitory in one study (537). However, both deprakine (399) and baclofen (398) have blunted the TSH response to exogenous TRH. In the case of deprakine, the patients were more or less hypo-

thyroid (399). Hence, in man, GABA may function at the anterior pituitary level, while in the rat the action is more central.

C. The Role of GABA in the Regulation of Growth Hormone (GH) Secretion

The action of GABA on GH secretion is not quite uniform. It is well established in man, however, that GH secretion is stimulated by high oral doses of GABA itself (196, 198) or a stimulatory GABA analogue, γ-amino-β-hydroxy-butyrate, parenterally (951) as well as an acute administration of diazepam, a probable GABA potentiator (704, 759, 1357, 1358), and baclofen to men (238, 761). Diazepam seems to be active in males only, since high estradiol levels appeared to prevent GH response (295). Similarly, bromazepam stimulated GH levels only in men (296). The effect of diazepam was even potentiated in acromegalic patients and totally lacking in patients with hypopituitarism (704). Further, Takahara et al. (1368) found enhanced GH secretion after an intrathecal administration of γ-amino-β-hydroxybutyrate in cerebrovascular patients. All these reports are uniformly in favor of the GABAergic stimulation of basal GH secretion in man.

On the other hand, several reports have confirmed that GABAergic pretreatment with GABA itself or with baclofen inhibits the hypoglycemia-induced GH secretion in man (197, 760). Finally, even a single dose of baclofen may inhibit the stimulated GH secretion (652). The inevitable conclusion from these studies is that the action of GABA, whether direct or mediated through a biogenic amine, involves two phases: acute stimulation when GH levels are normal or low and inhibition when GH levels are elevated.

In rats, the situation is even more confusing. Vijayan and McCann (1448) obtained a clear-cut increase of basal GH levels in conscious cannulated female rats after infusing GABA into the third ventricle. This action was logically antagonized by bicuculline but not by pimozide, suggesting a sort of specificity for direct GABAergic action (939, 1450). A stimulatory role for GABA has been proposed also by the results of Abe et al. (4) in urethane-anesthetized rats after intracerebroventricular GABA and γ-amino-β-hydroxybutyrate.

Also, the results of Martin et al. (915) showing a depressing effect of GH by convulsive doses of picrotoxin are in favor of the GABAergic stimulation. However, GABA infusions into the lateral ventricles of anesthetized male rats decreased GH secretion (144). Muscimol i.v. also inhibited GH secretion, supporting a peripheral inhibitory GABAergic action in GH regulation (251). The conclusion of Fiok et al. (444) was also quite clear: enhancement of the GABAergic tone decreased GH secretion, and weakening of the GABAergic activity elevated GH secretion. Finally, Arnstein et al. (60) did not find any significance for GABA in basal or pentobarbital-stimulated GH secretion. In their studies, baclofen decreased basal GH concentrations. Gluckman (518) has studied the effect of bicuculline and picrotoxin in chronically cannulated sheep, lambs, and ovine fetuses. He found that muscimol decreased and picrotoxin increased basal GH levels only in 115- to 140-day-old fetuses. Hence, a tonic GABA-mediated GH inhibition prevails in the late gestational ovine fetus.

To the best of our knowledge, there are three in vitro studies utilizing anterior pituitaries. The rat hemipituitaries responded well to K^+ stimulation, releasing GH, but addition of GABA did not modify GH release (444). However, addition of GABA into the incubation medium, containing both anterior pituitaries and hypothalamic tissue from the chicken, inhibited GH release. This action was abolished by bicuculline and picrotoxin (581). However, GABA, diazepam, and muscimol but not baclofen increased GH release from the anterior pituitaries of neonatal rats. This action was antagonized by both bicuculline and picrotoxin. No effect was apparent if rats older than 9 days were used (7). We want to emphasize the fact that profound hormonal changes occur during the maturation of mammalian fetus. These alterations are reflected also in the relative regulatory importance of a variety of neurotransmitters (519).

D. GABA and ACTH Regulation

Several groups have discovered that GABA can decrease either basal or stimulated CRH release from the isolated rat hypothalami in vitro (151, 152, 160, 162, 425, 678, 681). On the other hand, GABA did not release ACTH from cultured anterior pituitary cells (593) or from human anterior pituitary tumor cells in vitro (380, 679, 810).

In studies with conscious rats, small doses of GABA were not effective when given into the third ventricle (6). In pentobarbital-anesthetized rats, however, large doses of GABA prevented ACTH response to surgical stress, while basal ACTH secretion was rather stimulated, evidently owing to the injection stress (885). In another study on conscious rats, i.p. GABA injections (100 mg/kg) increased hypothalamic noradrenaline and plasma corticosterone concentrations (21).

GABA antagonists, picrotoxin and bicuculline, elevated basal ACTH levels after intracerebroventricular administration. On the contrary, in conscious cats, intracerebroventricular infusions of GABA antagonists did not affect plasma cortisol levels (496). The action of bicuculline was antagonized by GABA. Picrotoxin was active even when given i.p. at subconvulsive doses. Hypothalamic deafferentation did not abolish the action of GABA antagonists, suggesting that the action of GABA is mediated within the hypothalamus (885). In a recent study, i.p. picrotoxin elevated both ACTH and corticosterone levels. Moreover, the ACTH rhythm but not corticosterone rhythm was suppressed (663). The inhibitory effect of dexamethasone on resting and stress-induced corticosterone secretion was blocked by inhibiting GABA

synthesis by mercaptopropionic acid, suggesting that the negative feedback is mediated via the GABAergic system (8).

Assuming that benzodiazepines act at least partly by potentiating GABAergic tansmission, plenty of reports need consideration. The effect of benzodiazepines on corticosteroid and ACTH secretion depends on both the dose of the particular drug and on the prevailing corticosteroid level or stress. Hence, high doses of diazepam (around 10 mg/kg) and other benzodiazepines cause elevations of corticosteroids, especially in unstressed animals (74, 209, 728, 793, 905, 1099, 1402). Low doses (around 1 mg of diazepam per kg) are either ineffective (146, 905) or even decrease corticosterone secretion (784, 1099). It is also quite evident that various benzodiazepines antagonize the corticosteroid-elevating effect of stress (107, 728, 784, 792, 827, 892, 1402). This action of diazepam was abolished by a novel benzodiazepine receptor antagonist (107).

In Nelson's syndrome associated with high ACTH levels, sodium valproate (deprakine), a drug enhancing GABAergic activity, decreased ACTH secretion in some patients, but it was not effective if ACTH levels were normal (199, 397, 565, 679). In another study, sodium valproate was not effective in 11 patients with ACTH hypersecretion (859). It is noteworthy that, while reducing circulating ACTH levels in several patients, sodium valproate seems to promote the secretion of cortisol (cf. 380, 680). Valproate also decreased the early morning peak of ACTH secretion in a number of healthy subjects (396). Baclofen, an agonist GABA analogue, decreased both basal and hypoglycemia-stimulated cortisol secretion in man (652). Most of this evidence indicates that GABA has an inhibitory action on ACTH release, working at the hypothalamic level, possibly by inhibiting CRH release. The action is similar in rat and man, but possibly just the opposite in cat.

VII. Cholinergic Regulation of Pituitary Hormone Secretion

A. Prolactin

It is strange that cholinergic systems generally have been poorly studied in neuroendocrinology, even if there is a number of fairly specific pharmacological tools. Often, even the information available includes secondary findings from studies dealing with amine transmitters. Also, histochemical evidence is scanty, and there is no indication for the projections of the cholinergic neurons which are found dispersed in the arcuate nucleus and lateral hypothalamus (287b). However, cholinergic receptors are known to exist in the hypothalamus (114c).

Prolactin release was early reported to be inhibited by cholinergic stimulation (532, 535, 838b). However, atropine was also reported to inhibit prolactin release (838a, 944, 1047), although the doses may have been excessive. Nicotine (112) and muscarinic agonists blocked prolactin surges, and the latter inhibition was antagonized by atropine (53, 1348) which was ineffective alone. The mechanism of cholinergic inhibitory effects was suggested to be stimulation of the TIDA system (402, 535, 1348), and it was suggested to function only under special conditions and not to cause tonic inhibition. Muscarinic agonists may also inhibit prolactin release at the pituitary level (1492).

Injections of acetylcholine i.c.v. increased prolactin in the rat and caused a decrease in pituitary stalk plasma dopamine concentration (505). This finding is difficult to understand as compared to studies using systemic administration. Also, nicotine from cigarette smoking was reported to increase plasma prolactin in humans (1482), and pirenzepine, a muscarinic receptor antagonist which does not cross the blood-brain barrier, reduced prolactin (919). However, atropine changed neither basal nor TRH-induced prolactin levels in volunteers (1039).

In conclusion, cholinergic regulation is agreed not to be important for basal prolactin release, but beyond that there is some uncertainty. Most studies suggest an inhibitory function which may be mediated via the TIDA system. Also, the opioid system may be involved in this regulation (51, 1025, 1279).

B. TSH

The importance of the cholinergic nervous system in TSH regulation has not been thoroughly studied. In early experiments with rats, the cold-induced thyroidal colloid droplet formation was blocked by both a muscarinic agonist, oxotremorine (1070), and a muscarinic antagonist, atropine (757). In our experiments, however, neither physostigmine nor atropine altered the cold-stimulated TSH secretion in rats (1407, 1408). Holak and coworkers (632) gave a massive dose of pilocarpine into the lateral ventricle of the rats with no significant changes in basal TSH levels.

In a recent series of histochemical studies, i.v. (34), s.c. (33), or i.c.v. (34) injections of nicotine decreased basal TSH levels in the rat. Some of these actions could be blocked by mecamylamine, a ganglionic blocker (33, 37). The Swedish group states, however, that the central nicotinic receptors activate both dopamine and noradrenaline turnover and release in various hypothalamic catecholamine nerve terminal systems (33, 34, 37, 38). Hence, the action of nicotine is indirect, and the net effect on TSH secretion is determined by the relative action of nicotine on dopaminergic (inhibitory) and noradrenergic (stimulatory) circuits.

In vitro studies with various hypothalamic preparations have given completely negative results. Acetylcholine did not release TRH from the synaptosomes isolated from the sheep hypothalamus (87), from the rat hypothalamic fragments (687), or from the pulse-labelled mouse hypothalamic fragments (538). Addition of physostigmine or carbachol was without effect (538).

Finally, Chihara and coworkers (228) reported that

intracerebroventricular acetylcholine increased somatostatin levels in the hypophyseal portal blood. Bennett and coworkers (88), on the other hand, were not able to detect any effect by acetylcholine on the release of TRH from the synaptosomes isolated from the hypothalamus or the brain of the rats. In conclusion, cholinergic activation does not have a very important role in TSH regulation. If anything, activation of nicotinic receptors may inhibit TSH secretion by a central action executed indirectly through the catecholaminergic system or possibly also through stimulation of somatostatin liberation.

C. Growth Hormone

GH secretion seems to be activated by cholinergic mediators in several species. In man, β-methylnicotin (1317), physostigmine (302), and edrofonium (831) stimulated GH secretion. In dogs, the stimulatory receptor has been shown to be muscarinic, not nicotinic. The effects of physostigmine and oxotremorine were effectively antagonized by atropine (187).

In fact, nicotine slightly reduced both basal and pentobarbital stimulated GH levels in rats (35, 36). Mecamylamine did not attenuate the effect of nicotine on GH (35). The action of nicotine was evidently mediated through altered turnover of catecholamines in the hypothalamus (32, 35, 38). A similar outcome was evident in urethane-anesthetized rats (718), while acetylcholine enhanced GH levels (257). Also, i.p. pilocarpine and physostigmine augmented GH release. Since these actions were antagonized by atropine, pimozide, and phentolamine, the specificity is questioned (143). Kakucska and Makara (696) achieved enhanced GH concentrations by intracerebroventricular acetylcholine only in pentobarbital-anesthetized rats with anterolateral deafferentation. High doses of acetylcholine enhanced basal GH levels also in conscious rats (143). In sheep, carbachol infusions into the lateral ventricle elevated GH (382). In humans, GH increased 12-fold above baseline 30 min after smoking nicotine cigarettes but not after very low nicotine cigarettes (1482).

Cholinergic compounds did not affect GH release from perifused pars distalis of the rat adenohypophysis (764), while acetylcholine stimulated GH secretion from perifused bovine pituitary slices. These effects were blocked by atropine (102, 1508). Contrary to these findings, acetylcholine and pilocarpine inhibited the GH release from the anterior pituitaries of domestic fowl in vitro if the hypothalamic fragments were present (580).

Studies with anticholinergic drugs have partly confirmed the stimulatory influence of the cholinergic system on GH. Atropine abolished episodic GH peaks in several animal species (915), while in man it did not affect the hypoglycemia-induced GH secretion (110). Atropine-pretreatment suppressed the GH secretion induced by arginine, clonidine, and physical exercise in normal subjects (191). Methscopolamine prevented the sleep-associated GH secretion (965), but it did not modify basal GH secretion (831). The GH burst caused by intracerebroventricular naloxone was antagonized by atropine (643). Quite recently, a fairly specific muscarine$_1$-receptor antagonist, pirenzepine, was reported to block the GH increasing activity of both L-dopa, apomorphine, and clonidine in man (323).

D. ACTH

The hypothalamic cholinergic regulation of CRH-ACTH secretion is a unanimously accepted fact. It has been repeatedly demonstrated that cholinergic drugs stimulate ACTH or corticosteroid secretion. Administration of carbacholine into the brain ventricles increased corticosterone production in rats (6, 886, 1041). Carbachol was also active in cats when given directly into the medial basal hypothalamus (401, 771, 774). Atropine, but not dexamethasone, was an effective antagonist of this action (771). Carbacholine, acetylcholine, and oxotremorine did not affect plasma corticosterone levels in rats with hypothalamic deafferentation (886), but carbacholine was fully active in rats with mesencephalic transection (1041). Also, systemic injections of various cholinomimetics which reach the brain stimulated the adrenal cortex in rats (35, 42, 67, 171, 306, 363, 710), dogs (1350–1353), and man (302, 833, 1131, 1182–1185, 1317). The stimulatory action of nicotine was evident only in unstressed rats (67, 172). Daily i.p. injections of nicotine resulted in an adaptation of the nicotine-induced rise in plasma corticosterone (171). Analogous findings have been made in human studies on cigarette smoking. The introduction of smoking to inexperienced smokers (626) or to chronic smokers who have abstained from smoking for at least 12 h (731) resulted in a rise of plasma cortisol. However, habitual smoking did not activate the pituitary-adrenocortical axis (1315).

In stressed rats, nicotine reduced the high corticosterone levels (472, 573). Andersson and coworkers (42) noticed that noradrenergic activity in the median eminence was strongly decreased after nicotine injections and conclude that the action of nicotine could be indirect. Lewis and coworkers (833) concluded, however, that the actions of high doses of physostigmine in man were stress mediated rather than specific cholinergic actions. In dogs, the action of pilocarpine was abolished by hypophysectomy or much impaired by lesioning of the median eminence (1350, 1352).

Inhibition of the central cholinergic activity has not yielded quite uniform results. In dogs, intracerebral atropine did not modify the stress-induced ACTH release (488). This was the case also in cats whose cerebral ventricles were perfused with atropine and mecamylamine (496). However, in rats, atropine implants into the anterior hypothalamus (601, 602) or into the basal hypothalamus and the median eminence (886) prevented the stress-induced adrenocortical activation. Atropine also prevented electrically stimulated ACTH secretion

when implanted near the electrodes in the anterior hypothalamus (886). Similarly, atropine implants prevented the ACTH releasing action of a variety of stimuli, including i.m. carbacholine and adrenaline injections, i.v. histamine injections, laparotomy, or ether stress (710). An important observation was that atropine implants did not prevent vasopressin secretion. Hence, the two cholinergic systems stimulating ACTH and vasopressin release, respectively, could be dissociated (601). The stimulatory action of the CRH extract could not be prevented by atropine implants, excluding the significance of the cholinergic system at the anterior pituitary level (710). In support of this, systemic injections of massive doses of atropine did not block the stimulated ACTH secretion in dogs and cats (561, 773, 1076, 1351). However, a systemic injection of atropine just prior to the expected diurnal rise of 17-hydroxycorticosteroids prevented this elevation (773).

An interesting new approach has been the use of nicotinic acetylcholine receptor antibodies (1473). After intracerebroventricular injection of these antibodies to rats, basal ACTH and corticosterone levels were increased by approximately 2-fold. The responses of ACTH, corticosterone, and prolactin to ether stress were, however, completely inhibited (1473).

In vitro studies on isolated hypothalami and hypothalamic synaptosomes have yielded quite uniform results which support the significant cholinergic stimulation of CRH synthesis and release. Thus, very small concentrations of acetylcholine (0.1 to 100 pg/ml) increased the CRH content and release from isolated hypothalami (151, 152, 617, 677, 680). Nicotine and betanechol, selective nicotinic and muscarinic receptor agonists, respectively, were also active stimulators, but each of them alone was less potent than acetylcholine itself (152). The actions of acetylcholine were partially prevented by atropine, pempidine, and hexamethonium. The antagonism was complete only when atropine, a muscarinic antagonist, and pempidine, a nicotinic antagonist, were administered together. The action of nicotine was well antagonized by pempidine and that of betanechol by atropine. Hence, it was concluded that both muscarinic and nicotinic cholinergic receptors were involved. Hillhouse et al. (617), however, concluded that the cholinergic activation is mediated mainly through nicotinic receptors, since according to their results bethanechol, a specific muscarinic agonist, was not an active stimulant of CRH release at all. Edwardson and Bennett (392) demonstrated that very small concentrations of acetylcholine (4.4×10^{-9} to 4.4×10^{-11} M) enhanced CRH release from isolated hypothalamic sheep synaptosomes. This action was prevented completely by atropine.

As has been discussed above, the cholinergic action does not seem to be outside the brain. In vitro studies with anterior pituitary preparations support this view. Acetylcholine did not affect ACTH release from normal anterior pituitary cell cultures (133, 592, 593). The situation is different in AtT-20 tumor cells, since the forskolin-stimulated ACTH release was blocked by carbacholine. This inhibitory action was counteracted only by atropine but not by a nicotinic antagonist, gallamine (610). Finally, in the neurointermediate lobes, two studies have come to the conclusion that acetylcholine plays no role (133, 763), while in one study acetylcholine even enhanced ACTH liberation (446).

In conclusion, cholinergic pathways in the hypothalamus seem to enhance CRH synthesis and release. Both muscarinic and nicotinic populations may be involved, although nicotinic receptors may be more important.

VIII. Histaminergic Regulation of Pituitary Hormone Secretion

A. Prolactin

Histamine is phylogenetically a very old amine. Interest in its CNS functions has substantially increased recently. Histaminergic neurons are postulated to be located in the posterior hypothalamus and to project to hypothalamus, various parts of the forebrain, and the brain stem (1458). There is considerably less evidence on histamine as the regulator of pituitary hormones than on monoamines, but during the last decade, histamine has been reported to stimulate the secretion of most pituitary hormones. These include prolactin (376, 839), LH (376, 839), ACTH (1213, 1458), and vasopressin (373, 1409). On the other hand, histamine has been suggested to inhibit TSH secretion (1405).

The first reports to suggest histaminergic prolactin release were by Donoso and coworkers (376) and Libertun and McCann (839). Both groups infused histamine i.c.v. and observed a prolactin burst in male (376) or steroid-primed female rats (839). These results have been confirmed in several subsequent studies in rats (54, 374, 378, 967, 1190) but not in dogs (1213).

Histamine receptors involved in prolactin release have been subject to some controversy. Originally, H_1-receptor antagonists were reported to block suckling-induced (54) and stress-induced prolactin release (525, 839). This was interpreted to mean that H_1-receptors are involved in these processes. However, the direct antagonistic effect on histamine-induced prolactin release was not reported. Since the H_2-receptor antagonist, metiamide, caused an elevation of plasma prolactin, a dual effect with H_1-stimulation and H_2-inhibition was suggested (54). This histamine-releasing effect of H_2-antagonists both i.c.v. and systemically in rats was confirmed in several studies (53, 1177). On the other hand, metiamide, cimetidine, and ranitidine, all H_2-antagonists, were reported to block the prolactin release induced by histamine (375, 379, 1177). After studies with a number of agonists and antagonists, it seems likely that histaminergic stimulation is mediated via H_2-receptors (379) and that the effects of H_1-antagonists are nonspecific. However, sex differ-

ences have been suggested: in males only H_2-receptors whereas in females both types of receptors might be involved (26, 27).

It is assumed that the site of action of histamine is central, but there is not much evidence yet to substantiate this assumption, except that direct effects on pituitary were not reported (839, 1190). The H_2-antagonist ranitidine, too, had no effect directly on the pituitary secretion in vitro (1501). Histamine increases prolactin levels also after systemic injection or infusion (967, 1190), although the doses required i.c.v. are smaller. This may indicate a site of action which is partially beyond the blood-brain barrier.

Perhaps the most direct evidence for the central effect of histamine-induced prolactin release is that it simultaneously caused a fall in pituitary portal dopamine (505). Hence, it may inhibit TIDA neurons, and this site may also explain the partially deficient blood-brain barrier.

In humans, the results are also inconclusive. Histamine infusions have been reported to stimulate prolactin release in men (742, 1124). This stimulation was suppressed by mepyramine but increased by cimetidine (742); however, all changes were minor. Also, these results are somewhat difficult to interpret, since histamine is a polar compound and does not readily cross to the brain.

H_2-receptor antagonists are clinically known to cause gynecomastia and galactorrhea. They have been well demonstrated to cause increased prolactin secretion in patients (333), postpartum women (972), and volunteers (178, 298, 745, 1198, 1203, 1272, 1284), although negative results have also been reported (1250). Since a newer and more potent H_2-antagonist, oxmetidine (SK and F 92994), did not increase prolactin, and a H_2-agonist, impromidine, did not modify the releasing effect of cimetidine (1284), the effect of cimetidine (and metiamide) may be due to some other action than H_2-antagonism. One possibility suggested is serotonergic activation (79). Also, ranitidine differed from cimetidine in some studies in being unable to increase prolactin (294, 1223). However, the exact contribution of different penetration into the brain is not known, and doses may not have been equivalent.

In conclusion, there are open questions in the histaminergic regulation of prolactin, but H_2-receptors may be involved in the stimulation of the release.

B. TSH

There are about 20 studies dealing with the role of histamine in TSH secretion in animals and man, but conclusions are still hard to draw.

1. Animal studies. TSH secretion was not altered in rats fed a histidine-deficient diet to decrease brain histamine levels (664). Two studies are in favor of the stimulatory action of histamine in the rat. In one study, histamine increased basal TSH levels after i.v. injection (879). In another study, depletion of brain histamine levels by brocresin prevented the colloid droplet formation induced by a cold exposure (1070). We have not, however, observed peripheral histamine to alter basal TSH secretion (1403) or TSH response to cold exposure (1405). This was the case also with various histamine agonists and antagonists. Only fairly high doses of L-histidine prevented the TSH cold response (1405). Since L-histidine presumably penetrates the brain better than do the histamine agonists, the inhibitory action would rather be central than peripheral.

Histamine infusions directly into the brain have also been performed. Holak and coworkers (632) infused 100 μg/rat into the lateral ventricle, but they did not find any significant effect on basal TSH levels. In our studies in conscious rats, both histamine (1 to 50 μg/rat) and a H_2-agonist, impromidine (0.1 and 1 μg/rat), decreased the TSH cold response when given into the third ventricle. 2-Pyridylethylamine (2-PEA), an H_1-agonist, was active only at high doses. Histamine antagonists did not alter the TSH cold response, nor did they antagonize the effect of histamine (1405).

In a continuation study (1403), histamine was infused into the median eminence and bilaterally into the posterior hypothalamus or the caudal or rostral part of the anterior hypothalamus. The TSH cold response was always blunted, but the doses needed were much higher than those given into the third ventricle. Even now, H_1- and H_2-antagonists failed to antagonize the action of histamine. In adrenalectomized rats, histamine seemed to lose some of its TSH-depressing activity (1404). Neither dexamethasone nor various amine antagonists were able to alter the inhibitory effect of histamine (1403).

Some results are in favor of a direct action of histamine in the anterior pituitary gland. Peripheral histamine as well as impromidine decreased the TSH secretion induced by exogenous TRH, while fairly high doses of cimetidine and mepyramine further enhanced the action of TRH. Surprisingly enough, L-histidine was inactive (1405). It is noteworthy that even histamine, given into the third ventricle, was able to inhibit the TRH-induced TSH secretion (1403). This finding could be best explained by enhanced release of somatostatin.

Unfortunately, several in vitro studies with isolated anterior pituitary preparations do not generally support any clear action of histamine at the anterior pituitary level. Bowers and coworkers (122) reported that only high doses of histamine may liberate TSH from anterior pituitary explants. Edwards and coworkers (391) used isolated anterior pituitaries, and Yeo and coworkers (1501) isolated anterior pituitary cells, but they did not find any effect on the TSH release by ranitidine.

Finally, in vitro studies utilizing hypothalamic preparations have given evidence of the H_2-receptor mediated enhancement of TRH release. Histamine and dimaprit, an H_2-agonist, could liberate TRH from rat mediobasal

hypothalamic slices (215), from synaptosomes isolated from the whole sheep hypothalami or from median eminence [but not from synaptosomes isolated from other parts of the brain (89)], and from rat mediobasal hypothalamic fragments [but not from the synaptosomes (687)]. The action of histamine could be antagonized by H_2-antagonists but not by mepyramine (687). 2-PEA was not at all active (687).

2. Human studies. Histamine seems to have only a limited role in the secretion of TSH in man. Chronic cimetidine treatment enhanced the TRH-induced TSH secretion only in one study (936). Acute administration of histamine antagonists or agonists has not altered basal or TRH-stimulated TSH secretion in any of the studies available (177, 319, 331, 724, 745, 1250, 1429).

3. Conclusion. In conclusion, the role of histamine in the regulation of TSH secretion is summarized as follows. Histamine undoubtedly stimulates the release of TRH from certain hypothalamic preparations. In these preparations, the role of somatostatin cannot be considered. On the other hand, it has become quite evident that intracerebral histamine prevents the TSH secretion induced by cold exposure. This TSH burst is mediated through enhanced TRH activation in the hypothalamus. Since intracerebral histamine also prevented the action of the exogenous TRH on the anterior pituitary gland, the most probable explanation would be that histamine stimulates the release of somatostatin as well. As far as we know, there is no study dealing with the action of histamine on somatostatin liberation. Hence, at the moment it seems feasible to hypothesize that histamine enhances both TRH and somatostatin (as well as CRH) release. The net effect on the release of TSH from the anterior pituitary gland is not predictable.

C. Growth Hormone

Histamine does not seem to be an important neurotransmitter in the regulation of GH secretion, except perhaps in the rat. Most human studies used various antihistaminic drugs. Neither basal GH levels (319, 745) nor L-dopa-stimulated GH concentrations (177) were modified by diphenhydramine, cimetidine, or ranitidine. However, the sleep-induced GH elevation was blocked by ranitidine (937). Similarly, only high GH levels in cirrhosis (1511) or in acromegaly (754) were blunted by cimetidine; the normal values were not. A single dose of betazole, an unspecific histamine analogue, blunted to some extent the L-dopa response (177). Some evidence of the importance of histamine may be obtained from studies where meclastine, an H_1-antagonist, inhibited the GH response to arginine (1129), and a single dose (176) or repeated doses of cimetidine (1125) inhibited the GH response to insulin (1125). Finally, Knigge et al. (743) reported a paradoxical GH elevation by TRH during histamine infusion. This response was particularly augmented by adding cimetidine to the regimen but attenuated by mepyramine. Histamine and L-histidine infusions did not alter GH levels in man (1126).

Analogously to man, studies with dogs (1213), sheep (382), and Rhesus monkeys (975) have not indicated any specific role for histamine in the GH regulation. In vitro, addition of histamine into an incubation medium containing anterior pituitaries and hypothalamic fragments of the chicken caused GH liberation which was blocked by diphenhydramine (581).

In the rat, however, there is a special morphine stimulation model for studying GH release. In a thorough report by Netti and coworkers (1051), the stimulatory action of morphine was effectively counteracted by histamine as well as by two H_1-agonists, 2-methylhistamine and 2-PEA. These actions were in turn reversed by diphenhydramine which did not affect basal GH secretion. Unexpectedly, indeed, both H_2-agonists and antagonists also decreased the action of morphine on GH, but their action was concluded to be unspecific (1051). The opposite conclusion was reached by Rivier and Vale (1190), who found that diphenhydramine eliminated the morphine-induced GH secretion. In one study, basal GH levels in rats were elevated by an H_1-antagonist. In anesthetized rats, however, intracerebroventricular histamine did not modify GH secretion in either control rats or rats with anterolateral hypothalamic deafferentation (696). However, in another study utilizing anaesthetized rats, both i.c.v. histamine and amodiaquine, an inhibitor of histamine metabolism, decreased pulsatile GH secretion (1049).

D. ACTH

It has been known for years that systemic histamine injections cause rapid adrenocortical activation in rats (293, 710) and dogs (264, 400, 489, 723). The stimulation of the pituitary-adrenocortical axis by i.v. histamine was abolished by anterior but not posterior hypothalamic lesions in dogs (723). Methyrapone-induced activation, on the other hand, was abolished also by posterior hypothalamic lesions. Therefore, the negative feedback mechanism can be dissociated from histaminergic mechanisms (723).

Since most studies have used indirect analyses to document ACTH elevation (460, 536, 887, 1005, 1038, 1065, 1276, 1383), the study of Reilly and Sigg (1171) is of interest, because direct radioimmunoassay of ACTH was applied. Histamine injections are generally assumed to cause pain and alterations in blood pressure which are stressful and may unspecifically activate the adrenal cortex. Reilly and Sigg (1171) claim, however, that i.p. histamine (1.25 to 10 mg/kg) was not solely a stressful stimulus in rats since prolactin levels were not noticeably elevated. Neither was the action of histamine blocked by a tranquillizing diazepam pretreatment. Besides histamine, both an H_1-agonist, 2-PEA, and an H_2-agonist, dimaprit, stimulated ACTH release, but the H_1-agonist was more active. H_1-antagonists were also much more

active than H_2-antagonists in preventing the action of histamine. Hence, it was concluded that the ACTH elevating action of the i.p. histamine is mediated through H_1-receptors (1171). In a further study, Reilly (1170) observed that phentolamine, propranolol, and *p*-chlorophenylalanine augmented the ACTH elevation caused by i.p. histamine.

The most convincing piece of evidence for the role of histamine in ACTH regulation is the effect of α-fluoromethylhistidine (FMH) on ACTH. FMH irreversibly inhibits histidine decarboxylase and causes a rapid fall in brain non-mast cell histamine. Treatment with FMH completely abolished ACTH increase after bilateral adrenalectomy; in controls, it increased 10-fold (168b, 1458).

The action of histamine is evidently not important at the anterior pituitary level, because histamine does not liberate ACTH from anterior pituitary preparations in vitro (487, 1219, 1256), from anterior pituitaries transferred to the anterior chamber of the eye (452), or from isolated neurointermediate lobes (763). Unexpectedly perhaps, histamine did not affect the release of CRH from isolated hypothalami in vitro (425, 617, 681). Other evidence, however, supports the central action of histamine. Hypothalamic lesions prevented the ACTH elevating activity of histamine (887, 1071). Further, when given intracerebroventricularly, histamine increased ACTH secretion in both rats (155, 156, 1275) and dogs (1213). In two of these studies, the action was interpreted to be mediated through H_1-receptors only, and in the dog, H_2-receptors were inhibitory. However, Bugajski and Gadek (156, 157) concluded that both receptor types are needed for an effective stimulation of ACTH liberation in the rats. In a later study on stressed conscious rats, the same investigators gave high doses of histamine and histaminergic agonists i.c.v. and observed now that the stimulatory action on corticosterone production was effectively antagonized by prazocin, phenoxybenzamine, phentolamine, and yohimbine. All the antagonists were also given i.c.v. Hence, the action of histamine may be rather indirect (157). Propranolol and atropine i.c.v. were not effective antagonists.

The above animal studies suggest that histamine stimulates ACTH secretion, possibly through enhanced CRH release. The majority of the results suggest that H_1-receptors are of primary importance. Histamine may act outside the blood-brain barrier, most probably in the median eminence.

Some human studies, too, support the stimulatory role of histamine in ACTH secretion. Meclastine, a typical H_1-antagonist, prevented the ACTH response to hypoglycemia and metyrapone (24). Histamine infusion together with H_1-antagonist, mepyramine, caused ACTH stimulation, suggesting a stimulatory role for H_2-receptors. Ranitidine was not very effective in lowering ACTH but, rather, caused a late increase of ACTH, without any response in cortisol. Hence, nothing very convincing can be said about the histamine receptors involved in man (744).

Finally, it must be pointed out that indirect and quite unspecific mechanisms may also contribute. Histamine, for example, is a powerful stimulus of vasopressin secretion (373, 1409), and vasopressin is a well-known liberator of ACTH (604).

IX. Synthesis and Concluding Remarks

It is easy to see from the pages above that we are as yet only scratching the surface of the neural regulation of anterior pituitary function. It is plausible that in most cases one is dealing with the last neuron(s) of a complex network, both within and without the hypothalamus. The information presented is fragmentary with the exception of dopamine in the inhibition of prolactin release. Here we have the first example of a complete circuit, albeit still partially resolved. Enough is known, however, of the complex balance and feedback system with many factors integrating to a single hormonal message in the pituitary portal vasculature, to impress one of the complexity and delicacy of the regulation. Also here, it is apparent that the information on neurons affecting the TIDA neuron and having 5-HT, opioids, or GABA as their transmitter is hypothetical rather than accepted fact. No such hierarchical system can be even guessed for any hormone other than prolactin.

A simplified synopsis of neurotransmitters involved in the regulation of prolactin, TSH, growth hormone, and ACTH secretion is presented in Table 1. Many pieces of information are uncertain, and there are some conspicuous species differences.

It is quite clear that *dopamine* is the crucial monoamine in the regulation of prolactin, and it is basically a release inhibiting hormone rather than a neurotransmitter, exerting its action at the pituitary level after being released into the hypophyseal portal circulation. There is no other unanimously accepted transmitter acting in the same way, but there is some evidence of GABA inhibiting and adrenaline stimulating prolactin release at the pituitary level. At least in humans, dopamine may also inhibit TSH release after being secreted into the pituitary portal vessels. The same holds true of growth hormone and ACTH, especially in acromegaly and in Cushing's disease, respectively. In normal man, as well as in conscious rats, dopamine stimulates growth hormone secretion through central action. At least in the rat, dopamine has a central inhibitory action on TSH secretion. Evidently, dopamine, too, stimulates somatostatin release which may well mediate part of the general inhibitory actions of dopamine. Finally, the diurnal rhythm of TSH seems to be closely connected with the dopaminergic tone.

Noradrenaline seems to be a crucial transmitter in the regulation of TSH, noradrenaline neurons probably stimulating TRH neurons to release TRH into pituitary

TABLE 1

A simplified synopsis of neurotransmitters involved in the regulation of prolactin, TSH, growth hormone, ACTH, and somatostatin release in mammals. "Peripheral" is only a technical term indicating a site outside the blood-brain barrier. In some cases, it means a hypophyseal site of action and a potential action via pituitary portal circulation.

	Prolactin	TSH	GH	ACTH	Somatostatin
Dopamine					
Central	0	↓	↑	0	↑
Peripheral	↓	↓	↓	↓	
Noradrenaline, adrenaline					
Central	↑ α	↑ α_2	↑ α_2	↑ α_2	↑
Peripheral	↑ β_2 (?)	↓ α_1 (?)	↓ α_1 (?)	↓ α_1 (?)	
5-HT					
Central	↑	↑↓	↑	↑↓	↓
Peripheral	0	↓	0	0	
Opioid peptides					
Central	↑	↓	↑	↑↓	↓
Peripheral	↓(?)	↓↑	0	0	
GABA					
Central	↑	↓	↑↓(?)	↓	↓
Peripheral	↓(?)	0	0	0	
Acetylcholine					
Central	↓ (?)	0 (↓)	↑	↑	↑↓?
Peripheral	?	?	0	0	
Histamine					
Central	↑ (H_2)	↓ (?)	?	↑ (H_1)	?
Peripheral	?	↑↓ (?)	?	0	

portal vessels. Growth hormone resembles TSH in this respect. On the other hand, noradrenaline may be inhibitory in the regulation of ACTH via CRH. An interesting unifying hypothesis seems to emerge from studies with clonidine, an α_2-adrenergic agonist. Stimulation of presynaptic α_2-receptors, which decreases the release of noradrenaline from the nerve endings, has been associated with the enhanced secretion of growth hormone, TSH, and ACTH. On the other hand, stimulation of the postsynaptic α-receptors has generally caused inhibition of the secretion of growth hormone, TSH, and ACTH. In the case of TSH, α_2-receptors seem to locate inside and the α_1-receptors outside the blood-brain barrier. The role of adrenaline is far from clear.

5-HT neurons have clearly been the most difficult to approach. This is partially due to the unspecific tools available, but it seems also to be inherent with the system. Apparently, 5-HT is involved in many rhythms, and at least in some cases, for example, in prolactin regulation, it seems to have an influence on both the releasing hormone and the release inhibiting hormone. This is bound to mean difficulties in the interpretation. The net effect seems to be stimulatory on prolactin and growth hormone, but both stimulatory and inhibitory effects have been described on TSH and ACTH; thus, 5-HT may have a dual role. It may be intimately involved in the circadian rhythm of these hormones. The apparent stimulatory action of 5-HT on TSH and growth hormone may be mediated through the inhibition of somatostatin secretion.

Opioid peptides clearly increase prolactin secretion, but even here several sites of action have been suggested. Growth hormone secretion is also stimulated by opioids, but the physiological role is uncertain. TSH is decreased by opiates and opioid peptides, and there may be species differences with regard to ACTH. In many cases, opioid peptide neurons have been postulated to exert their actions via catecholamine or 5-HT neurons.

GABA has been suggested to increase prolactin by inhibiting dopamine release. Growth hormone secretion is also stimulated by GABA in some experimental arrangements, but stimulated growth hormone secretion may also be inhibited. The net effect on TSH and ACTH is inhibitory in most cases.

There are few studies on the *cholinergic* regulation of prolactin or TSH, and acetylcholine does not seem to be an important factor. Growth hormone and ACTH do seem to be released by cholinergic activation.

Histamine is stimulatory on prolactin and ACTH, but its role in the regulation of TSH and growth hormone is unclear, and there are species differences.

It must be emphasized that in many cases the above conclusions are simplified net results of several possible steps involved, and in only very few cases do we have some idea of the level of action. It is quite clear that it is necessary to proceed now with more refined methods to find interactions of various neurotransmitter systems and to resolve the hierarchy of neuronal systems involved and the localization of the respective neurons. This is a most challenging task in any area of neuropharmacology, but here we at least have the advantage of a clearly defined and precisely measurable outcome: the hormone. This is not the case in all areas of neuropharmacology.

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