DRUG EFFECTS AND HYPOTHALAMIC-ANTERIOR PITUITARY FUNCTION

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This review is restricted to a discussion of recent data concerning the neuroendocrine control of anterior pituitary function, which has been studied with the use of drugs that affect the release of hypothalamic hypophysiotropic factors through their action on brain neurotransmitters. Our knowledge of the polypeptide hypophysiotropic factors, including releasing as well as inhibiting factors of hormones, has rapidly expanded in the past decade and has been competently reviewed elsewhere (1–3). The hypothalamic control of the secretion of the hypophysiotropic principles is not precisely known and is subject to multiple systems which govern their discharge into the hypophyseal portal blood supply. Negative and positive feedback mechanisms have been implicated (4), comprising negative feedback action of target gland hormones and of pituitary hormones on the respective hypophysiotropic factors. In addition, a negative feedback action of the hypophysiotropic factors themselves has been indicated (2, 5).

Part of the regulatory mechanism in the secretion of hypophysiotropic factors is of neural origin. Dopamine (DA) and norepinephrine (NE) containing hypothalamic pathways have been observed. An intrahypothalamic tubero-infundibular DA system with cell bodies in the arcuate nucleus ends in the external layers of the median eminence close to the capillary loops of the portal vessels (6, 7). In the hypothalamus, fibers containing NE and serotonin (5-hydroxytryptamine, 5-HT) are found. These are primarily axons of neurons whose cell bodies are located in the mesencephalon and lower brain stem (6, 8, 9). Cholinergic hypothalamic pathways also exist (10). During the past five years a great many studies were performed to elucidate the role of brain transmitter activity in the modulation of pituitary function. A number of symposia and conferences reflect the remarkable interest in this area. Part of the data and inspiration for writing this review originated from the satellite symposium of the Fifth International Congress on Pharmacology: "Drug

Effects on Neuroendocrine Regulation," held at Aspen, Colorado on July 17–19, 1972.

PITUITARY ADRENOCORTICOTROPIN (ACTH) RELEASE

Introduction

Variation in pituitary-adrenocortical activity and stress may affect the turnover rate of catecholamines (CA) in the brain. Hypophysectomy decreases the turnover of DA and NE, while adrenalectomy slightly increases NE turnover in the CNS (9, 11). This increased NE turnover in adrenalectomized rats is normalized by administration of glucocorticoids (9, 12). Adrenalectomy and administration of metyrapone increase hypothalamic monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) activity (13). ACTH has no significant effect on brain NE turnover in hypophysectomized rats (12), but ACTH and the ACTH analog $ACTH_{4-10}$ increase brain NE turnover of intact rats (9, 14). Immobilization stress increases the turnover of CA in the brain and the spinal cord (15), and this occurs in hypophysectomized rats as well (12). Increased central NE turnover has also been found during exercise and exposure to cold (16) and after electric shock (17, 18). Surgical stress produces a rapid fall in hypothalamic NE (19). The increase in the turnover of NE following restraint is blocked by the tranquilizer chlordiazepoxide but not by high doses of dexamethasone (12).

Catecholaminergic Input in ACTH Release

In a recent review, Ganong (2) marshalled evidence, obtained in rats and dogs, indicating that the release of ACTH is under the inhibitory control of central NE containing neurons. Tullner & Hertz (20) and Ganong and associates (21) found that α-ethyltryptamine, an antidepressant with MAO inhibiting activity, blocks the release of ACTH in surgically stressed dogs. This inhibition is probably exerted at the hypothalamic level and correlates with the sympathomimetic activity of α-ethyltryptamine (21, 22). Systemic administration of L-dihydroxyphenylalanine (L-Dopa) and of several sympathicomimetic compounds (amphetamine, methamphetamine, α-methyltryptamine, tyramine, clopane, 2-aminoheptane) inhibits stress-induced ACTH release (2, 21, 23). Administration of L-Dopa, DA, NE, tyramine, α-ethyltryptamine, isoproterenol, and 5-hydroxytryptophan (5-HTP) into the third ventricle has a similar effect (2, 21, 24). Although these data support the thesis of a central noradrenergic inhibitory system for ACTH release, they do not necessarily indicate a specific receptor, and unfortunately large doses of amines have been employed to demonstrate inhibition of ACTH release.

Inhibition of tyrosine hydroxylase by α-methyl-*p*-tyrosine (α-MT) and of dopamine β-hydroxylase by bis-(1-methyl-4-homopiperazinylthiocarbonyl)-disulfide (FLA-63) causes an increase in plasma corticosterone and a decrease in hypothalamic NE content. α-MT induces a decrease in brain DA content as well (21, 25–27). These data suggest a primary role of NE and not of DA in the regulation of ACTH release. An inverse relation has been found between hypothalamic NE and DA content and plasma corticosterone (25, 26). In rats treated with α-MT both the

decrease of hypothalamic NE and the increase in plasma corticosterone are partially prevented by dihydroxyphenylserine (DOPS) (25). DOPS is directly decarboxylated into NE bypassing DA. Partial repletion of CA by administration of L-Dopa also reduces the effect of α-MT on plasma corticosterone (21, 26). Thus, making NE available in the hypothalamus counteracts ACTH release as a result of NE removal. Intraventricular guanethidine in rats increases plasma corticosterone and decreases hypothalamic NE. Guanethidine crosses the blood brain barrier poorly (28), and systemic injection of a dose 30 times the amount administered intraventricularly fails to affect plasma corticosterone (25). Systemically ineffective doses of α-MT given intraventricularly also cause a rise in plasma corticosterone (26).

The majority of available data that point to inhibition of ACTH release by NE containing brain neurons has been obtained in acute experiments. Chronic administration of α-MT fails to cause an increase in rat adrenal weight (2). Immediately after the intraventricular administration of 6-hydroxydopamine (6-OHDA), which acutely causes gross NE release, stress-induced ACTH release is blocked. One day after administration, an elevation of circulating corticosterone is associated with approximately 90% depletion of brain NE. However, no increase in plasma corticosterone is found 15 days after injection of 6-OHDA, although NE depletion is similar to that of day 1 (2, 29). Others reported 70–80% brain NE depletion one week after intraventricular 6-OHDA with normal or slightly elevated plasma corticosterone (30, 31). Provoost & De Jong (unpublished data) found a similar degree of brain NE depletion and failed to observe an increase in circulating corticosterone in rats 3 months after neonatal intraventricular 6-OHDA administration. This suggests that NE neurons are not necessarily involved in corticotropin releasing factor (CRF) or ACTH release. However, this treatment does not completely deplete hypothalamic NE (31), and supersensitivity to NE may occur under these conditions, resulting in a normal function at the receptor sites. Deafferentation of the hypothalamus may be a better means of removing the NE input to the hypothalamus, while the DA system from the arcuate nucleus remains more or less unaffected. Rats with a deafferented hypothalamus, or rats that have had section of the fornix, have chronically elevated resting corticosteroid levels (2, 32, 33). Deafferentation completely depletes NE but does not affect DA content of the hypothalamic island (34). This again points to NE as an inhibitory transmitter in the mechanism of ACTH release.

Only limited data are available concerning the type of receptor involved in the inhibitory central action of NE on ACTH release. The α-adrenergic blocking agent phentolamine, after systemic administration markedly increases plasma corticosterone in rats, while the β-adrenergic blocker propranolol was ineffective in this respect (25, 35). A systemic ineffective dose of phentolamine causes a similar rise in plasma corticosterone upon intraventricular administration (25). Inhibition of ACTH release by L-Dopa in dogs can be blocked by intraventricular administration of phenoxybenzamine, while phentolamine and also propranolol are ineffective (2). MAO inhibition prevents reserpine- and stress-induced ACTH release (36). De Schaepdryver et al (37), however, were unable to block the increase in plasma corticosterone as a result of restraint by the administration of nialamide. Laparotomy stress

can be blocked by prior iproniazid and dexamethasone, but neither drug alone was effective under the conditions used. Phentolamine reduces the blockade of adrenocortical activation by iproniazid plus dexamethasone, while propranolol is without effect (25). It is possible therefore that the inhibitory central noradrenergic effect on ACTH release is mediated by an α-adrenergic receptor.

Iproniazid potentiates dexamethasone in blocking ACTH release following stress in rats (38). This may be due to an increase in NE levels in the hypothalamus which may enhance the inhibitory effect of dexamethasone on CRF-ACTH secretion (21). Other amines may also be involved (39). MAO inhibitors also prevent reserpine-induced ACTH release in rats (21) and potentiate dexamethasone blockade of ACTH secretion in Cushing's disease as well (40). These data suggest that the negative feedback action of corticosteroids may be mediated at least in part via noradrenergic control of ACTH release. Several investigators (37, 41, 42) reported that depletion of monoamines by α-MT or reserpine does not affect the ability of the pituitary to release ACTH in response to stress. Interestingly, rats treated with drugs that deplete brain NE exhibit a disturbance in circadian variation in ACTH secretion, an increased adrenocortical response to ACTH and to metyrapone, and a decreased suppressibility of ACTH secretion by glucocorticoids. These disturbances can be overcome by brain NE repletion after L-Dopa administration (21). Similar disturbances are found in patients with Cushing's syndrome. However, Krieger (43) failed to find an alteration in plasma cortisol levels in patients with ACTH dependent Cushing's disease following acute or chronic L-Dopa administration. In addition, adrenocortical function in L-Dopa treated patients seems to be normal (44). A single oral dose of L-Dopa, which increases circulating growth hormone (GH), does not affect cortisol levels (45). The same has been found in children (46). Thus, in man, clear evidence for an aminergic inhibitory control of ACTH release so far is lacking.

Marks and associates have contributed considerably to our knowledge on the mode of action of centrally acting drugs on pituitary-ACTH release (36, 47, 48). Treatment of rats with chlorpromazine (CPZ) or reserpine produces a marked and long lasting depletion of CRF activity in the hypothalamus. This indicates removal of a central inhibitory control by these neuroleptics. In fact, pretreatment with a MAO inhibitor (pargyline) prevents reserpine-induced ACTH release and the decrease in hypothalamic CRF activity. Pargyline also reduces ACTH release in response to ether and laparotomy stress (36, 48). Intraventricular carbachol, NE, and DA in rats stimulate ACTH release, but the amounts required are greater than the transmitter content in the brain (48). However, reserpine-induced ACTH release is terminated following a lower dose of intraventricular NE, while DA is less effective and carbachol further stimulates ACTH release (48). The doses employed have little effect on ACTH release and on blood pressure in nonreserpinized rats. However, reserpine implants in the median eminence fail to alter ACTH secretion (49). This may indicate that noradrenergic inhibition is outside the CRF producing region, that the brain area involved is too extensive to be completely effective, or that NE depletion had not been complete. Bhattacharya & Marks (47) proposed that CA and 5-HT are important as inhibitory neurotransmitters for the steady state secretion of CRF.

Serotonergic Input in ACTH Release

Immobilization stress causes depletion of brain 5-HT which has been observed to disappear 16 hr after the stress (15). This may be due to an increased corticosterone secretion, since cortisol can produce a short lasting depletion of 5-HT (50). However, De Schaepdryver et al (37) observed a slight increase in brain 5-HT of rats after 6 hr restraint associated with elevated plasma corticosterone. Other types of stress such as electric shock have also been found to increase 5-HT levels slightly in the brain (51) and to increase 5-HT turnover (17, 18, 52). These discrepancies may in part be explained by the different time intervals used. Marked changes in 5-HT levels caused by MAO and tryptophan hydroxylase inhibitors, tryptophan deficiency, 4-chloramphetamine do not affect stress-induced ACTH release (37, 53).

Daily injections of corticosteroids do not change brain 5-HT levels (54), but a reduced 5-HT turnover has been found in adrenalectomized rats. This is restored to normal by cortisol or dexamethasone (12). Adrenalectomy decreases brain tryptophan hydroxylase activity, and administration of corticosterone and also of ACTH restores this activity (55, 56). Naumenko (57) reported that injection of 5-HT in the hypothalamus of intact and midbrain sectioned guinea pigs causes ACTH release. In unanesthetized cats, 5-HT implantation into the median eminence and septal area also causes an acute rise in circulating 17-hydroxycorticosteroids (17-OHCS) (58). 5-HTP produces adrenocortical activation in rats with complete deafferentation of the hypothalamus (59). The intraventricular injection of 5-HT, however, neither stimulates nor inhibits ACTH release in normal or reserpinized rats (48).

Scapagnini et al (60) have shown that the circadian variation of limbic 5-HT parallels changes in plasma corticosterone and that treatment with *p*-chlorophenylalanine (pCPA) abolishes the normal diurnal variation of plasma corticosterone (60, 61). Drugs that affect the level or action of 5-HT also abolish the daily rise in plasma 17-OHCS in cats but not the response to stress (62). These different treatments did not affect, or slightly decreased, the adrenocortical response to ACTH. Krieger & Rizzo (62) suggested a role of 5-HT in the nervous pathways mediating circadian periodicity of ACTH release. From these findings Scapagnini et al (60) suggested that the frontal cortex, hippocampus, and amygdala, which are rich in 5-HT fibers (63), are part of a serotonergic functional unit that plays a modulating role in the regulation of ACTH secretion. Vernikos-Danellis et al (39) studied the diurnal variation of plasma corticosterone in rats treated with pCPA for 2 or 4 days. These authors also found a disappearance of the diurnal rhythm in plasma corticosterone, but an enhancement of the circulating ACTH and corticosterone response to electric shock or ether stress and an increase in pituitary ACTH levels. They further showed that pCPA reduces the feedback action of prednisolone in stressed animals. Iproniazid potentiates dexamethasone in blocking ACTH release following stress (38). From these studies the hypothesis was proposed (39) that 5-HT mediates the corticosteroid negative feedback action. In this view, the absence of corticosterone due to adrenalectomy results in a decreased brain 5-HT turnover, thus allowing greater ACTH synthesis and release and an increased sensitivity to stress. In contrast, increased levels of corticosteroids stimulate 5-HT synthesis through which the hypothalamic-pituitary adrenal axis is suppressed. This is in

accord with the reported potentiation of stress-induced ACTH release in 5-HT depleted rats. Conversely, treatment with 5-HTP to increase brain 5-HT level raises circulating corticosterone slightly and somewhat suppresses the response to the stress of ether and laparotomy. However, tryptophan administration to adrenalectomized rats abolishes stress-induced release of ACTH. In addition, oral administration of the peripheral decarboxylase inhibitor L-α-hydrazinomethyldihydroxyphenylalanine (MK–486) and 5-HTP for several days produced a marked drop in 17-OHCS excretion in urine in four normal human volunteers (39). These studies suggest that 5-HT is involved in the circadian variation of pituitary-adrenal activity, in stress-induced ACTH release, and in the negative feedback action of glucocorticosteroids.

Cholinergic Input in ACTH Release

Krieger & Krieger (58) have investigated the chemical sensitivity of neurons in brain areas known to be associated with ACTH secretion in unanesthetized cats. They found that carbachol injections into the basal hypothalamus provoke ACTH release. This can be blocked by prior administration of atropine. In rats, in which ACTH release is blocked by pentobarbital even in the presence of morphine or CPZ, systemic carbachol is a powerful stimulus for the release of ACTH (64). Evidence for the existence of a cholinergic mechanism in the release of ACTH comes from studies by Hedge & Smelik (65) who showed that implantation of atropine in the anterior hypothalamus markedly inhibits stress-induced ACTH release. Interestingly, atropine in the same area does not block release of antidiuretic hormone activity which can under certain conditions be reduced by systemic atropine (66). In the dog, intraventricular atropine does not affect stress-induced ACTH release (2), and systemic administration of atropine fails to inhibit stress-induced ACTH release in dogs and cats (67, 68). In contrast, the circadian rhythm of circulating 17-OHCS in cats can be prevented by systemic administration of atropine just prior to the time of the expected circadian rise (68). Thus, a central cholinergic mechanism may be involved in the release of ACTH, but the significance of this mechanism is not well understood.

PITUITARY GONADOTROPIN AND PROLACTIN RELEASE

Introduction

Alterations in hypothalamic CA content, CA turnover, and MAO activity vary with the stage of the estrus cycle and the levels of circulating gonadal steroids (9, 69, 70). A steady increase in CA fluorescence from day one to estrus was found in the DA-containing nerve cells of the tuberal region, but not in the substantia nigra; ovariectomy prevents these changes (71, 72). Following removal of the inhibitory effects of gonadal steroids by castration, NE content and tyrosine hydroxylase activity increase and the rate of turnover of NE in the anterior hypothalamus is accelerated (73, 74), while DA turnover appears to decrease (9). No change in 5-HT synthesis was found in ovariectomized rats (74). The effect of castration disappears following hypophysectomy but can be reproduced in hypophysectomized-oophorec-

tomized rats by treatment with follicle stimulating hormone (FSH) (75). Ovariectomy, but also FSH increases ^{3}H-CA accumulation in rat brain (73). In addition, ^{3}H-CA accumulation is almost four times as rapid during proestrus as during diestrus (75). Turnover of DA in the median eminence, on the other hand, decreases during proestrus and early estrus. This is associated with a drop in luteinizing hormone (LH) content in the pituitary (76). Nigro-neostriatal DA turnover does not change under these conditions. Moreover, DA turnover is high during low pituitary FSH secretion as occurs during pregnancy, lactation, and treatment with gonadal steroids (7).

PROLACTIN RELEASE

Catecholaminergic Input in Prolactin Release

Chronic deafferentation of the medial basal hypothalamus of rats induces a complete depletion of NE, leaving the DA content intact, while the 5-HT concentration of the deafferented island decreases to 30% (34, 77). In male deafferented rats, gonadal function remains relatively normal, while in females ovulation is blocked (78). Thus, cyclic release of gonadotropins depends on neural input to the medial basal hypothalamus. Others found that, following deafferentation, animals become diestrus and circulating levels of FSH and LH decrease, while serum prolactin levels remain normal (34, 79, 80). Administration of α-MT causes a rapid rise in circulating levels of prolactin in completely deafferented rats (34), suggesting that DA is involved in the secretion of prolactin. Donoso et al (81) found that α-MT also increases serum prolactin in castrated male and female rats. Diethyldithiocarbamate (DDC), which inhibits dopamine-β-hydroxylase, has no effect on circulating prolactin. L-Dopa lowers prolactin levels in nontreated and α-MT-treated castrated rats and blocks the prolactin response to suckling. The L-Dopa effect is maintained in the presence of DDC. Treatment with α-MT and DOPS results in a further rise in circulating prolactin (81, 82). It may be, therefore, that NE stimulates and DA inhibits prolactin secretion.

That DA exerts an inhibitory control on prolactin secretion has been suggested by Van Maanen & Smelik (83), who reported that implants of reserpine in the basal hypothalamus of rats induce pseudopregnancy. This local effect of reserpine is blocked by iproniazid. These authors suggested that DA is identical to prolactin inhibiting factor (PIF). This suggestion is supported by observations that not only DA but also NE and epinephrine (E) decrease prolactin secretion from incubated pituitaries in vitro without affecting GH release (84, 85). DA is most effective, and the effect is not due to destruction of prolactin (85) and can be abolished by α- and β-adrenergic blockers (84). However, the amounts of the various amines used in vitro are far greater than the physiological amounts that reach the pituitary from the median eminence (86). Koch et al (87) found that low concentrations of NE and E stimulate in vitro prolactin release while high doses of these amines reduce prolactin release from incubated rat pituitaries. In view of the stimulatory effects of low levels of NE and E on prolactin release in vitro (87), Nicoll (88) suggested that one of these catecholamines may function as the prolactin releasing factor

(PRF). However, intrapituitary infusion of DA, NE, E, or 5-HT has no effect on plasma prolactin, and injection of DA into the stalk median eminence complex via the peduncular artery fails to stimulate prolactin release (70). In contrast, intraventricular administration of 1.25 μg DA and of 100 μg NE or E in intact rats decreases circulating prolactin levels (70, 89), while intraventricular propranolol and phenoxybenzamine increase prolactin secretion (90). Systemically administered MAO inhibitors depress prolactin release, as does the COMT inhibitor pyrogallol in moderate amounts (81, 91). The precursor of DA and NE, L-Dopa, markedly affects prolactin release. L-Dopa decreases while methyldopa increases serum prolactin in young and aged male rats (92). L-Dopa in hypophysectomized rats with pituitary transplants decreases circulating prolactin and increases hypothalamic PIF (93). The same is found on hypothalamic PIF content in intact rats. Intravenous thyrotropin releasing factor (TRF) has been found to augment prolactin secretion in man (94, 95). Surprisingly, L-Dopa inhibits TRF-induced prolactin secretion (96). This would suggest a direct inhibitory action of L-Dopa on pituitary prolactin release if TRF acts on the pituitary directly in mediating prolactin secretion. L-Dopa reduces basal prolactin levels in normal individuals (96). Long-term treatment with L-Dopa decreases prolactin levels in patients with Forbes-Albright syndrome with galactorrhoea. Withdrawal of L-Dopa therapy is associated again with high prolactin levels and galactorrhoea (97).

Inhibition of prolactin secretion by ergot alkaloids has been extensively reviewed recently (98). Ergocornine and 2-Br-α-ergokryptine suppress prolactin secretion in rats (98, 99). These compounds seem to have DA receptor stimulatory effects (9) and reduce the increased turnover of DA in lactating rats with a high prolactin secretion. In rats with a pituitary tumor that secretes prolactin, treatment with ergocornine reduces circulating prolactin and the size of the tumor. The effect of ergocornine on PIF is believed to be of minor importance under these conditions (100). Various ergot alkaloids in lactating rats decrease circulating prolactin levels and lactation (98). The same is found in pituitary grafted hypophysectomized rats (101). Ergocornine also prevents the rise in circulating prolactin in rats bearing lesions in the median eminence (102). Thus, ergot alkaloids have a direct effect on the pituitary. Additional evidence for this has been obtained from in vitro studies (98). 2-Br-α-ergokryptine lowers circulating prolactin levels in normal subjects. Postpartum it causes a marked suppression of elevated serum prolactin and inhibits lactation. In patients with idiopathic galactorrhoea and amenorrhoea it leads to cessation of galactorrhoea and normal menstrual cycles (98, 103). L-Dopa has a similar effect, although it has a shorter duration of action and is more potent. 2-Br-α-ergokryptine decreases circulating prolactin in male and female patients with prolactin secreting tumors and in patients with Chiari-Frommel syndrome (104). The TRF effect on prolactin is inhibited by ergokryptine, suggesting a direct effect of the compound on prolactin secreting cells. Interestingly, during ergokryptine treatment, circulating FSH and LH levels rise considerably (104).

Psychotropic drugs markedly affect the release of prolactin (105). After a single injection, reserpine, CPZ, α-MT, and α-methyl-metatyrosine (α-MMT) elevate circulating prolactin in rats and decrease pituitary prolactin, except α-MMT which

increases prolactin concentration in the pituitary (106). Reserpine and perphenazine increase prolactin secretion in rats without affecting GH release (85). Interestingly, the prolactin stimulatory effect of reserpine depends on the presence of estrogens, since it does not occur in ovariectomized rats (107). However, when the pituitary secretes high amounts of gonadotropins as in ovariectomy, the secretion of prolactin in response to perphenazine is markedly decreased (108). Reserpine and perphenazine also restore the reduced release of prolactin of incubated anterior pituitary tissue of rats bearing prolactin producing tumors (85). Perphenazine in rats increases plasma levels of prolactin by a factor of 10 in relatively low doses (109). Haloperidol, which is an antagonist of DA (110), also causes a marked increase in circulating prolactin in proestrus rats, while pituitary prolactin content decreases concomitantly with hypothalamic PIF. The same occurs in male rats although to a lesser extent (111). In vitro addition of perphenazine does not release prolactin from the pituitary, and this drug slightly affects the release of prolactin in vivo in rats with pituitary transplants in the kidney (109). Addition of low levels of haloperidol and perphenazine to incubated pituitary glands has no effect on prolactin release. However, in the presence of DA both drugs block the inhibitory effect of DA on prolactin release in vitro (112). The effect of apomorphine, a DA receptor stimulating agent (113), and ergokryptine on prolactin release from incubated pituitary glands is also blocked by haloperidol or perphenazine (114). The effect of the two neuroleptic drugs, therefore, may be partially explained by a direct action in the anterior pituitary.

Chronic treatment with CPZ, imipramine, amitriptyline, and haloperidol increases prolactin secretion in animal and man (96, 105, 115). CPZ in man markedly stimulates prolactin release which does not occur in patients with a disease of the hypothalamic-pituitary unit (116). These authors also found that L-Dopa inhibits CPZ-induced prolactin release in healthy volunteers. Apomorphine also blocks CPZ- and suckling-induced prolactin release in rats (117).

In conclusion, DA administration seems most effective in reducing prolactin secretion, and it follows that prolactin secretion may be under the inhibitory control of the tubero-infundibular DA neurons in the hypothalamus by affecting PIF release and/or by a direct action of DA on prolactin secreting cells in the anterior pituitary. Prolactin, but not FSH, LH, ACTH, or TSH, stimulates DA turnover in the median eminence of intact, castrated, and in particular of hypophysectomized rats, which also occurs following intraventricular administration of prolactin (9). This fact lends support to the existence of an intimate relation between this hormone and DA. However, central serotonergic stimulatory pathways may be involved in the release of prolactin as well.

Serotonergic and Cholinergic Input in Prolactin Release

Suckling-induced rise in prolactin secretion is inhibited when 5-HT synthesis is blocked 0–96 hr before the suckling stimulus (118). It reappears after 5 days when 5-HT stores are normal again or sooner if repleted by administration of 5-HTP. Kordon (118) suggests that increasing the 5-HT level in the hypothalamus facilitates

prolactin release. Intraventricular administration of high doses (50 μg) of 5-HT and N-acetylserotonin in intact male and estrogen-treated female rats stimulates prolactin release. This, however, is not found in castrated rats (89). Intraventricular 5-HT and melatonin (1–50 μg) stimulate the release of prolactin in a dose-dependent fashion, as does systemic administration of 5-HTP (70). Electrical stimulation of the ventral medial hypothalamus augments prolactin secretion, which can be somewhat reduced by intraventricular atropine (90), and pilocarpine and physostigmine increase prolactin secretion in ovariectomized rats. This effect is blocked by atropine pretreatment (119). This may indicate the existence of cholinergic stimulatory influences on prolactin release.

FSH AND LH RELEASE

Catecholaminergic Input in FSH/LH Release

Many reports indicate that hypothalamic CA affect the release of gonadotropin hormones. Using an in vitro system, Schneider & McCann (120) found that DA releases LH releasing factor (LRF) from hypothalamic fragments, thus enhancing LH release from incubated pituitaries in vitro. DA had no direct effect on pituitary LH release and did not affect the pituitary response to LRF. In addition, DA injected via a hypophyseal portal vein did not affect FSH and LH release (121). DA injected intraventricularly stimulates LH release via release of LRF in intact rats and increases LRF in portal vessel and peripheral blood of hypophysectomized rats (121–123). Systemic administration of the α-blockers phentolamine and phenoxybenzamine, in contrast to β-blocking agents, prevents the release of hypophysiotropic factors from hypothalamic tissue in vitro by DA (70, 120, 124). The LH response to DA is blocked by prior intraventricular estradiol, while estradiol added in vitro also blocks the effect of DA (122, 124).

Discrepancies as to which of the catecholamines are involved in the release of gonadotropins still exist. Rubinstein & Sawyer (125) found that intraventricular E is more potent than other amines to trigger ovulation in proestrus pentobarbital blocked rats. L-Dopa stimulates LH- and FSH release in ovariectomized estrogen-progesterone primed rats (70). LH release by progesterone-induced stimulation of the preoptic area can be blocked by α-MT or a dopamine-β-hydroxylase inhibitor and is restored by DOPS, indicating NE as the mediator of LH release (123). A single intraventricular injection of 6-OHDA in male rats reduces LH secretion for approximately 8 hr only, while FSH release remains unaltered (126). Marked decrease of hypothalamic amine concentration as induced by reserpine, tetrabenazine, and α-methyldopa suppresses FSH and LH secretion in pregnant mare serum (PMS)-treated immature rats (127). When in PMS-treated immature rats, CA synthesis is blocked with α-MT prior to the "critical period," ovulation is reduced (reduced number of ova). α-MT reduces DA before NE levels in the hypothalamus are decreased (128). In fact, L-Dopa restores ovulation in α-MT-treated rats, while restoration of NE alone by DOPS is ineffective (82). Thus, DA may be involved in α-MT-induced blockade of ovulation. Conversely, α-methyldopa blocks ovulation

only when applied to the region of the tubero-infundibular tract or the median eminence.

These data indicate that a stimulatory dopaminergic control is involved in PMS-induced ovulation. This is not in accord with data on DA turnover (76, 123), which appears low during the critical period in PMS-treated rats (9). The day after the critical period, DA turnover rates are high. Testosterone, in amounts that block ovulation and reduce LH release in PMS-treated immature rats, markedly increases DA turnover in the tubero-infundibular neurons during the critical period (9, 129, 130). These studies suggest that the tubero-infundibular DA neurons might act to inhibit LRF/LH release. Also, a mixture of DA and cholesterol implanted in the median eminence causes prolonged diestrus in normal, cycling rats (131). Although Cramer & Porter (89) failed to find an effect of DA on plasma LH in either intact or estrogen-treated animals, these authors found that DA is a potent inhibitor of LH release in the castrated male rat elicited by the intraventricular injection of 0.15 *M* NaCl via strain receptors in the vicinity of the ventricle. This measure does not release FSH. However, these authors used very high doses of DA. In this respect it is relevant to mention that intraventricular DA in relatively low doses and large amounts of NE and E stimulate LH and FSH release, while high amounts of DA appeared to decrease the discharge of the gonadotropins (70, 132). In man L-Dopa slightly decreases circulating LH (45), but in a study in children L-Dopa was unable to affect FSH or LH levels in blood (46), and L-Dopa in Parkinson patients does not alter the excretion of gonadotropins in urine (44). Chronic treatment with L-Dopa also fails to affect circulating LH and testosterone (133).

Castration hypersecretion of FSH and LH in rats is prevented by α-MT (134). This effect is counteracted by MAO inhibitors or CA precursors. Administration of L-Dopa or DOPS restores the post-castration rise of FSH but not of LH in orchidectomized α-MT-treated rats. L-Dopa shortly after α-MT treatment restores both FSH and LH secretion following castration (135). In contrast, α-methyldopa does not affect circulating LH levels in castrated female rats (118). Thus, the post-castration rise in gonadotropins, which occurs as a result of the removal of the negative feedback of gonadal steroids, may be due to increased NE or DA activity (135).

The positive feedback action of gonadal steroids also seems under CA influence. Using progesterone-induced release of FSH and estradiol-induced release of LH in spayed estrogen pretreated rats, Kalra & McCann (123) studied the interaction of catecholamines in the stimulatory effects of these steroids on the release of gonadotropins. Haloperidol and phenoxybenzamine block the surge of FSH and LH, following progesterone or estradiol respectively. The blockade by these drugs indicates the participation of an α-adrenergic component in the steroid-induced gonadotropin secretion. In fact, blockade of DA and/or NE synthesis with α-MT, DDC, or U 14,624 [1-phenyl-3-(2-thiazolyl)-2-thiourea] inhibits progesterone or estradiol-evoked stimulation of gonadotropin release. Whereas L-Dopa is effective in restoring steroid-induced release of gonadotropin secretion in α-MT-treated rats, it is ineffective when the conversion of DA to NE is blocked by DDC. Repletion of NE by

DOPS in the presence of a low DA concentration in the hypothalamus reverses the blockade (123). These studies suggest that NE plays a role in the regulation of the positive feedback action of estradiol and progesterone on the release of FSH and LH.

The phenothiazines have long been known to inhibit the release of FSH and LH and to block ovulation (for review see De Wied, 115). These drugs interfere with the release of FSH and LH and in particular in high doses, with the sensitivity of the gonads to gonadotropins. The same holds for reserpine. Barraclough & Sawyer (136) were among the first to show that reserpine and CPZ block ovulation when administered prior to the critical period of LH discharge at proestrus. This effect is counteracted by pretreatment with MAO inhibitors (137). PMS-induced ovulation in immature rats is also blocked by reserpine (138). Reserpine given after the critical period does not affect ovulation, suggesting that the effect of reserpine is mainly on LH release (137). PMS plus human chorionic gonadotropin (HCG)-induced ovulation in intact or hypophysectomized immature rats is also blocked by reserpine (139). This effect is not dose related and pargyline partially reverses the inhibitory action of reserpine. Thus, reserpine appears to act on both LH release and on the ovary. Treatment with reserpine on the morning of proestrus inhibits spontaneous ovulation and elevates the electrical threshold of the preoptic area to induce ovulation but not of the median eminence region (125). Reserpine 18–20 hr after treatment completely blocks ovulation evoked by electrical stimulation, and MAO inhibition in these rats restores electrically stimulated but not spontaneous ovulation. FSH release is also affected by reserpine. The depletion of FSH, which occurs in the pituitary of rats of 34–39 days of age, is reduced by reserpine (140). The foregoing discussion does not allow a conclusion as to which CA is involved in FSH/LH release. Presumably more than one transmitter participates in the cyclic and noncyclic secretion of these pituitary hormones.

Serotonergic Input in FSH/LH Release

The level of plasma testosterone in rats is reduced following treatment with α-MT or pCPA, indicating that both CA and serotonergic pathways are involved in the regulation of gonadotropic hormone release (141). Nialamide given during the critical period of PMS-treated immature rats (82) blocks ovulation. This blockade is prevented by prior treatment with pCPA but unaffected by α-MT. A tonically inhibitory effect of 5-HT neurons on copulation has been suggested (69), because pCPA can substitute for progesterone. In addition, progesterone is capable of reversing the antiovulatory effect of MAO inhibition (82). pCPA reduces ovarian weight increase in immature rats and prevents FSH depletion in rats of 34–39 days of age (140). A single injection of 5-HT or melatonin on the day of operation blocks compensatory ovarian hypertrophy and FSH release in a dose-related fashion. The blockade is most effective when substances are given on the day of diestrus. 5-HT is less effective than melatonin (142). Melatonin and 5-methoxytryptophol in the lateral ventricle of immature rats from the 25th day of birth delays vaginal opening, indicating blockade of gonadotropin release (143). Intraventricular 5-HT and melatonin in moderate amounts have been shown to suppress the release of FSH and LH. Systemic administration of 5-HTP in castrated male and female rats

reduces LH and FSH release. The proestrus surge of FSH and LH can be inhibited by intraventricular administration of 5-HT and melatonin in rats (70).

5-HT administered systemically on the day before proestrus blocks spontaneous ovulation. This effect can be overcome by methysergide or LH (144). In addition, multiple intraventricular or intracardiac injections of 5-HTP or melatonin on the day of proestrus inhibit ovulation. 5-HT has the same effect upon central administration as 5-HTP after intracardiac injection. This blockade of ovulation is preceded by inhibition of gonadotropin release and is prevented by LH or hypothalamic extracts (70). Blockade of ovulation after the administration of MAO inhibitors has been specifically linked to increased brain 5-HT levels (82). Microinjection of a MAO inhibitor in the median eminence increases 5-HT levels and blocks ovulation (82). The same is found when the MAO inhibitor mebenazine is given in combination with 5-HTP. Mebenazine plus L-Dopa has no such effect (145). A single injection of α-MT, which inhibits DA and NE synthesis without affecting 5-HT synthesis, blocks ovulation, while α-MMT, which also decreases 5-HT, does not. Donoso et al (81) reported that α-MT does not affect FSH/LH release in castrated rats. The same was reported for pCPA. Kordon & Glowinski (82) found that pCPA facilitates ovulation only when administered just before the critical period. It has an opposite effect when given 20 hr before. This suggests that different 5-HT neurons are involved in cyclic and noncyclic LH release. This paradoxical effect of pCPA may partly explain existing controversies in the literature on the influence of 5-HT neurons on gonadotropin release.

In conclusion, the evidence summarized above indicates that serotonergic pathways exert an inhibitory control over the release of gonadotropins. These effects are exerted via FSH releasing factor (FRF) and LRF release, while the injection of 5-HT into the portal vessel system does not affect the release of gonadotropic hormones (70, 132).

Cholinergic Input in FSH/LH Release

Kato & Minaguchi (146) have reported changes in choline acetylase activity during cyclic changes of gonadotropin secretion. Atropine has been known for a long time to block ovulation (147), and atropine administered subcutaneously or intraventricularly suppresses FSH and LH release and blocks ovulation. This blockade can be reversed by LH or by a crude hypothalamic extract (70, 148). In the presence of hypothalamic fragments, acetylcholine stimulates the release of gonadotropins from anterior pituitary tissue in vitro (70, 148, 149), while atropine has the reverse effect. Atropine given intraventricularly on the day of proestrus suppresses FSH and LH surge and inhibits ovulation (149). Pilocarpine and physostigmine reduce plasma LH but not FSH levels. This reduction is followed by a sharp rise in LH 1.5–6 hr after injection. Atropine, which in itself does not affect FSH/LH release, partly prevented the effect of these cholinomimetics (119). Oxotremorine reduces LH secretion in ovariectomized rats. This effect is blocked by atropine but not by methylatropine. Thus, central muscarinic receptors are involved in the blocking effect of oxotremorine on LH secretion (150). Nicotine, when injected at half-hour intervals on the afternoon of proestrus, delays the ovulatory surge of LH and blocks

spontaneous ovulation in rats, indicating an inhibitory effect of nicotine receptors in the neural mechanism of LH release (151).

PITUITARY GROWTH HORMONE (GH) RELEASE

Catecholaminergic Input in GH Release

Numerous reports have appeared indicating the existence of catecholaminergic regulation of GH secretion in man, monkey, sheep, and rat. However, contradictory data exists, and species differences in GH release complicate the picture. Man and rat respond differently to stress with respect to GH secretion. Stress stimulates the release of GH in man and monkey (152, 153), while it inhibits the discharge of GH in rats (154, 155). Administration of E to monkeys induces a significant rise in GH secretion (156). In baboons, intraventricular administration of DA inhibits GH secretion (157). The same is found after microinjection of DA in the ventromedial nucleus, while NE in the same structure stimulates GH release (158). In contrast, microinjection of 5-HT in the ventromedial nucleus does not affect GH release, while DA and NE in other hypothalamic areas do not change the secretion of GH in baboons. Phentolamine depresses, while β-adrenergic and ganglionic blockade increase GH levels in blood of baboons (159). The stimulatory action of β blockers and ganglionic blockade on GH release is prevented by phentolamine. Thus, in primates α-adrenergic activity stimulates, while DA- and β-adrenergic activity inhibit GH release. A recent study in rhesus monkeys points to a stimulatory influence of DA, NE, and 5-HT on GH release (160). In these monkeys, equipped with a chronic indwelling intraatrial cannula, L-Dopa infusion causes a GH peak, which is enhanced in animals pretreated with the dopamine-β-hydroxylase inhibitor disulfiram. DOPS also causes an increase in circulating GH, as does 5-HT infusion (160).

In sheep, infusion of E decreases circulating GH (161). In the same species, administration of E blocks the GH response to arginine (162). This effect of E is not blocked by phentolamine (163). Intracarotid injection of phenoxybenzamine or of arginine increases circulating GH in sheep, while L-Dopa blocks arginine-induced GH secretion (163). Because phenoxybenzamine does not block DA receptors (8), central NE activity may tonically inhibit GH release in sheep. Interestingly, Davis & Borger (163) found the same mechanism operating in the release of prolactin in sheep.

In rats, CPZ and reserpine, as well as α-methyldopa and α-MMT, block insulin-induced depletion of GH activity in the pituitary. This effect is prevented by prior administration of iproniazid. Peripheral depletion of CA with guanethidine is ineffective (164, 165). Injection of low doses (0.1–0.5 μg) of NE and DA into the lateral cerebral ventricle of rats induces depletion of bioassayable GH activity in the pituitary. E is also active, but only at higher dose levels, and NE (5 ng) appeared to be the most active amine in this respect (166). Intraventricular injection of 5-HT, acetylcholine, histamine, vasopressin, or oxytocin is without effect (167). Intraventricular NE and DA in doses that cause depletion of pituitary GH activity, decrease GH releasing factor (GRF) activity in the hypothalamus of intact and hypophysec-

tomized rats and increase circulating GRF activity (166). Rats with a transplanted pituitary tumor secreting high quantities of GH and prolactin have markedly lower circulating GH only if pretreated with L-Dopa (168). The authors suggest a direct effect of L-Dopa on GH secretion from the tumor. However, neither E, NE, nor DA affect the discharge of GH from rat pituitaries incubated in vitro (84).

Urethane anesthesia in rats induces constant and low circulating GH levels. Collu and associates (169), with the aid of a radioimmunoassay, explored the role of central CA on GH release in urethanized rats. It was found that intraventricular DA induces a decrease in GH level shortly after administration. NE has a similar effect. Propranolol had no effect in itself, but it prevented DA-induced suppression of GH release. Intraventricular administration of 5-HT was followed by a rapid rise in GH levels which was prevented by intraventricular phenoxybenzamine. Phenoxybenzamine elicited a prompt inhibition of GH release.

In view of this, Collu et al (170) proposed that in the rat, central DA tonically inhibits and 5-HT stimulates GH release. In fact, DA is found in the same band as GRF activity of fractionated nerve terminals of rat median eminence (171). However, Müller et al (172) were unable to affect GH release with 1 μg intraventricular 5-HT in urethane anesthetized rats. These authors found that central CA depletion by 6-OHDA or α-MT does not affect plasma GH level. L-Dopa in α-MT-treated rats, which is associated with high hypothalamic DA level, reduces GH secretion. FLA-63 plus L-Dopa had the same effect, while the DA receptor blocking agent pimozide had the reverse influence on GH release. Therefore DA may inhibit and NE may stimulate GH release in rats.

Evidence for an inhibitory DA control of GH secretion has also been obtained in deafferented rats. Ether stress and auditory stress reduce plasma GH levels in sham-operated rats, as well as in frontally and in incompletely deafferented rats. Auditory stress does not reduce GH release in totally deafferented rats but ether stress does (173). Treatment of totally deafferented rats with α-MT prevents GH reduction in response to ether stress. Because DA neurons are preserved in the totally deafferented rat hypothalamus, DA appears responsible for the inhibitory effect of stress on GH release in the rat. This is in accord with the fact that deafferented young rats grow fairly well (78).

A considerable number of reports has appeared on the influence of L-Dopa on GH release in humans. In contrast to rats, L-Dopa increases circulating GH levels of normal human subjects and of patients with Huntington's chorea (174). Chronic treatment of Parkinson patients with L-Dopa, however, is not associated with increased fasting levels of GH, although the GH response to insulin hypoglycemia is subnormal (175). In children, oral L-Dopa for several days increases GH levels within 0.5–2 hr. No such increase is found in children with idiopathic hypopituitarism (46). The same has been observed following a single oral dose of L-Dopa in normal subjects and in patients with Parkinson's disease (45, 175–177).

L-Dopa given orally induces a gradual rise in circulating GH. This effect is blocked by pretreatment with phentolamine (178). The effect on circulating GH after orally administered L-Dopa, is more consistent in young than in older subjects, and a high percentage of nonresponders is found in depressive illness (179). In

acromegalic patients, however, L-Dopa suppresses GH release (180), while L-Dopa treatment in Cushing's disease fails to affect plasma GH levels (43). Phentolamine inhibits and propranolol enhances plasma GH response to insulin hypoglycemia in human subjects. Infusion of L-Dopa, and of E plus propranolol increases circulating GH and enhances insulin- and arginine-induced GH release (178, 181, 182). None of these treatments increases plasma GH levels in pituitary dwarfs (182). The increase in circulating GH following E and propranolol is blocked by phentolamine but not by glucose or aminophylline (178). In addition, exercise-induced GH release in normal and in nonobese juvenile diabetics is suppressed by phentolamine and enhanced by propranolol (183). Propranolol in a single oral dose augments glucagon-induced GH secretion in normal subjects. This does not occur in hypopituitarism (178). The poor GH response to glucagon in hypothyroid patients is converted to normal by propranolol treatment (184). Thus, α-adrenergic stimulation and possibly β-adrenergic inhibition in man are associated with GH release.

PITUITARY THYROTROPIN HORMONE (TSH) RELEASE

Catecholaminergic Input in TSH Release

It has been suggested that TSH release is also under the control of central CA activity (185). Martini (186) found that intraventricular administration of E in dogs increases plasma TSH. However, application of NE or E in the hypothalamus of rats failed to stimulate the release of TSH (187). In addition, propylthiouracil treatment has no effect on DA turnover in the median eminence of male rats (7). Deafferentation of the medial basal hypothalamus of rats slightly reduces TSH release as determined by ^{131}I uptake and biological half life of thyroidal ^{131}I (78). Thus, the absence of hypothalamic NE only slightly affects TSH release.

Direct stimulating effects of E added in vitro and of systemically administered CA and 5-HT on anterior pituitary and thyroid gland have been found (188, 189). Cervical sympathetic stimulation also increases thyroidal hormone release; this effect is blocked by phentolamine (190), but phenoxybenzamine and phentolamine reduce the thyroid response to TSH (191). Daily injection of propranolol for 21 days does not affect circulating TSH in intact rats. However, propranolol increases circulating thyroxin (T_4) levels in intact as well as in hypophysectomized rats (192), indicating a direct stimulatory effect of β-adrenergic receptor blockade on thyroid gland activity. Thus, a peripheral TSH-like effect of the biogenic amines and the β-blocking agents on thyroid hormone secretion is present. This is in accord with recent studies (193) in which the effect of various CA depleting agents on thyroid activity in rats was investigated. Thyroid activity was compared with NE depletion in hypothalamus and heart. Chronic treatment with reserpine, α-methyldopa, α-MT, and guanethidine reduces thyroid secretion rate. Tetrabenazine, which acts mainly centrally, did not affect thyroid secretion rate, while guanethidine, which acts mainly peripherally, decreased thyroid activity. Thus, peripheral NE depletion rather than depletion of central NE is correlated with a decrease in thyroid function (193). The effect of cold exposure, which causes an acute and marked increase in intrathyroidal colloid droplets, is blocked by phentolamine, reserpine, and atropine. These drugs do not interfere with the action of TSH releasing factor (TRF) on the

pituitary-thyroid axis (194), suggesting that their effect on pituitary TSH release is centrally mediated.

The phenothiazines affect the pituitary-thyroid axis. Acute and chronic administration of CPZ and related phenothiazines depress thyroid activity. This probably is not only the result of inhibition of TSH release, but also of a direct effect on the thyroid gland and on the metabolism of T_4 in the body (for review see De Wied, 115). Onaya et al (195) found evidence for a direct inhibitory effect of CPZ on TSH-stimulated colloid droplet formation in dog thyroid slices. This is attributed to a stabilizing effect of CPZ on lysosomes. Reserpine given chronically to rats lowers circulating TSH and reduces TRF synthetase concentration in the hypothalamus (196). This was interpreted to indicate a central catecholaminergic input in pituitary TSH release. 5-HT, however, may be involved. Treatment of rats with pCPA for five days decreases circulating triiodothyronine (T_3) levels, without affecting T_4. However, a marked depression of serum TSH is associated with 5-HT depletion. The intrathyroidal 5-HT and 5-hydroxyindole acetic acid (5-HIAA) decrease induced by pCPA suggests a peripheral effect of pCPA, but the fall in TSH points to a central stimulatory influence of 5-HT neurons on TRF/TSH release (197).

Studies in man also fail to reveal a central aminergic control of TSH secretion. Eddy et al (177) found no change in circulating TSH following the acute administration of L-Dopa, and no alteration in various parameters of thyroid function was observed following two weeks of L-Dopa treatment in Parkinson's patients (44). In children, chronic L-Dopa does not affect plasma TSH levels (46). L-Dopa administration to normal human subjects and to patients with Parkinson's disease does not materially affect T_4 levels in blood. Chronic treatment increases circulating T_4 (175). This could be due to increased TSH levels, but also to alterations in distribution, binding, metabolism, and excretion of T_4, because infusion of E causes a decrease in fecal excretion of T_4, increased binding, and a shift of tissue T_4 stores to the vascular compartment (198). Ericson et al (199) obtained evidence for a direct stimulating effect of CA and 5-HT on thyroid hormone release in mice. Interestingly, chronic L-Dopa treatment in patients with Parkinson's disease results in inhibition of TSH secretion in response to TRF (200). Infusion of isoproterenol, NE, phentolamine, or propranolol does not alter TRF-induced TSH release nor do these agents affect circulating TSH levels (201). Neither α- nor β-adrenergic blockade has an effect on the serum TSH response to cooling in young adult human subjects (202).

GENERAL CONCLUSION

The evidence summarized in this review supports the hypothesis that monoamines and other transmitter substances participate in the control of hypophysiotropic hormones from the releasing factor cells in the median eminence of the hypothalamus. These cells can be regarded, as Wurtman (69) has put it, as neuroendocrine transducer cells that differ from neurons as well as from endocrine cells, in that they convert a neuronal input to a humoral output.

Variations in pituitary-adrenal activity and stress, and cyclic changes in pituitary gonadotropin release are associated with variations in neurotransmitter activity in the hypothalamus as determined by alteration in content, turnover, rate of synthesis

from labeled precursors, enzyme activity, and histochemical fluorescence. The tubero-infundibular DA system, which is not affected following deafferentation of the hypothalamus, plays an important role in the release of various pituitary hormones. Conclusive evidence has been obtained that this system tonically inhibits the release of prolactin. This may be achieved by a stimulatory influence of DA on PIF, although a direct inhibitory effect of DA on pituitary prolactin release as demonstrated in in vitro studies cannot be excluded. These effects are brought about by amounts that probably never reach the pituitary under physiological conditions (86, 132). In addition, intrapituitary infusion and injection of these amines into the stalk median eminence complex via the local blood supply (70, 121) do not affect the release of prolactin. A number of studies point to a direct effect of L-Dopa on pituitary prolactin, TSH, and GH release, because TRF-induced release of prolactin and TSH in man is blocked by pretreatment with L-Dopa, and this amino acid in rats lowers circulating prolactin and GH from extrapituitary tumors.

The release of gonadotropins according to Fuxe et al (7) is also related to the tubero-infundibular DA neurons because DA turnover may be high when FSH/LH release is low and conversely low when FSH/LH release is high. This could be explained if the release of FSH/LH and prolactin would be inversely related as has been maintained for many years (203). In fact, when the pituitary secretes high amounts of gonadotropins as in ovariectomized animals, perphenazine has a much smaller effect on prolactin release as in intact rats (108). However, evidence has also been presented that NE is the transmitter involved in LH- and FSH release elicited by stimulation of the preoptic area (123), in PMS-induced ovulation in immature rats, and in the negative and positive feedback action of gonadal steroids on gonadotropin release. The issue, however, is not clear, and controversies as to which transmitter is involved exist.

An inhibitory noradrenergic control of ACTH release has been suggested (2), and available data support this hypothesis in acute preparations. In chronic situations a persistent depletion of brain NE as induced by α-MT and 6-OHDA is not associated with a rise in pituitary-adrenal activity and these observations suggest that either NE is not essentially involved in ACTH release or that the hypothalamus under these conditions is not completely devoid of this transmitter. A small active pool may be present (29), and supersensitivity to NE may exist. However, resting pituitary-adrenal activity is chronically increased in rats in which the medial basal hypothalamus is completely deafferented.

In various species, E, NE, and DA affect GH release. Phentolamine is capable of blocking the effect of these amines, suggesting that NE is the transmitter involved. α-Adrenergic blockade in various species has an effect on the release of GH opposite to β-adrenergic blockade. However, DA may also be the transmitter, since GH secretion is maintained in rats with a complete deafferentation of the medial basal hypothalamus (78), and GRF activity is found in the same band as DA in fractionated rat median eminence nerve terminals (171). Conclusions from the different studies on GH release are limited because of the existence of species differences and profound effects of stress and of anesthetics used.

Surprisingly, little is known of the neural input to the neuroendocrine TRF-

producing transducer cell whose hormonal output was the first to be identified (3). Data on the neuroendocrine regulation of TSH release are scarce, but should be available soon, because the radioimmunoassay of TSH has come into operation. Studies on TSH release are obscured by a direct TSH-like effect on various amines on the thyroid gland.

Other transmitter systems seem to be involved in the input to the releasing factor cells as well. Atropine can block the diurnal variation in pituitary-adrenal activity and inhibits stress-induced ACTH release when implanted in the anterior hypothalamus but not when administered systemically. In addition, atropine is capable of blocking ovulation and reduces FSH/LH release. Depletion of brain 5-HT also abolishes the diurnal variation in plasma corticosterone (60, 62). Since there appears to be a correlation between the daily variation of 5-HT concentration in the limbic system and that of circulating corticosteroids (60), it is not surprising that circadian variation in pituitary-adrenal activity is disturbed when 5-HT levels in the brain are altered. The same may hold for other transmitters as well. A daily rhythm in anterior and posterior hypothalamic NE has been observed, the concentration being highest at the middle of the dark period (204), and drugs that deplete brain NE disturb the circadian variation in ACTH secretion (21). Depending on the time of the day the experiments were performed, depletion of amine stores, as has been used in many of the studies reported here, may interfere with cyclic phenomena and with pituitary hormone release. 5-HT is involved in other pituitary functions as well. It reduces the feedback action of adrenal steroids on pituitary ACTH release, and systemic administration of 5-HT blocks spontaneous ovulation. However, 5-HT also inhibits ovulation by local vasoconstriction in the ovary (205). Moreover, 5-HT may be a stimulatory transmitter in the release of GH. Thus, the input to the releasing factor cells is complex and of catecholaminergic, cholinergic, and serotonergic character.

Finally, the feedback action of target gland hormones on the release of anterior pituitary hormones may be mediated by brain neurotransmitter activity. Corticosteroid-sensitive neurons in the hypothalamus are inhibited by NE (206). Dexamethasone does not block the increased NE turnover following immobilization stress (12), but the corticosteroid negative feedback action on pituitary ACTH release is potentiated by MAO inhibition and reduced by pCPA (39). Testosterone in amounts that reduce LH release during the critical period increases DA turnover in the tuberoinfundibular DA system (129, 130), and estradiol blocks LH release as induced by intraventricular DA (122). pCPA can substitute for progesterone in copulatory behavior (69), and progesterone is as effective as pCPA in reversing the anti-ovulatory effect of MAO inhibitors (82). These are interesting observations that need additional experiments to explore the interaction of target gland and pituitary hormones with neurotransmitter activity in the hypothalamus.

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