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Psychoneuroendocrine research in depression

II. Hormonal responses to releasing hormones as a probe for hypothalamic-pituitary-endorgan dysfunction

Review Article

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Summary. The rapid growth of fundamental research in neuroendocrinology includes advances in our understanding of the role of neurotransmitters in the control of hypophysiotropic neurons, the concept of neurosecretion, the portal circulation chemotransmitter hypothesis of anterior pituitary regulation, and the chemical structures of the hypophysiotropic hormones. These advances correspond to the emergence of psychoneurobiology, with the appreciation of the roles of neuropeptides, such as hypothalamic releasing and inhibiting hormones, their relevance to brain function and possible involvement in psychiatric disease, and their introduction into psychoneuroendocrinological studies. The subject of the present review is to summarize and integrate current knowledge of the neuroendocrinology of hypothalamic releasing and inhibiting hormones, to apply it to the understanding of the pathogenesis of depression, and to evaluate their relevance as psychoneuroendocrine research tools.

Keywords: Thyrotropin-releasing hormone; corticotropin-releasing hormone; somatostatin; growth hormone-releasing hormone; psychoneuroendocrinology; depression.

Introduction

The hypothalamus has traditionally been considered the pivotal brain region linking experimental and clinical neurosciences, namely endocrinology, neurology and psychiatry. This review aims to provide further insight into the relationships between hypothalamic dysfunction and depression. In the first place, clinical recognition of specific hypothalamic dysfunction clearly initiated the research that led to the discovery of neuronal control over the pituitary. The major contribution to that research, the isolation and identification of

hypothalamic hypophysiotropic hormones and their neuronal origins, has in turn permitted recognition of new signalling factors and new functional intercellular regulatory connections at all levels of the neuroendocrine axes.

Although the concept of neurosecretion was developed by E. and B. Scharrer in 1928, the topic of hypothalamic neuropeptide identification represents one of the more recent important aspects of cellular and molecular neuroscience with relevance to psychiatry. Neurosecretory cells were characterized by their release of messenger molecules directly into the systemic circulation. According to the concept of Harris (1948) it was recognized that neurons terminating in the external layer of the median eminence are involved in the control of anterior pituitary hormone secretion. Their products, primarily representing releasing and inhibiting peptide hormones, have been isolated and sequenced by Guillemin, Schally, Vale and collaborators and include thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), somatostatin [somatotropin-release-inhibiting hormone (SRIH)], corticotropin-releasing hormone (CRH) and growth hormone-releasing hormone (GHRH). These release and inhibiting hormones are also present in numerous suprahypothalamic structures as well as in endocrine tissue and the circulation, and have been shown to exert distinctive actions within defined regions of the central nervous system and spinal cord, thus coordinating complex behavioural and/or physiological processes.

The availability of synthetic releasing hormones, in particular TRH, CRH and GHRH, has greatly enhanced the capacity of clinical psychoneuroendocrinologists to explore the integrity of hypothalamic-pituitary-thyroid (HPT), -adrenal (HPA), and -somatotropic (HPS) function in affective illness.

Hypothalamic-pituitary-thyroid system

The HPT axis has served neuroendocrinology as the example par excellence of a negative feedback regulatory system (Martin and Reichlin, 1987). This regulation is achieved by the interaction of three groups of hormones. TRH, a tripeptide (Boler et al., 1969) primarily localized to the median eminence and dorsomedial, ventromedial, arcuate and paraventricular nuclei, stimulates the synthesis and release of thyrotropin (TSH), while SRIH inhibits TSH secretion. TSH activates iodide uptake, hormonogenesis, and the release of the thyroid hormone thyroxine (T_4) and triiodothyronine (T_3), which, in turn, exert negative feedback effects on the pituitary to regulate TSH secretion and possibly on the hypothalamus to influence TRH release. Although this model describes most of the regulatory factors in HPT function, other mechanisms influence the rate of TSH secretion. The hypothalamic production and release of TRH is principally controlled by noradrenergic and serotonergic innervation (Morley, 1983). In addition, dopamine (DA), various neuropeptides [opioid peptides, neurotensin (NT), cholecystokinin (CCK), etc.] and steroid hormones (glucocorticoids, gonadal steroids) exhibit a modulatory function at the level of the hypothalamus and/or pituitary (Fig. 1).

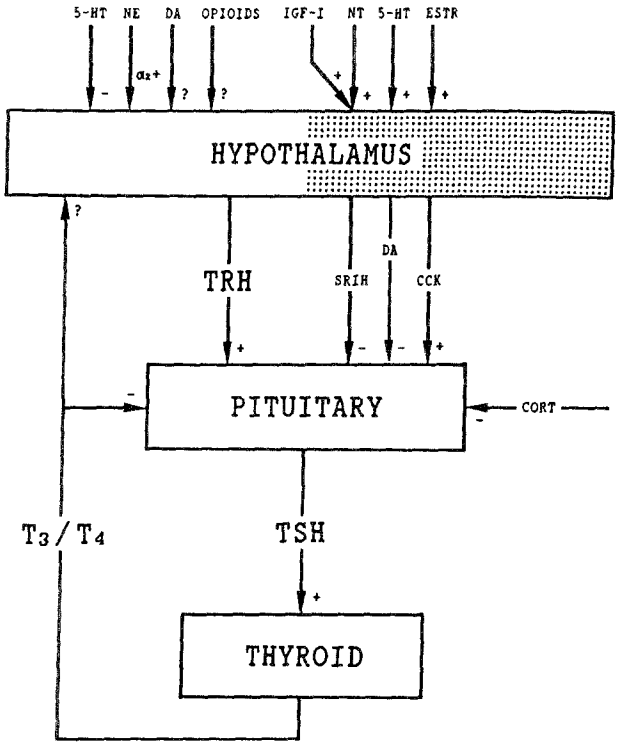

Fig. 1. Regulation of the hypothalamic-pituitary-thyroid (HPT) system. T_3/T_4 Thyroxine/triiodothyronine; *TSH* thyrotropin; *TRH* thyrotropin-releasing hormone; *SRIH* somatostatin; *CCK* cholecystokinin; *CORT* corticosteroids; *5-HT* serotonin; *NE* norepinephrine; α_2 α_2-adrenoceptor; *DA* dopamine; *Opioids* endogenous opioid peptides; *IGF-I* insulin-like growth factor I; *NT* neurotensin; *ESTR* estrogens. ± Stimulating/inhibiting pathways

In depression HPT function has been assessed mainly by measuring the TSH response following intravenous administration of 200 µg or 500 µg TRH. Loosen and Prange (1982) reviewed 41 studies on 917 euthyroid, depressed patients and concluded that attenuated TSH responses occur in approximately 30% of patients with depression. However, the clinical value of the TRH test in depression is currently a controversial issue, since abnormal responses to TRH have also been reported in patients with mania, panic disorder, anorexia nervosa, and alcoholism.

TSH blunting may be due to chronic hypersecretion of endogenous TRH (Loosen, 1987). In this condition, the thyrotroph cells would become hyporesponsive to TRH, possibly because of down-regulation of TRH receptors, consequently leading to deficient thyrotroph responsiveness after such exogenous stimulation. This hypothesis rests on the report that patients with depression exhibit elevated concentrations of TRH in CSF (Kirkegaard et al., 1979) and on studies in which TRH was given chronically in healthy subjects showing deficient TRH-induced TSH responses (Snyder and Utiger, 1973) as well as an inhibition of normal TSH increments during evening hours and a loss of the

diurnal TSH rhythm (Spencer et al., 1980). The latter findings has been reported to occur also in depressed patients (Golstein et al., 1980).

Alternative mechanisms involve the status of the thyrotroph cells which may be malfunctioning or receiving increased inhibitory input in patients with TSH blunting. Although it still remains to be determined whether small alterations in free T_3/T_4 are responsible for TSH blunting, endogenous as well as exogenous glucocorticoids suppress the TSH response to TRH, and the hypercorticolism found in depression has been postulated to be responsible for diminished TRH-induced TSH release (Rupprecht et al., 1988). This concept is not unambiguously accepted since no consistent correlation was found between the maximum TSH increase following TRH and the basal or post-dexamethasone plasma and CSF cortisol concentrations (Loosen, 1987). Comparison of CRH-induced ACTH and cortisol release and TSH responses to TRH, however, revealed a trend toward a positive correlation in depressed patients, suggesting that both neuroendocrine systems may be under common control (Holsboer et al., 1986a; Müller et al., 1988). In addition to the inhibitory action of glucocorticoids, excessive SRIH activity due to CRH hypersecretion (Peterfreund et al., 1983; Rivier and Vale, 1985b; Katakami et al., 1985; Lesch et al., 1987b, 1989a) or increase of somatomedin-dependent SRIH release (Rosenthal et al., 1986; Lesch et al., 1987a) may further contribute to the relationship between TSH and ACTH output following specific challenges, although no convincing evidence for a related disturbance of HPT and HPS regulation in depression has been demonstrated (Lesch et al., 1989b). However, the significance of these findings is obscure and it remains unclear whether other, as yet unidentified, factors interfere with HPT function in affective illness.

Hypothalamic-pituitary-adrenal system

The function of the hypothalamic-pituitary-adrenal (HPA) axis can be regarded as a model system demonstrating the way that the central nervous system (CNS) and the glandular secretory system interact to coordinate and maintain vital homeostatic functions, the response to stress, and the regulation of circadian rhythms (Axelrod and Reisine, 1984; Martin and Reichlin, 1987). In fact, the HPA axis is looked upon as the quintessential neuroendocrine system. The principal abnormalities of HPA function associated with severe depression that appear to be established are elevated 24-hour cortisol secretory patterns (Linkowski et al., 1985; Linkowski et al., 1987) and resistance to dexamethasone suppression (Carroll, 1982; Rupprecht and Lesch, 1989). In order to understand what this may mean for a hypothesis of CNS dysfunction it is essential to summarize current knowledge of hypothalamic-pituitary control for adrenocortical cortisol release, and the mechanisms of feedback regulation.

This area has been impressively advanced by the isolation of ovine corticotropin-releasing hormone (CRH) (Vale et al., 1981) and the subsequent characterization of human CRH, a 41-amino acid peptide that differs by seven

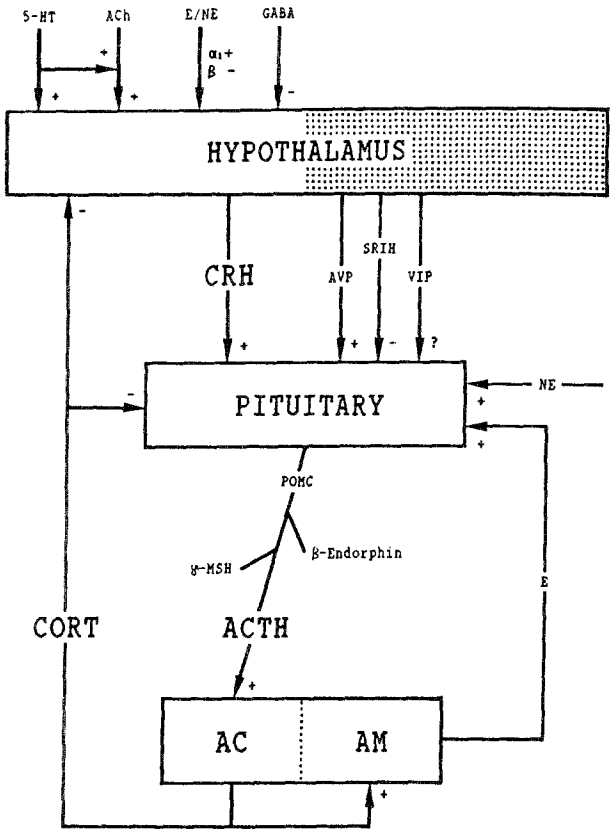

Fig. 2. Regulation of the hypothalamic-pituitary-adrenal (HPA) system. *AC* Adrenal cortex; *AM* adrenal medulla; *CORT* corticosteroids (e.g., cortisol); *POMC* pro-opiomelanocortin; *γ-MSH* γ-melanocyte-stimulating hormone; *ACTH* corticotropin; *CRH* corticotropin-releasing hormone; *AVP* arginine vasopressin; *SRIH* somatostatin; *VIP* vasoactive intestinal peptide; *5-HT* serotonin; *E* epinephrine; *NE* norepinephrine; α_1 α_1-adrenoceptor; β β-adrenoceptor; *GABA* γ-aminobutyric acid. ± Stimulating/inhibiting pathways

amino acids from the ovine hormone (Shibahara et al., 1983) and by developments in the molecular biology of pituitary regulation. CRH secreting neurons have been demonstrated by immunohistochemical means to make up a subgroup of cells in the paraventricular nucleus (Martin and Reichlin, 1987). Hypothalamic production and release of CRH, which has been identified as the primary neuroregulator of the secretion of pro-opiomelanocortin (POMC)-derived peptides, is controlled by various neurotransmitter systems acting through the hypothalamic control network (Fig. 2). Acetylcholine (ACh) and serotonin (5-HT), possibly via cholinergic interneurons, are stimulatory, γ-aminobutyric acid (GABA) and catecholamines are inhibitory to CRH release, although pituitary-adrenal responses to insulin-induced hypoglycaemia are augmented by β-adrenergic antagonists and α_1-adrenoceptor agonists and suppressed by α-adrenergic blockers, suggesting that there may be a stimulating α_1-adrenergic regulation pathway (Jones, 1978). At the level of the pituitary, CRH interacts

synergistically with arginine vasopressin (AVP) (Lamberts et al., 1984) and epinephrine/norepinephrine (E/NE) (Rivier and Vale, 1985). E is secreted into the systemic circulation from the adrenal gland and NE is released from sympathetic nerve terminals, while AVP originates from tuberoinfundibular neurosecretion and from the neurohypophysis via retrograde circulation. In addition, numerous neuropeptides [opioid peptides, somatostatin (SRIH), vasoactive intestinal peptide (VIP), delta sleep-inducing peptide (DSIP), etc.] exert a modulatory influence on ACTH secretion at the level of the hypothalamus and/or pituitary (Buckingham, 1986; Grossman et al., 1986; Brown et al., 1984; Axelrod and Reisine, 1984; Graf et al., 1985; Okajima and Hertting, 1986). The physiological importance of these interactions is supported by the neuronal colocalization of CRH with some of these neuromodulators.

Opposed to the stimulating effects of CRH, AVP and E/NE is the glucocorticoid-dependent negative feedback regulation. Glucocorticoids act at at least two general sites (Keller-Wood and Dallman, 1984). Cortisol-specific cellular and nuclear receptors (GR) are demonstrable on the corticotrope cells of the anterior pituitary, and the effects of stimulating factors to accumulate mRNA for ACTH are effectively but not completely inhibited by cortisol. Moreover, there is evidence that the ambient glucocorticoid concentrations influence the secretion of both CRH and AVP, but attempts to demonstrate GR on the CRH neurons have not been successful. However, there is an extensive distribution of GR in various brain structures such as the hippocampus, septum and amygdala (Martin and Reichlin, 1987). These regions have inhibitory influences on hypothalamic CRH release, and may therefore suppress CRH when exposed to high concentrations of glucocorticoids. It has been realized that these same regions containing GR are probably the locus of the effect of glucocorticoids on higher brain function, and in the propagation of steroid-induced psychopathological changes. Thus, the CNS integrates neural factors and feedback mechanisms controlling circadian and ultradian rhythms (closed loop control) and the open loop control due to stress. Distorted HPA function linked to affective illness reverts to normal following clinical remission and hence can be considered as a state variable secondary to, or associated with, the primary CNS disturbance (Linkowski et al., 1987).

The availability of synthetic CRH has permitted the comparative evaluation of pituitary ACTH and adrenocortical cortisol responses in major depressive disorder. As compared to control subjects, depressed patients with elevated basal cortisol concentrations exhibited a markedly attenuated ACTH but a nearly identical cortisol response to 1 μg/kg of the long-acting ovine analogue of CRH (Gold et al., 1984) or 100 μg human CRH (Holsboer et al., 1984; Lesch et al., 1987 b, 1988 a; Müller et al., 1988). While ovine and human CRH are not capable of inducing prolactin (PRL) luteinizing hormone (LH), follicle-stimulating hormone (FSH) and TSH release in depressed patients, while abnormal growth hormone output has been demonstrated in patients suffering from acromegaly (Pieters et al., 1984) or depression (Gold et al., 1984; Lesch et al.,

1988 c) following CRH administration. These observations are consistent with the view that the pituitary corticotroph cells respond to the negative feedback of increased basal cortisol concentrations with blunted ACTH responses to exogenous CRH. Accordingly, the apparent normal functioning of the ACTH-secreting cells and the presumed integrity of the glucocorticoid-dependent negative feedback regulation suggests that hypercortisolism in patients with depression reflects an abnormality at or above the level of the hypothalamus, leading to an increased synthesis and release of CRH into the hypothalamic-hypophysial portal system. This hypothesis is supported by the observations that continuous infusion of ovine CRH to normal subjects produces a pattern in cortisol secretion that is similar to that seen in patients with depression (Schulte et al., 1985) and by the report that depressed patients show elevated CSF CRH concentrations (Nemeroff et al., 1984). The proportionally higher cortisol output in relation to ACTH release after CRH stimulation is in accordance with reports demonstrating increased cortisol output in response to an ACTH challenge and is compatible with the development of a moderate functional hyperplasia of the adrenal cortex, which occurs after prolonged exposure to exogenous ACTH or as a result of experimentally-induced stress (Amsterdam et al., 1983; Holsboer et al., 1986 a; Gold et al., 1987).

The failure to demonstrate a relationship between cortisol resistance to the suppressive action of dexamethasone and deficient CRH-induced ACTH responses or CSF CRH concentrations, however, indicates that dexamethasone nonsuppression linked to depression is not clearly explained by a central CRH hypersecretion, and underscores the possibility of a GR abnormality as another factor contributing to HPA dysfunction (Holsboer et al., 1986 b; Rupprecht and Lesch, 1989). Since HPA axis regulation is the final outcome of a complicated interplay of neuroendocrine systems including the hypothalamus, pituitary, adrenal cortex and adrenal medulla, either defective glucocorticoid-dependent negative feedback control, possibly due to a GR abnormality, or CRH hypersecretion, possibly in concert with disturbed function of other neuropeptides, such as AVP (von Bardeleben et al., 1985), SRIH (Lesch et al., 1989 a) or DSIP (Lesch et al., 1988 a), may result in abnormal HPA axis regulation. However, it is important to recognize that the interdependence between the aminergic-cholinergic interactions, which are probably disordered in affective illness and the functional activity of central neuropeptide systems remains unsolved (Lesch et al., 1987 b; Ihl et al., 1989). Further study of hypothalamic neuropeptide systems using highly selective pharmacological challenge agents, such as adrenergic, serotonergic or cholinergic agonists, combined with dynamic neuroendocrine measures may allow a clearer understanding of the underlying pathophysiology of HPA axis dysfunction in depression.

Hypothalamic-pituitary-somatotropic system

Early efforts to identify the hypothalamic stimulating hormone for growth hormone (GH) release from the anterior pituitary unintentionally resulted in

discovery of a hypothalamic inhibitor of GH secretion. SRIH, a 14-amino acid peptide, was isolated and structurally characterized in 1973 by Brazeau et al., although another decade passed before the structure of the GH-releasing hormone (GHRH) was similarly elucidated (Guillemin et al., 1982; Rivier et al., 1982). Thus studies of the neuropsychiatric relevance of GHRH are in their relative infancy while the role of SRIH in neuropsychiatric disorders has been extensively investigated (Lesch et al., 1988 e; Lesch, 1989).

There is now a general consensus that GH release is regulated by the noncompetitive antagonism of GHRH and SRIH (Fig. 3), while the effects of other hormones (e.g., glucocorticoids, thyroid hormones, gonadal steroids) on GH secretion are apparently mediated via alterations in the secretion of or sensitivity to GHRH and/or SRIH (Vale et al., 1983; Martin and Reichlin, 1987; Lesch et al., 1989 e). Feedback inhibition of GH secretion may depend on GH itself or may be mediated by GH-induced somatomedin [e.g., insulin-like growth factor I (IGF-I) = somatomedian C (Sm-C)] production (Berelowitz et al., 1981; Nakamoto et al, 1986; Ross et al., 1987; Ceda et al., 1987). Both GH and somatomedins may have an effect at the level of the pituitary, directly inhibiting GH release, and/or at the level of the hypothalamus, stimulating SRIH secretion and possibly suppressing GHRH output (Rosenthal et al., 1986; Lesch et al., 1987 a, 1989 c).

Somatostatin

SRIH-containing neuronal cell bodies are selectively distributed throughout a variety of brain structures including the preoptic and periventricular nuclei, amygdala, hippocampus, striatum, locus coeruleus and neocortex (Martin and Reichlin, 1987). SRIH-containing nerve terminals and SRIH-specific receptors are even more widely scattered, with highest concentrations in the hypothalamus. SRIH influences the release and/or turnover of brain cholinergic and monoaminergic neurotransmitters and, in turn, its release is attenuated by NE, 5-HT und GABA, and is stimulated by ACh and possibly DA (Cella et al., 1987) (Fig. 3). The physiological importance of these interactions is supported by the neuronal co-localization of SRIH with a variety of neuroactive substances. In addition to its physiological role in the regulation of basal and stimulated GH and TSH release, SRIH appears capable of inhibiting the secretion of a wide array of hormones. SRIH may be involved in the control of HPA activity, as it inhibits stimulated ACTH secretion following administration of a variety of secretagogues and can diminish stress-induced CRH secretion (Axelrod and Reisine, 1984; Brown et al., 1984). However, CRH may stimulate hypothalamic SRIH release in vitro and in vivo (Peterfreund et al., 1982; Rivier and Vale, 1985 b; Katakami et al., 1985; Lesch et al., 1989 a).

Observations of decreased CSF SRIH concentrations in depression have been consistently replicated (Rubinow et al., 1983, 1987). Moreover, Doran et al. (1986) and Serby et al. (1986) demonstrated an inverse relationship between CSF SRIH concentrations and maximum post-dexamethasone plasma cortisol

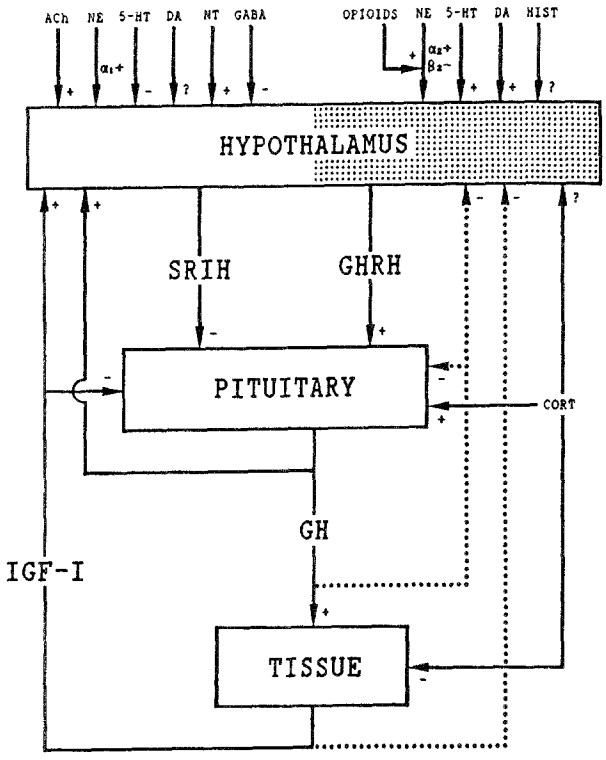

Fig. 3. Regulation of the hypothalamic-pituitary-somatotropic (HPS) system. IGF-I insulin-like growth factor I [= somatomedin C (Sm-C)]; *GH* growth hormone; *GHRH* growth hormone-releasing hormone; *SRIH* somatostatin; *CORT* corticosteroids; *ACh* acetylcholine; *5-HT* serotonin; *NE* norepinephrine; $\alpha_{1/2}$ $\alpha_{1/2}$-adrenoceptor; β_2 β_2-adrenoceptor; *DA* dopamine; *GABA* γ-aminobutyric acid; *HIST* histamine; *Opioids* endogenous opioid peptides; *NT* neurotensin. ± Stimulating/inhibiting pathways, ··· likely pathways

concentrations in depressed patients. However, decreased levels of CSF SRIH suggestive of functional alterations were also observed in Alzheimer's disease and Parkinson's disease (Lesch et al., 1988 e; Lesch, 1989), while in Huntington's disease post mortem studies demonstrated increased concentrations of SRIH (Rubinow et al., 1987). These findings, in conjunction with reports of CRH-induced SRIH release and SRIH-dependent inhibition of stimulated ACTH secretion and stress-induced CRH release indicate that decreased hypothalamic SRIH, possibly due to CRH hypersecretion, may induce the HPA disinhibition observed in depression or may reflect a central neurotransmitter abnormality that results in both diminished SRIH and increased CRH output (Lesch et al., 1989 a).

Growth hormone-releasing hormone

Peptides with GH-releasing activity isolated from human pancreatic islet cell tumours have been shown to represent the postulated human hypothalamic GHRH (Rosenthal et al., 1983; Thorner et al., 1983; Ling et al., 1984). While GHRH appears structurally related to brain-gut peptides, no physiological role

for GHRH outside the brain has been clearly defined. As compared to other hypothalamic releasing hormones, GHRH displays a far more restricted central distribution, with highest concentrations in the pituitary stalk and infundibular, arcuate, and ventromedial nuclei. GHRH release is controlled by a complex regulatory mechanism involving several neurotransmitter systems (Terry, 1984; Cella et al., 1987; Siever et al., 1987; Lesch et al., 1989 d). While NE is stimulatory via α_2- and inhibitory via β_2-adrenoceptors, GHRH secretion is also influenced by serotonergic, dopaminergic, histaminergic, and opioidergic innervation (Fig. 3). Unlike SRIH, the regulatory effects of GHRH seem to be circumscribed and are specific for GH release.

Studies of CSF GHRH in psychiatric populations and, in particular, of disturbances of GHRH-stimulated GH secretion in depression are at a relatively early stage. However, aberrant hypothalamic-pituitary-somatotropic (HPS) function, as indicated by a reduction in sleep-associated GH release (Jarrett et al., 1986), episodic hypersecretion of GH during the daytime hours with secretory pulses occurring before, rather than after, sleep onset (Mendlewicz et al., 1985; Linkowski et al., 1987), and decreased response to pharmacological challenges, such as insulin-induced hypoglycaemia and d-amphetamine, have been described in patients with major depressive disorder (Gruen et al., 1975; Langer et al., 1976; Laakmann et al., 1986). Moreover, the ability of clonidine, a centrally acting α_2-adrenoceptor agonist, to induce GHRH-mediated GH release (Miki et al., 1984) suggests that the impairment of GH output to specific pharmacological challenge in depression is due to central α_2-adrenoceptor dysfunction (Matussek et al., 1980; Charney et al., 1982; Siever et al., 1982; Lesch et al., 1989 d; Erb et al., 1988). Few recent studies using GHRH support the view that pituitary-somatotropic function is intact in major depressive disorder. Elevated plasma IGF-I concentrations in depressed patients have been associated with significant blunting of the net GH responses after human GHRH-44 amide administration in a dose of 1 µg/kg or 50 µg (Lesch et al., 1987 a, 1989 b; Müller et al., 1988). There are several possible explanations for blunted GH responses to GHRH in depressed patients. The increased plasma IGF-I concentrations could have resulted from diurnal episodic hypersecretion of GH, previously demonstrated in patients with unipolar and bipolar depression (Mendlewicz et al., 1985; Lesch et al., 1989 c), and the diminished GH responses to GHRH may reflect normal IGF-I-mediated negative feedback at the level of the pituitary (Rosenthal et al., 1987; Lesch et al., 1987 a). The presumed GH hypersecretion may be due to decreased hypothalamic SRIH release associated with depression (Rubinow et al., 1983; Doran et al., 1986; Serby et al., 1986) and/or hyperactivity of GHRH-containing neurons (Lesch et al., 1987 a). In addition to the feedback effects of IGF-I, relative hypersecretion of GHRH may lead to a depletion of the GH pool (Vance et al., 1985) and/or to a receptor-mediated desensitization of pituitary somatotrophs (Rittmaster et al., 1987), thus contributing to the deficient GH output in response to GHRH administration. Therefore, attenuated GHRH-induced GH release as well as concor-

dance between GH responses to GHRH and clonidine-evoked GH output in depressed patients (Lesch et al., 1988 d) implies that distorted α_2-adrenergic receptor function may not be the primary cause of deficient GH secretion in response to specific pharmacological challenges.

This hypothesis is further supported by the view that abnormal regulation of the HPA and/or HPT axis in depression may contribute to an altered GH output at different levels of the HPS system, although no direct relationship between blunted GH responses to GHRH and the severity of hypercortisolism, as assessed by maximum post-dexamethasone plasma cortisol concentrations (Lesch et al., 1988 b) and diminished TSH responses to TRH administration (Müller et al., 1988; Lesch et al., 1989 b) or attenuated ACTH release after CRH (Lesch et al., 1988 f, 1989 e) has been demonstrated. Despite some controversy regarding the effect of GHRH on PRL secretion, no difference in PRL responses to GHRH has been demonstrated between depressed patients and healthy subjects, suggesting that abnormal HPS function may be unrelated to the altered circadian PRL associated with depression (Mendlewicz et al., 1980; Lesch et al., 1988 b). From these preliminary studies it may be concluded (a) that the pathophysiological process resulting in aberrant GH secretion in depression may be due primarily to a suprapituitary disturbance, (b) that attenuated GH responses to pharmacological challenges may involve other pathomechanisms in addition to α_2-adrenoceptor dysfunction and (c) that a disturbance in HPA and HPT axis regulation may be precipitated by independent factors.

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