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The hypothalamic-pituitary-adrenal axis in anorexia nervosa

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Abstract

Studies examining the function of the hypothalamic-pituitary-adrenal (HPA) axis in anorexia nervosa are reviewed. A principal finding is that of hypercortisolism, associated with increased central corticotropin-releasing hormone levels and normal circulating levels of adrenocorticotropic hormone. Similarities between neuroendocrine findings in anorexia nervosa and in affective disorder are reviewed. The contribution of circadian rhythm disturbances and malnutrition to observed HPA axis abnormalities in anorexia nervosa is also considered. Directions for future research are discussed.

Keywords: Cortisol; Adrenocorticotropic hormone; Corticotropin-releasing hormone; Circadian rhythms; Depression

1. Introduction

Anorexia nervosa is a severe eating disorder, with a mortality rate of up to 22%. The incidence of anorexia, although not large in the overall population, is significant in the population at risk, namely young women. Patients with anorexia have a characteristic clinical picture of endocrine dysfunction, such as amenorrhea, abnormal temperature regulation, abnormal growth hormone (GH) levels, and abnormal eating. This picture is suggestive of pituitary or hypothalamic dysfunction. For this reason, endocrine function has been intensively studied in anorexia nervosa, with the goal of identifying potential endocrine defects as key pathophysiological mechanisms or even etiologic mechanisms in this puzzling and difficult-to-treat disorder. We will focus our attention on one component of hypothalamic-pituitary function in anorexia nervosa, namely the hypothalamic-pituitary-adrenal (HPA) axis.

2. Synopsis of HPA axis function and dysfunction

The HPA axis is a key constituent of the stress response. This axis has central and peripheral components. The central component consists of corticotropin-releasing hormone (CRH). CRH stimulates the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to produce cortisol, the peripheral component of the HPA axis (Chrousos and Gold, 1992). The central CRH system is spread

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throughout the brain, and is best characterized in the paraventricular nucleus of the hypothalamus (PVN) (Cummings et al., 1983). Central CRH administration causes behavioral and physiological responses which facilitate the response to stress. Those include stimulation of the HPA axis, resulting in increases in functions essential during stress, such as cortisol production, and activation of the sympathetic system, resulting in increased blood glucose levels, and increased heart rate and blood pressure; central CRH also inhibits vegetative functions, such as feeding and reproduction, which are not crucial during stress. The behavioral effects of moderate doses of CRH include enhanced arousal and cautious restraint, while in higher doses it causes hyper-responsiveness to sensory stimuli, assumption of the freeze posture, decreased exploration in unfamiliar environments, and enhanced conditioned fear responses during aversive stimuli (Chrousos and Gold, 1992).

The peripheral arm of the HPA axis, cortisol, is a hormone with two classes of effects: (1) those on intermediary metabolism; and (2) those on water and electrolyte metabolism. The effects of cortisol include promotion of gluconeogenesis, increase in protein breakdown, increases in plasma glucose and insulin, increase in body fat, and suppression of immunity; cortisol also contributes to the maintenance of normal blood pressure and cardiac output (Bondy, 1985). Cortisol is essential to life. Adrenal insufficiency may cause death, particularly in the context of inability to respond to stress.

The HPA axis is regulated at multiple levels. CRH is produced in the hypothalamus, transported through the portal system to the pituitary, where it stimulates the production of pro-opiomelanocortin gene products, such as β-endorphin, and ACTH. ACTH circulates systemically and stimulates the adrenal cortex to produce cortisol. Cortisol, via glucocorticoid receptors (GR), directly inhibits the pituitary production of ACTH, and the hypothalamic production of CRH. Moreover, cortisol acts on GR receptors in hippocampus, resulting in an inhibitory signal from the hippocampus to the PVN, and decreasing CRH production via negative feedback from the hippocampus (Herman et al., 1989). Thus, cortisol provides negative feedback to the HPA axis at three levels, pituitary, hypothalamus, and hippocampus. Normally HPA axis function exhibits rhythmicity at the circadian and ultradian levels. Abnormal HPA function can be characterized by abnormal levels of HPA axis hormones with maintenance of circadian rhythms or by abnormal levels and rhythmicity. Several illnesses are associated with or caused by abnormal HPA functioning. Decreased HPA axis activity is observed in Addison's syndrome, atypical depression, chronic fatigue syndrome, hypothyroidism, some forms of obesity, and post-traumatic stress disorder. Increased HPA axis activity has been described in Cushing's syndrome, melancholic depression, severe chronic disease, alcoholism, withdrawal states, chronic excessive exercise, malnutrition, hyperthyroidism, and anorexia nervosa (Chrousos and Gold, 1992).

3. Studies of the HPA axis in anorexia nervosa

We have conducted a detailed search of the literature of the past 27 years using as data sources published original peer-reviewed articles from human studies of HPA function in anorexia nervosa. Literature was surveyed using MEDLINE, the *Index Medicus*, and cross-referencing by the authors. The results of this detailed review of the literature are summarized in Table 1.

We reviewed a total of 20 peer-reviewed articles published in a 25-year period, from 1986 to 1991 on HPA function in anorexia nervosa. We looked at findings from those articles regarding the following aspects of the HPA axis: central CRH levels, ACTH levels (central and peripheral), cortisol levels (central and peripheral), cortisol metabolism, GR levels, and response to stimulation with dexamethasone, ACTH, and CRH. These parameters provide a detailed assessment of most aspects of HPA function. We found that two groups report elevated central CRH levels, one group reports decreased central ACTH level, four groups report normal peripheral ACTH levels, one group reports elevated central cortisol levels, and 17 groups report ele-

Table 1
HPA axis studies in anorexia nervosa

	CSF CRH	CSF ACTH	P ACTH	CSF Cort	P Cort	Cort metab	GR	DST (p.o.)	DST (i.v.)	ACTH stim	CRH stim
Landon et al., 1966					↑						
Danowski et al., 1972					↑			50% non-suppr		↑cort	
Warren and Wiele, 1973					↑						
Garfinkel et al., 1975					↑						
Vigersky et al., 1976					↑						
Boyar et al., 1977					↑	↓					
Walsh et al., 1978					↑						
Casper et al., 1979					↑	↓					
Doerr et al., 1980					↑	↓					
Fichter et al., 1982					↑	↓					
Kontula et al., 1982							↓				
Gold et al., 1986			↔		↑						↓ACTH; ↑cort
Hotta et al., 1986	↑		↔		↑						↓ACTH; ↓cort
Kaye et al., 1987	↑				↑						
Gwirtsman et al., 1989		↓	↔	↑	↑						
Ferrari et al., 1990					↑						
Vierhapper et al., 1990					↑					↑cort	
Estour et al., 1990								60% non-suppr	93% non-suppr		
Schweitzer et al., 1990			↔					50% non-suppr			
Kennedy et al., 1991					↑						

ACTH, adrenocorticotropic hormone; Cort, cortisol; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; DST, dexamethasone suppression test; GR, glucocorticoid receptors; i.v., intravenous; metab, metabolism; P, peripheral; p.o., oral; stim, stimulation test; suppr = suppressor; ↑, increased; ↔, normal; ↓, decreased.

vated peripheral cortisol. The studies of Boyar et al. (1977) and Ferrari, Fraschini and Brambilla (1990) show that the elevated levels of cortisol in anorexia nervosa are associated with maintenance of a highly significant circadian rhythm of plasma cortisol.

We can state at this point that there is indeed hypercortisolism in anorexia nervosa, associated with increased central CRH, and normal circulating levels of ACTH. Elevation in cortisol levels could be caused by increased cortisol production, decreased clearance, or by a combination of both factors. Boyar et al. (1977) were the first to report decreased cortisol metabolism in anorexia ner-

vosa, a finding confirmed by three other groups. Furthermore, Boyar et al. reported normal cortisol production, and postulated that the hypercortisolemia of anorexia nervosa was caused by decreased cortisol metabolism. Walsh et al. (1978), however, reported that cortisol production was overall normal in anorexia nervosa, but that when body size was taken into account, cortisol production/kg was significantly increased in anorexia nervosa. From those reports it seems that the hypercortisolism of anorexia nervosa is due to a combination of both increased secretion of cortisol/kg of body weight and decreased cortisol metabolism. As might be expected in a state of hypercortisolism, GR levels are decreased in mononuclear leukocytes of patients with anorexia nervosa (Kontula et al., 1982).

Given the fact that cortisol inhibits CRH production, both directly and via the hippocampus, it is reasonable to state that, especially in the light of peripheral hypercortisolism, the elevation of central CRH in anorexia nervosa is caused by a state of increased CRH production in the central nervous system (CNS), which causes the observed hyperactivity of the HPA axis. Stimulation test results confirm this notion. The oral dexamethasone suppression test (DST) is positive in 50–60% of patients. In the study of Schweitzer et al. (1990) plasma dexamethasone levels were higher in suppressors than in non-suppressors. This raises the possibility that the result of this test can be a function of individual dexamethasone kinetics. To circumvent this methodological limitation, Estour et al. (1990) administered dexamethasone intravenously in 15 patients with anorexia nervosa and observed non-suppression of cortisol levels in 93% (14/15). The ACTH stimulation test performed by two groups also shows increased cortisol response. These results further confirm that the adrenal gland overproduces cortisol in anorexia nervosa, and that the hypercortisolemia of that disorder is not suppressible by dexamethasone. The CRH stimulation test shows decreased ACTH response. Our group (Gold et al., 1986b) showed increased cortisol response (Fig. 1), while Hotta et al. (1986) showed decreased cortisol response, to CRH. Both groups interpret the findings obtained as an indication that in anorexia nervosa there is increased HPA axis activity due to increased CRH secretion.

4. Pathophysiology of HPA axis hyperactivity in anorexia nervosa

Hypercortisolism has been extensively documented in underweight anorectics (Table 1). Several different mechanisms have been postulated, including decreases in cortisol clearance, affinity for cortisol-binding globulin, and glucocorticoid-receptor concentration. However, defects in clearance or protein binding alone cannot produce hypercorticosolism in patients with normal hypothalamic and pituitary responsiveness to the negative feedback of cortisol. On the other hand, sustained elevations in cortisol can occur with tissue resistance to glucocorticoids, even in the presence of normal neuroendocrine regulation of adrenal function. Such a defect in GR function could explain not only the hypercortisolism but also the absence of any obvious signs of glucocorticoid excess in underweight anorectics (Chrousos et al., 1982; Iida et al., 1985). However, patients with anorexia probably lack sufficient substrate for the kind of increased lipogenesis, fat deposition, or gluconeogenesis required to produce Cushingoid features. Moreover, the blunted ACTH responses to CRH noted in underweight patients with anorexia are inconsistent with a functionally relevant defect of GR. If anything, one would expect exaggerated rather than blunted ACTH responses in this context.

The blunted ACTH responses to CRH in underweight anorectics (Fig. 1) suggest that the negative feedback effect of their hypercortisolism is intact at the level of the pituitary corticotroph cell. This suggestion is supported by the negative correlation between basal cortisol concentrations and the ACTH responses to CRH in the controls and underweight patients.

In view of the apparently normal glucocorticoid-feedback responsiveness of the corticotroph cell in underweight anorectics, the hypercortisolism in anorexia nervosa patients

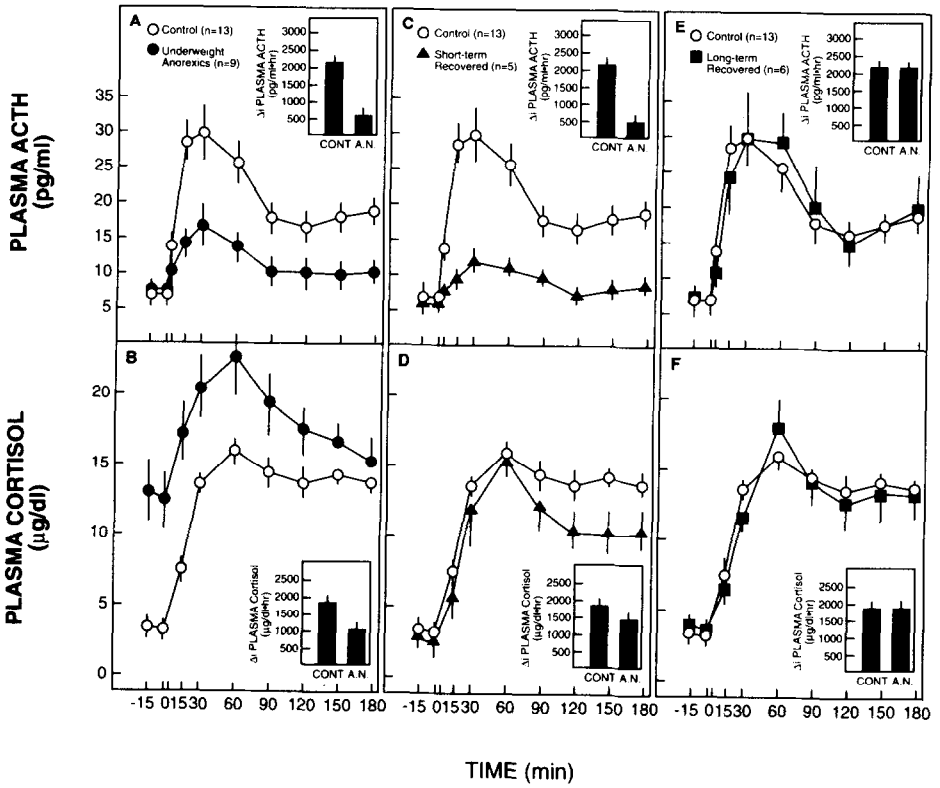

Fig. 1. (A) and (B): ACTH and cortisol responses to the CRH stimulation test in underweight anorectics; (C) and (D): in anorectic patients, within one month of weight restoration (short-term weight recovered); (E) and (F): and in long-term weight restored patients. Reproduced from the *New England Journal of Medicine* (314, 1335–1342, 1986) with permission.

suggests an abnormality at or above the hypothalamus that causes hypersecretion of CRH. This postulate is supported by the observation that continuous infusion of high doses of CRH in normal volunteers produces a pattern in the 24-h secretion of cortisol that is similar to that reported in patients with anorexia nervosa (50% increase in the mean amplitude of 24-h cortisol secretion, preservation of its circadian rhythm, and a 24-h urinary free cortisol excretion rate of up to 250 µg per day). Moreover, it has been noted that the cerebrospinal fluid level of CRH is increased in underweight anorectic patients (Kaye et al., 1987).

As compared with controls, underweight patients have a relatively higher cortisol response to the ACTH released during CRH stimulation. This finding is most compatible with the development of hyperplasia and hyperresponsiveness of the adrenal cortex, which has long been known to occur after even a few days of stimulation with exogenous ACTH (Renold et al., 1952) or after experimentally induced stress (Symington, Duguid and Davidson, 1955). Alternatively, this could simply reflect the fact that in most normal subjects, the higher ACTH responses substantially exceed the maximal secretory capacity of the adrenal cortex. The possibility that the underweight patients responded to CRH by releasing a substance other than pituitary ACTH that is capable of adrenocortical stimulation cannot be excluded. It is known that the adrenal medulla contains receptors for CRH (Udelsman et al., 1986) and is capable of synthesizing a variety of peptide hormones, including small amounts of ACTH (Evans et al., 1983).

The finding of normal evening levels of plasma ACTH in underweight anorectics with hypercortisolemia cannot be definitely accounted for. However, one can speculate that it reflects the presence of a normal pituitary corticotroph cell caught in the balance between excessive endogenous CRH stimulation from above and a hyperresponsive adrenal cortex from below. In this situation, the corticotroph cell, though restrained by negative feedback to secrete at a normal rate, would nevertheless be sufficiently stimulated by CRH to promote hypersecretion of cortisol by hyperplastic adrenals.

Normal weight patients during the depression phase of primary affective disorder have also been reported to have hypercortisolism associated with attenuated ACTH responses to CRH (Gold et al., 1984; Gold et al., 1986a). Moreover, like underweight anorectics, patients with depression have increased levels of CRH in cerebrospinal fluid (Nemeroff et al., 1984). Hence, the proposed hypersecretion of CRH in anorexia nervosa may be a finding independent of weight loss, which cuts across the boundaries of the current classification of psychiatric disorders. In this regard, anorexia nervosa and major depressive disorder have many clinical, pathophysiologic, and genetic features in common, and some investigators have hypothesized that both illnesses lie on a broad continuum of depressive spectrum disorders (Cantwell et al., 1977). Of note is the fact that the ACTH responses in the underweight anorectics were attenuated in some who were not obviously depressed. Ferrari, Fraschini and Brambilla (1990) have also suggested, in their study of hormonal (including cortisol) circadian rhythms in anorexia nervosa that the internal desynchronization of hormonal circadian rhythms they observed in those patients seems not to be linked to depression, and appears to be specific for eating disorders.

The proposed hypersecretion of CRH in anorectic subjects may not reflect a defect intrinsic to anorexia nervosa (or to a group of depressive spectrum disorders), but may represent a nonspecific manifestation of inanition. It is well established that patients who have protein-calorie malnutrition also have hypercortisolism, presumably as a consequence of an altered hypothalamic set point for pituitary adrenal regulation (Vigersky et al., 1977; Fichter and Pirke, 1986).

The possibility of CRH hypersecretion in anorexia nervosa may be relevant to certain components of its symptom complex, regardless of whether hypersecretion becomes established only after a critical amount of weight loss or represents a defect more intrinsic to the illness. Hence, intracerebroventricular (icv) administration of CRH in animals produces a variety of behavioral and physiologic responses often associated with anorexia nervosa (and depression), including not only activation of the HPA axis (Rock et al., 1984) but also hypothalamic hypogonadism (Rivier and Vale, 1984), diminished sexual activity (Sirinathsinghji et al., 1983), decreased feeding (Britton et al., 1982) and increased activity or agitation (Sutton et al., 1982). The finding that the eating disturbance, hypercortisolism and amenorrhea are more pronounced or consistent in anorexia nervosa than in depression could reflect factors unique to anorexia nervosa that interact with CRH. For instance, in contrast to patients with depression (Gold et al., 1983), those with anorexia have an elevation of arginine vasopressin in cerebrospinal fluid. In vivo and in vitro studies have shown that arginine vasopressin markedly potentiates the biologic effects of CRH (Rivier and Vale, 1983).

5. Directions for future research

The HPA axis has been intensively investigated in anorexia nervosa. The main finding in this disorder is a state of central activation of the HPA axis, characterized by increased CRH levels, normal ACTH levels, and increased cortisol, with circadian rhythmicity.

There are two issues that still have the potential to be fruitful areas of investigation in this field. The first is the determination of actual rates of secretion of HPA axis hormones, namely, ACTH, β-endorphin and cortisol. The ultradian pulsatility and circadian variation of the actual secretion rates of HPA axis hormones in anorexia still remain to be determined by the use of

state-of-the-art deconvolution and pulse analysis methodologies. The HPA axis secretion rate studies in anorexia (Boyar et al., 1977; Walsh et al., 1978) pre-date the development of current deconvolution techniques (Veldhuis et al., 1987) and pulse analysis algorithms, such as Cluster (Veldhuis and Johnson, 1986) or Detect (Oerter et al., 1986).

A key question remains to be addressed in this field: why is there CRH hyperproduction in anorexia nervosa? One likely explanation would be continued stress in the presence of decreased negative feedback to CRH production secondary to decreased levels of GR centrally. There are two ways to test the hypothesis that GR levels are decreased centrally in anorexia nervosa: (1) directly, in post-mortem studies; (2) indirectly by imaging studies using a radiolabelled receptor-ligand to central GR. Unfortunately, such a ligand has not been developed yet.

6. Role in diagnosis and treatment

The cause of anorexia nervosa is not known. Two of the key clinical issues in anorexia nervosa are (1) the development of tools for early diagnosis, and (2) treatment. Many patients with anorexia nervosa develop a chronic disorder prior to diagnosis. An endocrine test could potentially be a useful instrument in the evaluation of early cases of the disorder. However, the abnormalities in HPA function present in anorexia are not specific enough to make it feasible to use an endocrine test targeted to the HPA axis as a diagnostic tool for the early diagnosis of anorexia nervosa. Elevated cortisol, normal ACTH, elevated central CRH, and abnormal response to dexamethasone and to CRH stimulation are found not only in anorexia nervosa, but also in depression, and possibly in starvation or malnutrition of other causes (Gold et al., 1984; Vigersky et al., 1977; Fichter and Pirke, 1986). Therefore, an abnormal test of HPA function would not be specific enough to make the early diagnosis of anorexia nervosa. In terms of treatment, there are at present no specific endocrine treatments for the kind of HPA axis abnormalities seen in AN, and it is known that the HPA axis abnormalities in anorexia improve with nutritional rehabilitation. Therefore, it seems logical to propose that careful nutritional rehabilitation should precede any efforts to treat HPA axis abnormalities in anorexia nervosa with currently available endocrine treatments.

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