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Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus–pituitary–adrenal axis

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Abstract

Following the assumption that stressors play an important part in the etiology and maintenance of psychiatric disorders, it is necessary to evaluate parameters reflecting stress-related physiological reactions. Results from these examinations may help to deepen the insight into the etiology of psychiatric disorders and to elucidate diagnostic uncertainties. One of the best-known stress-related endocrine reactions is the hormonal release of the hypothalamic–pituitary–adrenal (HPA) axis. Dysregulations of this axis are associated with several psychiatric disorders. Profound hyperactivity of the HPA-axis has been found in melancholic depression, alcoholism, and eating disorders. In contrast, posttraumatic stress disorder, stress-related bodily disorders like idiopathic pain syndromes, and chronic fatigue syndrome seem to be associated with diminished HPA activity (lowered activity of the adrenal gland). Hypotheses referring to (a) the psychophysiological meaning and (b) the development of these alterations are discussed.

Keywords: HPA-axis; Hypocortisolism; Hypercortisolism; Depression; Posttraumatic stress disorder; Stress-related disorders; Chronic fatigue syndrome

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1. Introduction

Based on the seminal contributions of Cannon (1914), Selye (1956), Mason (1968), it is known that deviations from physiological and psychological equilibrium result in a physiological response to restore homeostasis, such as the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Under certain circumstances, like high intensity or chronic duration of stress, or a lack of personal and psychosocial resources, stressful situations may provoke emotional disturbances and hormonal dysregulations that can, in turn, result in psychosomatic or psychiatric disorders.

The HPA-axis is activated following exhaustion, loss of control or the perception of loss of control (Chrousos and Gold, 1998). The physiologic response to stress is largely mediated by an increase in the production and secretion of corticotropin releasing hormone (CRH), which is released from the paraventricular nucleus (PVN) of the hypothalamus into the portal circulation. This stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH activates the adrenal gland to release cortisol. This hormonal pathway is suppressed by the negative feedback inhibition of cortisol on the pituitary and hypothalamus. The physiological and behavioral effects of cortisol, which follows a circadian rhythm with high levels in the early morning hours and a decrease over the day, depend on the ability of cortisol to bind to glucocorticoid receptors. Alterations in the number and sensitivity of glucocorticoid receptors modulate the functioning of the HPA-axis (Bamberger et al., 1996; Sapolsky et al., 2000). Furthermore, the HPA-axis is regulated by CRH receptors, which are widely spread over the brain, endocrine, and immune tissues. CRH receptor expression is influenced by the secretion of CRH in a reciprocal manner, supporting a physiological role of the peptide in regulating endocrine responses to stress. For example, increased CRH secretion following stress or adrenalectomy (in animal studies) down-regulates CRH receptors in the anterior pituitary (De Souza, 1995).

2. Paradigms for the study of the HPA-axis

The integrity of the HPA-axis can be evaluated with a variety of psychological, physiological, and pharmacological paradigms. A hormonal response is observed in real-life situations or experimental laboratory stressors, which are appraised as being threatening or demanding without perceived resources for coping in the sense of Lazarus and Folkman (1984). According to Mason (1968), these situations can usually be characterized as novel, unpredictable, or uncontrollable. Unlike naturally occurring stressors, laboratory stress provocation procedures allow the assessment of physiological stress reactions under standardized conditions. Commonly used procedures are video tapes, interviews referring to negative critical life events, the Stroop test, mental arithmetic, or speech tasks (Biondi and Picardi, 1999). In contrast to situations with high personal relevance, HPA activation can also be achieved without such ego-involvement through neuroendocrine challenge tests or by physical strain like treadmill exercise (Petrides et al., 1994).

Several standardized neuroendocrine challenge tests have been developed for the induction of HPA-axis activation (for review see Heim and Ehlert, 1999). The insulin tolerance test (ITT) is known to be the 'gold standard' to evaluate the integrity of the entire HPA-axis (Fish et al., 1986). The CRH stimulation test with either ovine or human CRH assesses the sensitivity and secretory capacity of the pituitary corticotrophs (Orth, 1992). The magnitude of the cortisol responses to different dosages of exogenous $ACTH_{1-24}$ serves as an indicator of the sensitivity and integrity of the adrenals (Rasmuson et al., 1996). Negative feedback loops can be inhibited by the administration of dexamethasone or methyrapone. Dexamethasone is a ligand of glucocorticoid receptors and suppresses ACTH and cortisol secretion (Cole et al., 2000). The combined administration of the dexamethasone suppression test and the CRH test is used to examine HPA activity under the condition of suppressed glucocorticoid feedback (Heuser et al., 1994). The application of metyrapone induces a blockade of cortisol production, which can be described as a temporary adrenalectomy (Chattoraj and Watts, 1986).

For an understanding of the mechanisms underlying specific dysregulations of the HPA-axis in different psychiatric disorders, it is of high relevance to carry out the above-mentioned neuroendocrine challenge tests. However, to elucidate the etiological role of psychological stress for the onset or maintenance of psychiatric disorders, it is important to study the effects of acute and chronic stressors in real-life situations.

3. HPA reactions following chronic or traumatic stress

Naturally occurring stressors can be classified according to their magnitude, i.e. high versus low subjective burden, and according to the duration of the stress, i.e. acute versus chronic strain. Working conditions often constitute prolonged stressors due to adverse ecological conditions or high workload. Correlations between elevated cortisol levels and working conditions were observed not only in industrial workers but also in air traffic controllers and pilots (Melamed and Bruhis, 1996; Rose et al., 1982a,b,c; Tarui and Nakamura, 1991). In ambulance personnel, it has been shown that morning cortisol levels after two non-working days are positively correlated with occupational stress during the last 24 h shift (Heinrichs et al., in preparation). In other studies, however, an unexpectedly low cortisol secretion was observed in employees, including teachers, who reported high workload, low job satisfaction, multiple bodily complaints, and high vital exhaustion (Caplan et al., 1979; Pruessner et al., 1999). Lower cortisol levels were also found in ambulance paramedics during shift hours than during leisure time (Dutton et al., 1978).

Prolonged unemployment is often described as a chronic stressor because of social isolation, decreased social support, reduced financial security, and deprivation of skill use. Basal cortisol levels in unemployed subjects were assessed in several studies. Elevated cortisol levels were found during the anticipatory phase of unemployment but not after the onset of the unemployment (Arnetz et al., 1991; Brenner and Levi, 1987; Ockenfels et al., 1995). No evidence has been found for a

disturbed reactivity of cortisol secretion related to daily hassles in unemployed subjects (Ockenfels et al., 1995).

The experience of combat missions during war, bomb attacks, enforced captivity, rape or battering, nuclear accident, fatal illness or death of a close relative can be seen as a paradigm to study the effects of traumatic life stressors (Kessler et al., 1995). Victims of accidents or women who experienced rape for the first time in their life show increased concentrations of cortisol shortly after the incident (Hetz et al., 1996; Resnick et al., 1995). Long-term effects of critical or traumatic life events seem to be associated with distinct dysregulations of the HPA-axis.

Early critical life events, such as preterm birth, parental separation, childhood sexual abuse or violence could result in the development of physiological vulnerability characterized as a persistent sensitization of the HPA-axis. Kaufman et al. (1997) compared depressed children with a history of abuse to depressed children without abuse experiences and also healthy controls, and found the highest ACTH responses, following exogenous CRH application, in the group of children with the history of abuse. Moreover, a recent study demonstrates that depressed women with a history of childhood sexual abuse also show increased pituitary–adrenal responses to a standardized psychosocial laboratory stressor when compared to controls (Heim et al., 2000a,b).

In summary, there is evidence that stressors with a high subjective burden are usually associated with an arousal of the HPA-axis at least after the onset of the stressful situation. Early-life stress seems to result in a persistent sensitization of the hypothalamic–pituitary–adrenal axis to stress in adulthood. Under chronic stress conditions, some studies suggest an exaggerated activation of the HPA-axis with a hypersecretion of cortisol (hypercortisolism) while a few others find a reduced adrenocortical activity (hypocortisolism). In the following, findings referring to hyper- or hypocortisolism as a relevant factor in the pathogenesis of different psychiatric disorders are outlined. While hypercortisolism is a well-known biological marker in melancholic depression, anorexia nervosa (Gold et al., 1986; Duclos et al., 1999), and alcoholism (Inder et al., 1995), for the last decade hypocortisolism has been discussed as a biological marker of posttraumatic stress disorder (PTSD) and stress-related bodily disorders (Chrousos and Gold, 1992).

4. Dysregulation of the HPA-axis in depression, PTSD, and stress-related bodily disorders

One of the best-documented psychiatric disorders related to hypercortisolism is major depression. Over 40 years ago, Board et al. (1957) reported elevated cortisol levels in depressed patients. Since then, hypersecretion of cortisol in major depression has been confirmed in a large number of studies (Gold et al., 1988). In addition to the assessment of basal cortisol levels, Carroll et al. (1981) reported a failure to suppress endogenous cortisol secretion following the administration of dexamethasone in patients with major depression. In summarizing the multitude of studies on the dexamethasone suppression test (standard oral dose of 1 mg dexamethasone)

in depressive patients, Gold et al. (1995) suggest that half of all patients with major depression show a non-suppression of cortisol. Referring to the actual differentiation of major depression in the melancholic and atypical, according to the DSM-IV (American Psychiatric Association, 1994), hypercortisolism and non-suppression of dexamethasone is related to melancholic depression, while atypical depression (e.g. chronic fatigue syndrome, CFS) seems to be associated with a hypofunctional HPA-axis.

Referring to melancholic depression, a number of studies suggest that the high levels of cortisol are centrally mediated by a hypersecretion of CRH. This is reflected in (a) a blunted response of ACTH but normal cortisol response following exogenous CRH stimulation (Gold et al., 1988; Lesch et al., 1988); (b) an exceeding ACTH response following exogenous CRH administration in dexamethasone pretreated patients (Heuser et al., 1994); (c) increased concentrations of CRH in the cerebrospinal fluid (Nemeroff et al., 1984; Wong et al., 2000); (d) a decreased number of CRH receptors in the frontal cortex of suicide victims (Nemeroff et al., 1988); and (e) symptom reduction following CRH-1-receptor blockade (Zobel et al., 2000). In summary, melancholic depression can be characterized by hypercortisolemia with a lowered feedback sensitivity, which is the consequence of a central CRH hyperactivity.

Since it is verified that the experience of overwhelming traumatic stress like combat missions, natural disasters, serious accidents or rape is accompanied in some persons by re-experiencing trauma-related stimuli, avoidance behavior, and hyperarousal, large efforts have been made to find out whether these symptoms are correlated with a dysregulation of the HPA-axis. In contrast to other psychiatric patients or healthy volunteers, patients suffering from PTSD show low to normal 24 h urinary free cortisol levels (Baker et al., 1999; Mason et al., 1986; Yehuda et al., 1990, 1995). Low plasma cortisol levels were found in patients with combat-related PTSD relative to patients suffering from depression and healthy controls (Yehuda et al., 1994), in female PTSD patients with a history of childhood sexual abuse (Stein et al., 1997), and in PTSD adolescents who were exposed to an earthquake (Goenjian et al., 1996). Elevated urinary or saliva cortisol levels were found in female PTSD patients with childhood sexual abuse experiences (Lemieux and Coe, 1995), in patients with PTSD related to a nuclear accident (Baum and Fleming, 1993), and in firefighters suffering from PTSD (Wagner et al., submitted). These inconsistent findings may be due to the variation of the psychiatric symptomatology in PTSD patients over time, which seems to be accompanied by a fluctuation of HPA-axis hormones as described by Wang et al. (1996).

Unlike the above-stated results of patients suffering from melancholic depression, normal suppression of cortisol was found in PTSD patients using the standard 1 mg dexamethasone suppression test (Kosten et al., 1990) whereas an enhanced suppression was observed in PTSD patients, compared to healthy controls, using the low dose dexamethasone suppression test (0.5 mg) (Stein et al., 1997; Yehuda et al., 1995). To test the hypothesis of an increased feedback sensitivity of the HPA-axis in PTSD patients, Yehuda (1997) assessed the metyrapone test in PTSD patients and found an exaggerated ACTH response. Additionally, Yehuda et al. (1993)

observed an increased number of glucocorticoid receptors on lymphocytes in Vietnam veterans with PTSD. Consistent with the findings in depression, PTSD patients showed a blunted ACTH response following CRH administration (Smith et al., 1989; De Bellis et al., 1994) and increased cerebrospinal fluid CRH levels (Bremner et al., 1997; Baker et al., 1999). To summarize, PTSD is associated with alterations of the HPA-axis, which can be interpreted as a mainly latent hypocortisolism and an increased feedback inhibition of the pituitary and adrenals, while neuronal CRH release seems to be hyperactive.

Dysregulations of the HPA-axis have not only been observed in psychiatric disorders like depression or PTSD but also in bodily disorders, which are related to stressful experiences in general as well as to trauma (for review see Heim et al., 2000a,b). Especially in pain disorders, which were not related to organic causes, low cortisol concentrations have been found. Johansson (1982) reported lower plasma cortisol levels in idiopathic chronic pain patients as compared to chronic pain patients with organic disease. Several other studies confirmed this finding of lowered cortisol concentrations in idiopathic pain (von Knorring and Almay, 1989; Valdés et al., 1989), recurrent abdominal pain in children (Alfvén et al., 1994), and in chronic headache (Elwan et al., 1991). Using basal morning cortisol levels as a discriminating parameter between subgroups of patients with functional gastrointestinal disorders (FGD), our workgroup found lower cortisol concentrations in FGD patients who predominantly suffered from somatization and pain symptoms in comparison with patients with depressive mood and FGD. All patients reported excessive workload, ineffective coping strategies, and a high number of critical and traumatic life events (Boehmelt et al., submitted).

In a series of studies, we examined the possible relationship between idiopathic pain and a reduced adrenocortical activity by assessing HPA-axis functions in women with idiopathic chronic pelvic pain (Ehlert et al., 1994; Heim et al., 1998; Ehlert et al., 1999). Compared to controls, this group of patients showed (a) normal to low basal cortisol concentrations, (b) normal ACTH response but blunted cortisol response to administered doses of CRH, and (c) enhanced suppression of cortisol after low dose (0.5 mg) dexamethasone intake. Psychological screening revealed high rates of sexual and physical abuse and resulting PTSD symptomatology along with a high extent of somatization behavior, but no symptoms of depression.

While discussing the involvement of HPA-axis disturbances in idiopathic pain, it is worth having a look at further symptoms that may be associated with a subtle adrenal insufficiency. Patients suffering from primary adrenal insufficiency (Addison's disease) show, apart from mostly life-threatening symptoms, also a high extent of fatigue and malaise. These symptoms disable patients from carrying out routine tasks. CFS is also characterized by mental and physical fatigue, and somatic complaints like myalgia, arthragia, and sleep and cognitive disturbances in the absence of established pathological conditions (Fukuda et al., 1994). Several studies indicate that chronic stress or trauma is associated with the onset of CFS (Jones and Wessely, 1999; Salit, 1997; Theorell et al., 1999). Although the findings regarding basal and reactive cortisol secretion are inconsistent, with both low and

normal cortisol levels being found (Scott and Dinan, 1998; Wood and Wessley, 1998), studies employing multiple tests of the HPA-axis point to a subtle hypoactivity, probably of tertiary origin, including (a) an attenuated ACTH response following CRH application, and (b) an increased sensitivity and reduced maximal secretory capacity of the adrenals (Demitrack et al., 1991; Scott et al., 1998, 1999).

Even though the above-mentioned results confirm the hypothesis of a dysregulation of the HPA-axis in CFS patients, there is some uncertainty about the morphological origin of these findings and its relevance. For that reason, we investigated HPA-axis functioning in CFS patients with two pharmacological (insulin tolerance test, dexamethasone suppression test), physical, and psychosocial stress tests to assess HPA-axis functioning at different hormonal levels (Gaab et al., 2001a,b). Following the application of 0.5 mg dexamethasone, patients showed an enhanced and prolonged suppression of cortisol in comparison to healthy controls. Referring to the insulin tolerance test and the physical and psychosocial stress, CFS patients showed attenuated ACTH responses and normal cortisol responses in all three tests. The neuroendocrine correlates of CFS can be described as follows: (a) the super-suppression of cortisol following dexamethasone can be interpreted as an enhanced negative feedback of the HPA-axis while (b) the reduced response of ACTH accompanied by normal cortisol release following HPA stimulation suggests a diminished release of CRH at the central level.

5. Conclusions

It has long been assumed that maladjustment to stress, either in the face of depression or prolonged or traumatic stress, is associated with a prolonged hyperactivation of the HPA-axis. The results of PTSD studies changed the picture about the consequences of stress, at least for traumatic experiences, since the majority of studies show relative hypocortisolism in PTSD patients. Although melancholic depression and PTSD can be discriminated by elevated or lowered cortisol levels and their opposing effects on the negative HPA-axis feedback, both disorders seem to share a common pathophysiological mechanism, i.e. hypersecretion of central CRH. It is unclear why, in some traumatized persons, the observed activation of the HPA-axis following acute stress and trauma reverses to a relative deficiency of cortisol at the time of obvious signs of PTSD. Aardal-Eriksson et al. (1999) studied the effects of traumatic events on cortisol levels over time in two rescue workers. Elevations of cortisol were moderately correlated with posttraumatic avoidance behavior at seven days after the trauma. After four weeks, cortisol concentrations were comparable to those levels measured prior to the traumatic event. Such an adaptive process to overcome trauma without long-lasting psychiatric impairment does not seem to characterize the neurobiological adaptation of persons who develop PTSD. Possibly, these patients show inadequate coping strategies, genetic risk factors for HPA-axis dysregulations or developmental risk factors like prenatal or early-life stress that may favor maladaptation to traumatic experiences (Heim et al., 2000a,b).

Although the general distinction between hyper- and hypoactive HPA-axis activity is a valuable heuristic for distinguishing clinical syndromes, one should take into account specific differences in these syndromes. For example, the observed CRH overdrive in melancholic depression and PTSD differs from the HPA-axis dysregulations found in pain and fatigue syndromes, the latter being associated with a central deficiency of CRH (Lariviere and Melzack, 2000; Gaab et al., 2001a,b). It is therefore necessary to identify specific mechanisms that characterize the more global HPA-axis dysfunctions associated with particular clinical syndromes.

This review summarizes 'work in progress' concerned with the pathological effects of HPA dysregulations in psychiatric disorders. Studies referring to disorders associated with an alteration of HPA-axis functioning show that these disorders are, in fact, stress-related. The shift from the activation of the HPA-axis following stress to the distinct dysregulations of the axis associated with psychological and physical disturbances remains unexplained, so that firm conclusions concerning the etiology and treatment of stress-related bodily disorders must be studied further. Prospective studies of stress or trauma in high-risk populations are particularly vital to the understanding of the etiology of psychosomatic disorders.

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