PERGAMON

Psychoneuroendocrinology 25 (2000) 1–35

PNEC

www.elsevier.com/locate/psyneuen

Invited review

The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders

Christine Heim, Ulrike Ehlert, Dirk H. Hellhammer *

Center for Psychobiological and Psychosomatic Research, Building D, University of Trier, 54286 Trier, Germany

Received 12 February 1999; accepted 29 April 1999

Abstract

Representing a challenge for current concepts of stress research, a number of studies have now provided convincing evidence that the adrenal gland is hypoactive in some stress-related states. The phenomenon of hypocortisolism has mainly been described for patients, who experienced a traumatic event and subsequently developed post-traumatic stress disorder (PTSD). However, as presented in this review, hypocortisolism does not merely represent a specific correlate of PTSD, since similar findings have been reported for healthy individuals living under conditions of chronic stress as well as for patients with several bodily disorders. These include chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis, and asthma, and many of these disorders have been related to stress. Although hypocortisolism appears to be a frequent and widespread phenomenon, the nature of the underlying mechanisms and the homology of these mechanisms within and across clinical groups remain speculative. Potential mechanisms include dysregulations on several levels of the hypothalamic–pituitary–adrenal axis. In addition, factors such as genetic vulnerability, previous stress experience, coping and personality styles may determine the manifestation of this neuroendocrine abnormality. Several authors proposed theoretical concepts on the development or physiological meaning of hypocortisolism. Based on the reviewed findings, we propose that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote an increased vulnerability for the development of stress-re

* Corresponding author. Tel.: +49-651-201-2929; fax: +49-651-201-2934.
E-mail address: hellhamm@uni-trier.de (D.H. Hellhammer)

PII: S0306-4530(99)00035-9

lated bodily disorders. This pathophysiological model may have important implications for the prevention, diagnosis and treatment of the classical psychosomatic disorders.

Keywords: Hypocortisolism; Stress-related bodily disorders; Adrenal gland

1. Introduction

In recent years, a novel and paradox phenomenon has emerged from neurobiological studies on the effects of stress. There is increasing evidence for a relatively decreased, rather than an increased cortisol secretion in individuals who have been exposed to severe stress or suffer from stress-related disorders. The phenomenon of hypocortisolism has received growing attention in the field of stress research, inasmuch as it challenges, or virtually reverses, prevailing concepts on the neuroendocrinology of stress.

Ever since the seminal studies by Selye (1936), stress has been associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis, ultimately resulting in an increased secretion of cortisol from the adrenal glands. The physiological effects of cortisol help the organism to maintain homeostasis under conditions of stress. The association between stress and increased cortisol secretion has been consolidated over the past decades to such an extent that stress and increased cortisol secretion merely have become synonyms in the literature and, moreover, the presence of cortisol hypersecretion has been used to define states of stress.

In a remarkable series of studies, however, Yehuda and her colleagues have most prominently described the phenomenon of hypocortisolism for patients who have experienced a traumatic event and subsequently developed post-traumatic stress disorder (PTSD; DSM-IV 309.81; for review see Yehuda, 1997). In the face of these striking observations, earlier studies from the 1960s and 1970s have regained consideration. These studies revealed hypocortisolism in healthy individuals who lived under conditions of ongoing stress (Friedman et al., 1963; Bourne et al., 1967, 1968; Mason et al., 1968; Caplan et al., 1979). More recently, hypocortisolism has also been reported for patients suffering from bodily disorders, such as burnout with physical complaints, chronic fatigue syndrome, fibromyalgia, chronic pelvic pain and asthma among others (Hellhammer, 1990; Demitrack et al., 1991; Crofford et al., 1994; Kruger and Spiecker, 1994; Heim et al., 1998a). Taken together, these findings suggest that hypocortisolism is not a specific correlate of PTSD, but may be a more widespread phenomenon.

Another line of evidence suggests that the above bodily disorders may be related to chronic or traumatic stress as well as PTSD. For example, increased numbers of major life events and high rates of sexual or physical abuse have been reported for patients with fibromyalgia and other chronic pain syndromes (Ahles et al., 1984; Boisset-Pioro et al., 1995; Heim et al., 1998a). Similar associations have also been reported for patients with rheumatoid arthritis or asthma (Wallace, 1987; Boxer et al., 1988). Interestingly, high rates of comorbidity between PTSD and such physical

disorders have been reported in several studies (Baker et al., 1982; Davidson et al., 1991; Culclasure et al., 1993; Amir et al., 1997; Iowa Persian Gulf Study Group, 1997; Heim et al., 1998a). These findings suggest that these disorders may represent a family of stress-related disorders with similar psychological antecedents and endocrine features, namely hypocortisolism.

The mechanisms involved in the development of hypocortisolism have received limited attention to date and, as yet, are a matter of speculation. Alterations on several levels of the HPA axis may contribute to the presence of hypocortisolism and, in addition, many factors, such as genetics, gender or early stress experiences among others, may determine the development of hypocortisolism. To complicate the picture, mechanisms and determining factors may vary across and within patient populations. Based on experimental data and theoretical considerations, several authors have posited theories on the development and the physiological meaning of hypocortisolism (Dienstbier, 1989; Hellhammer and Wade, 1993; Henry, 1993; Yehuda et al., 1993b; McEwen, 1998).

The findings of hypocortisolism in bodily disorders have led us to posit the following hypothesis: Hypocortisolism may be a relevant factor in the pathogenesis of bodily disorders, inasmuch as a lack of cortisol availability may promote an increased vulnerability to bodily disorders, such as autoimmune disorders, inflammation, chronic pain, asthma and allergies. In the following pages, we outline findings of hypocortisolism in PTSD, in stress-related bodily disorders as well as for chronic stress. Hypocortisolism refers to a deficiency of cortisol, including: (a) reduced adrenocortical secretion, at least temporarily during the circadian cycle; (b) reduced adrenocortical reactivity; or (c) enhanced negative feedback inhibition of the HPA axis. Furthermore, reduced effects of cortisol on target cells may occur due to an increased clearance or binding of cortisol as well as due to a reduced sensitivity of target cells for cortisol. The concept of hypocortisolism has not yet been sufficiently elaborated. We here summarize some of the available findings and we further discuss potential mechanisms underlying the phenomenon of hypocortisolism and theoretical concepts on the meaning of hypocortisolism that have been suggested in the literature. Finally, we elaborate on implications of hypocortisolism for immune function and disease vulnerability. The overall goal of this article is to provide an integrated overview of current knowledge and speculations on the phenomenon of hypocortisolism and to propose a medical hypothesis, which may form an important basis for future research.

2. HPA axis abnormalities in post-traumatic stress disorder

Since PTSD is a sequel of extreme stress experience and often coincides with major depression, it has been investigated whether patients with PTSD demonstrate specific alterations of the HPA axis (Yehuda et al., 1991a). Initial studies revealed decreased 24 h-urinary cortisol excretion in Vietnam veterans suffering from PTSD as compared to healthy controls and patients with other psychiatric disorders (Mason et al., 1986; Yehuda et al., 1990, 1993a). Decreased 24 h-urinary cortisol

excretion was also observed in Holocaust survivors with PTSD (Yehuda et al., 1995a). However, urinary cortisol excretion does not directly reflect adrenal activity, but also depends on cortisol metabolism. Several studies have, therefore, evaluated cortisol concentrations in single plasma or saliva samples obtained from patients with PTSD. Results are somewhat conflicting, however, the majority of studies to date suggest low rather than high cortisol levels in different patient populations. These include Vietnam veterans with PTSD (Boscarino, 1996), sexually abused women with PTSD (Stein et al., 1997a), and children exposed to the Armenian earthquake with PTSD (Goenjian et al., 1996). Moreover, in a chronobiological study, Yehuda et al. (1996) measured cortisol concentrations in 0.5 h-intervals over 24 h. As compared to healthy controls and depressed patients, Vietnam veterans with PTSD demonstrated a decreased nadir and an increased peak of cortisol release.

In order to identify further neuroendocrine correlates of PTSD, Yehuda et al. (1991b, 1993a) measured glucocorticoid receptor (GR) binding in peripheral mononuclear cells of Vietnam veterans with PTSD. As compared to healthy controls and other diagnostic groups, Vietnam veterans with PTSD were shown to demonstrate an increased number of GR in lymphocytes. As lymphocyte GR number may serve as a model for receptor changes in the brain, it was hypothesized that PTSD may be associated with an increased sensitivity of the HPA axis to negative feedback inhibition (Yehuda et al., 1991b).

In support of this latter hypothesis, Vietnam veterans with PTSD were shown to demonstrate enhanced suppression of cortisol relative to healthy controls and Vietnam veterans without PTSD, as identified using low doses of dexamethasone (Yehuda et al., 1993c, 1995a). To further substantiate the hypothesis of increased HPA axis feedback sensitivity in PTSD, Yehuda et al. (1995a) determined GR binding after the intake of dexamethasone. Vietnam veterans with PTSD demonstrated a more pronounced decrease in GR binding when compared to controls, possibly reflecting increased translocation of the activated GR from the cytoplasm to the nucleus of the cell, where the hormone–receptor complex affects gene transcription. In a recent study, increased feedback action of circulating cortisol on the HPA axis in PTSD was further supported by the observation of exaggerated ACTH responses to the β-hydroxylase inhibitor, metyrapone, which produces a state of pharmacological 'adrenalectomy', in these patients (Yehuda et al., 1997a). The latter result also shows that there is a pronounced central corticotropin-releasing activity in patients with PTSD despite of hypocortisolism. Consistently, blunted ACTH and normal cortisol responses have been reported for Vietnam veterans with PTSD and for sexually abused girls (Smith et al., 1989; DeBellis et al., 1994), and Vietnam war veterans with PTSD further show increased cerebrospinal fluid (CSF) CRF immunoreactivity (Bremner et al., 1997a).

In summary, neuroendocrine correlates of PTSD are: (1) low baseline cortisol secretion; (2) increased GR binding in lymphocytes; (3) supersuppression of cortisol by dexamethasone; (3) exaggerated ACTH response to metyrapone; (4) blunted ACTH response to CRF; and (5) increased CSF CRF concentrations. These findings can be interpreted as hypocortisolism and increased feedback inhibition of

the pituitary–adrenal level of the HPA axis, whereas the central CRF system seems to be hyperactivated. Hypocortisolism and increased feedback sensitivity are contrary to findings in major depression, which is rather characterized by hypercortisolemia, decreased GR binding in lymphocytes and nonsuppression of cortisol by dexamethasone (see Nemeroff, 1996 for review).

3. Hypocortisolism in stress-related bodily disorders

The phenomenon of hypocortisolism, however, has not only been reported for patients with PTSD, but was also observed in patients with several bodily disorders, many of which have been related to stress experience in general as well as, more recently, to trauma and PTSD.

In an initial study, our group observed decreased basal salivary cortisol levels in the morning along with relatively high cortisol levels in the afternoon and evening in a group of nurses who suffered from burnout and multiple bodily complaints (Hellhammer, 1990). In another early study on the neuroendocrinology of chronic fatigue syndrome, Poteliakhoff (1981) observed low plasma cortisol concentrations along with increased self-ratings of life stress in these patients as compared to non-fatigued controls. In a series of studies, Demitrack et al. (1991) identified reduced 24 h-urinary cortisol excretion, low basal plasma cortisol concentrations, blunted ACTH responses to CRF stimulation and decreased responsiveness of the adrenal cortex to maximal doses of $ACTH_{1-24}$ (250 μg) as correlates of chronic fatigue syndrome. Recently, Scott et al. (1998a) replicated the finding of blunted ACTH responses to CRF for patients with chronic fatigue syndrome and, moreover, cortisol responses were also decreased. They also observed blunted cortisol responses to a low dose of $ACTH_{1-24}$ (1 μg) in patients with chronic fatigue syndrome (Scott et al., 1998b). Reduced adrenocortical reactivity was also observed in a fenfluramine challenge test, while ACTH responses were exaggerated in this study (Bearn et al., 1995). In contrast, the adrenal cortex seems to be sensitized to minimal doses of $ACTH_{1-24}$ (0.01 μg/kg), possibly reflecting up-regulation of adrenal ACTH receptors in consequence of pituitary hypoactivity or alterations at higher levels of the HPA system (Demitrack et al., 1991).

Similar neuroendocrine correlates have been reported for patients with fibromyalgia and other chronic pain syndromes. Three studies found reduced 24 h-urinary cortisol excretion in patients with fibromyalgia relative to healthy controls (McCain and Tilbe, 1989; Crofford et al., 1994; Griep et al., 1998). In two of these studies, evening plasma cortisol levels were increased, suggesting that the circadian rhythm of cortisol release may be disturbed (McCain and Tilbe, 1989; Crofford et al., 1994). Several other studies suggest low morning cortisol levels for patients with idiopathic pain syndromes of diverse location and for children with recurrent abdominal pain (Valdés et al., 1989; von Knorring and Almay, 1989; Alfvén et al., 1994). Decreased basal cortisol concentrations have also been measured in serum and CSF of patients with chronic headache (Elwan et al., 1991). Some evidence suggests that low adrenal activity may not be the consequence of chronic pain.

Johansson (1981) was able to discriminate patients with idiopathic chronic pain from patients with chronic pain due to organic disease using basal cortisol levels, inasmuch as patients with idiopathic chronic pain demonstrated decreased and patients with organic chronic pain demonstrated increased cortisol levels.

Neuroendocrine challenge studies provide further evidence for adrenocortical impairment in fibromyalgia or other chronic pain syndromes. In two studies, patients with fibromyalgia demonstrated reduced adrenocortical reactivity in a CRF stimulation test, with ACTH responses being normal in one study and increased in the other study (Griep et al., 1993; Crofford et al., 1994). Griep et al. (1998) recently replicated their finding. The same group also observed reduced adrenocortical reactivity to physical stress in patients with fibromyalgia (van Denderen et al., 1992). In the face of frequent comorbidity between chronic pain syndromes and depression, several investigators have applied the standard DST to assess cortisol suppression in patients with chronic pain. Although two studies report increased rates of non-suppressors among patients with fibromyalgia (McCain and Tilbe, 1989; Ferraccioli et al., 1990), several other studies revealed rather low rates of non-suppressors in this patient population. For example, Hudson et al. (1984) observed an escape from DST suppression (>5 μg/dl) in only 4% of patients with fibromyalgia as compared to 9% of healthy controls. Similar low rates of non-suppressors were reported for patients with other idiopathic chronic pain (Sharav et al., 1987; Valdés et al., 1989). Griep et al. (1993) even report that none of their patients with fibromyalgia demonstrated escape from DST suppression, whereas the average non-suppressor rate in healthy subjects is known to be 9% (Stokes et al., 1984). In their recent replication study, Griep et al. (1998) found again only 5% nonsuppressors among 40 patients with fibromyalgia. In both studies, these authors did not control for comorbid depression. Interestingly, France and Krishnan (1985) observed DST non-suppression in 40% of depressed patients with chronic back pain (mean post-dexamethasone cortisol: 4.84 μg/dl) versus 0% of non-depressed patients with chronic back pain (mean post-dexamethasone cortisol: 1.17 μg/dl), suggesting DST non-suppression of cortisol is typically present in patients with chronic pain and comorbid depression. Based on these findings, one may expect that, similar to findings in PTSD, idiopathic pain syndromes per se may be related to increased negative feedback sensitivity, which may only be identified using a low dose DST.

In a series of studies, we assessed HPA axis function, stress history and psychopathology in women suffering from chronic pelvic pain. Women with chronic pelvic pain with no identified organic correlate demonstrated normal to low diurnal salivary cortisol levels (Ehlert et al., 1993; Heim et al., 1998a). In response to CRF stimulation, we observed normal plasma ACTH, but reduced salivary cortisol concentrations. After intake of a low dose of dexamethasone (0.5 mg), these patients exhibited enhanced suppression of salivary cortisol. Psychological assessments revealed increased prevalence rates of sexual and physical abuse experiences and PTSD as well as a higher total number of major life events for these women, while the mean extent of depression was within the normal range (Heim et al.,

1998a). Interestingly, we recently obtained similar findings for women with chronic pelvic pain and verified pelvic adhesions (Heim et al., 1999). We recently also documented the triad of burnout symptoms, physical complaints (e.g. pain), and hypocortisolism in a population of teachers, who reported living under chronic stress (Pruessner et al., 1999). Teachers with low morning cortisol levels and a supersuppression of cortisol to dexamethasone showed high numbers of physical complaints.

Similar findings have also been reported for patients with bodily disorders, which have a more obvious pathophysiological basis. Chikanza et al. (1992) found subnormal diurnal cortisol plasma levels in patients with rheumatoid arthritis as compared to healthy controls. Cortisol levels lower than normal were also measured in patients with rheumatoid arthritis at mild stages of the disease when compared to healthy controls and patients with high inflammatory activity (Neeck et al., 1990). Furthermore, Hedman et al. (1992) report low cortisol and dehydroepiandrosterone sulphate (DHEAS) levels for patients with rheumatoid arthritis when compared to healthy controls. Patients with rheumatoid arthritis were also shown to demonstrate reduced adrenocortical responsiveness in the CRF stimulation test (Cash et al., 1992) as well as in response to surgery (Chikanza et al., 1992). One study suggests that patients with rheumatoid arthritis do not show non-suppression of cortisol in a standard DST (Ferraccioli et al., 1990). For the interpretation of findings of hypocortisolism in rheumatoid arthritis, it is important to consider whether these patients were treated with corticosteroids or not, because corticosteroid treatment may be a cause for reduced adrenal activity. While the patients studied by Cash et al. (1992) were treated with a low dose of prednisone, the patients of the studies by Neeck et al. (1992) and Chikanza et al. (1992) were not treated with corticosteroids. Hedman et al. (1992) report that some of their patients were on corticosteroid treatment; however decreased cortisol and DHEAS levels were also observed in untreated subjects.

In line with the above findings, patients with asthma have been shown to exhibit low basal adrenal activity and hyporesponsiveness of the adrenal cortex in a CRF stimulation test (Kruger and Spiecker, 1994). Moreover, our group and others have observed attenuated cortisol responses to psychosocial stress in patients with atopic diseases (Buske-Kirschbaum et al., 1997; Schmid-Ott et al., 1998). However, a lack of information on basal adrenal activity and pituitary responsiveness does not allow a definite conclusion on whether these findings reflect hypocortisolism or not. In support of hypocortisolism in this patient population are findings of increased cytosolic GR binding in patients with atopic dermatitis (Rupprecht et al., 1991).

In summary, there is considerable evidence for decreased adrenal activity or reactivity in patients suffering from bodily disorders. These bodily disorders have been related to stress or trauma experience, and there seems to be considerable symptom overlap among these disorders (Waylonis and Heck, 1992), suggesting a spectrum of related bodily disorders with similar neuroendocrine correlates.

4. Hypocortisolism in chronic stress

Hypocortisolism, however, does not seem to be an exclusive correlate of stress-related pathology, but has also been reported for healthy subjects living under ongoing stress as well as for some animal models of chronic stress. There are a small number of studies in humans suggesting reduced adrenocortical activity or reactivity in states of chronic stress. Friedman et al. (1963) measured urinary excretion of the cortisol metabolite, 17-hydroxycorticosterone (17-OHCS), over several months in parents of fatally ill children. While there were great differences in the amounts of 17-OHCS excretion across subjects, the intraindividual pattern showed remarkable stability. Many of these parents demonstrated decreased 17-OHCS excretion below baseline, even in phases of acute medical complications in their children. Lower than normal 17-OHCS excretion was also observed in soldiers of a special team in Vietnam, who had been warned to expect an enemy attack; interestingly, 17-OHCS levels dropped even further on the day when the attack was anticipated (Bourne et al., 1968). In another study, the same authors measured 17-OHCS excretion of helicopter medics in Vietnam (Bourne et al., 1967). These medics demonstrated a stable pattern of decreased 17-OHCS excretion regardless of whether they were flying or not. On flying days, some medics even demonstrated lower 17-OHCS levels than on days off. Similar findings were obtained in civilian paramedics who demonstrated lower cortisol levels on work days as compared to days off (Dutton et al., 1978). More recently, decreased plasma cortisol concentrations were measured in Bosnian prisoners of war (Dekaris et al., 1993). All of these instances of stress may be arguably traumatic and may be related to PTSD; however, Bourne et al. (1967, 1968) report that there were no signs of clinical disease in their study subjects. Moreover, hypocortisolism has also been reported for individuals exposed to daily work stress. For example, white collar employees with high work load were shown to demonstrate decreased basal plasma morning cortisol levels as well as blunted cortisol responses to increases in their work responsibilities (Caplan et al., 1979).

Animal models of chronic stress typically consist of repeated exposure to the same stressor. Dependent on the nature of the stressor, a habituation of the pituitary–adrenal stress response develops, which is typically accompanied by slightly increased baseline levels (for review see Yehuda et al., 1991a). We believe that this adaptive habituation is distinct from the phenomenon of hypocortisolism as described in this paper. However, there are two studies using animal models of repeated stress, which identified gradual decreases in basal adrenal activity relative to basal adrenal activity before the beginning of the experiment, thus meeting our defintion of hypocortisolism (Mason et al., 1968; Natelson et al., 1988). The common feature of these studies is a relatively long time latency or resting period between the application of the stressors. After several weeks of baseline measures, Mason et al. (1968) subjected rhesus monkeys to a 72 h-shock avoidance paradigm, in which the monkeys had to press a lever to avoid electric shocks. Thereafter, the monkeys were allowed to rest for 3 to 5 weeks until the stress session was repeated. Stress sessions were repeated at least twice. During the shock avoidance sessions,

monkeys exhibited substantial increases of urinary 17-OHCS excretion. Nine days after cessation of the shock avoidance session, 17-OHCS levels had returned to normal and even dropped below initial baseline levels in many animals. With repeated shock avoidance sessions, baseline levels between the sessions decreased constantly to extremely low values, which remained stable over 3 to 5 weeks. Besides decreased basal 17-OHCS excretion, there was a progressive habituation of 17-OHCS responses to shock avoidance. Similar to these findings, Natelson et al. (1988) observed a gradual decrease in basal corticosterone levels in rats, which were weekly exposed to the same stressor. Interestingly, the authors report that there were high and low responders to stress among the rats. Initial low responders maintained a stable pattern of low responsiveness throughout several sessions of repeated stress, regardless of stressor intensity. These findings parallel findings in parents of fatally ill children, and point to the importance of interindividual differences.

Another approach to evaluate effects of chronic stress on HPA axis function in animal models is to expose animals to continuous stress over several hours or days. Continuous exposure of rats to electroshocks or immobilization induces an initial increase and a subsequent decrease of ACTH and corticosterone secretion as well as reduced responsiveness to subsequent challenge. The decrease of hormone secretion is independent from feedback effects, since it was also observed in adrenalectomized rats (Rivier and Vale, 1987; Hauger et al., 1988).

Taken together, there is a considerable body of evidence for reduced adrenal activity and reactivity in human subjects living under conditions of chronic stress. Only few studies in animal models have provided evidence for basal hypocortisolism along with adrenocortical habituation to repeated stress. Complementary findings are decreases in hormonal output throughout or after continuous stress induction.

5. Potential mechanisms and determinants of hypocortisolism

Several mechanisms may underlie the development and persistence of hypocortisolism. Among potential mechanisms of hypocortisolism are: (1) reduced biosynthesis or depletion at several levels of the HPA axis (CRF, ACTH, cortisol); (2) CRF hypersecretion and adaptive down-regulation of pituitary CRF receptors; (3) increased feedback sensitivity of the HPA axis; and (4) morphological changes. Besides these basic mechanisms, superimposed factors, such as the nature of the stressor, coping styles, and dispositions, may determine the manifestation of hypocortisolism (see Fig. 1).

5.1. Mechanisms

5.1.1. Reduced biosynthesis or depletion

One mechanism that may account for the phenomenon of hypocortisolism may be reduced availability of hormones at several levels of the HPA axis (CRF, ACTH,

cortisol). Reduced availability of cortisol may reflect decreased biosynthesis of the hormone or depletion of the gland. The findings of a relative decrease in adrenocortical reactivity in several stress-related disorders suggest that there may be an adrenal insufficiency in these disorders. This adrenal insufficiency may either be primary or secondary to alterations at higher levels of the HPA axis, and available evidence to date remains inconclusive. In support of a primary adrenal insufficiency are findings of low basal cortisol levels together with elevated ACTH levels in patients with chronic fatigue syndrome and fibromylagia as well as findings of reduced cortisol responses to moderate to high doses of $ACTH_{1-24}$ and in the CRF stimulation test (together with normal or elevated ACTH responses) in patients with fibromyalgia or chronic pelvic pain (Demitrack et al., 1991; Griep et al., 1998; Heim et al., 1998a; Scott et al., 1998b). On the other hand, findings of normal or increased cortisol responses to minimal doses of $ACTH_{1-24}$ in chronic fatigue syndrome and fibromyalgia are generally thought to reflect up-regulation of adrenal receptors for ACTH, possibly secondary due to low ACTH secretion (Demitrack et al., 1991; Griep et al., 1998). However, one may argue that a primary deficient adrenal gland may also adapt to normal or increased ACTH pulses by enhancing its sensitivity. Since CRF is involved in the regulation of arousal and vigilance, it has also been suggested that a subtle CRF deficiency may account for symptoms of fatigue and exhaustion in these disorders (Sternberg, 1993). However, in one study normal CSF CRF levels were measured in patients with chronic fatigue syndrome, although CSF CRF levels may not adequately reflect CRF activity in the hypothalamus or brain areas involved in the regulation of arousal (Demitrack et al., 1991).

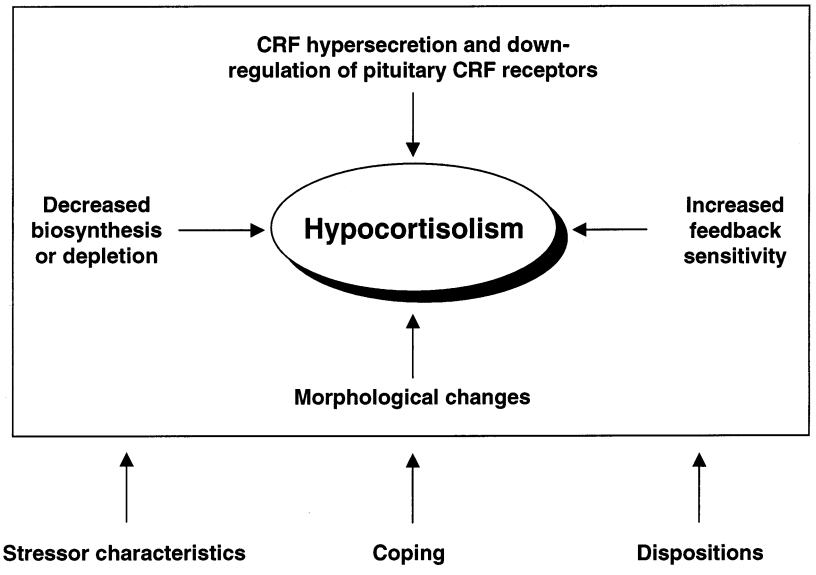

Fig. 1. Potential mechanisms and determinants underlying the development and persistence of hypocortisolism in traumatic or chronic stress (CRF, corticortropin releasing factor).

Interesting in this regard are findings in Lewis rats, which have a high susceptibility to develop arthritis. Whereas HPA axis function appears to be normal under baseline conditions, Lewis rats demonstrate reduced hypothalamic CRFmRNA expression and corticosterone responses to acute stress when compared to genetically comparable Fischer rats (Sternberg et al., 1989a,b). However, when chronically stressed, Lewis rats develop a relative hyporesponsiveness to ACTH at the adrenal level as compared to several rat strains, whereas CRFmRNA expression is increased (Gómez et al., 1996).

Although there is evidence that the hypothalamic–pituitary system may not be insufficient in PTSD, it remains basically unknown, whether the adrenal gland is fully functioning in these patients or not. Clinical observations suggest that patients with PTSD show pronounced cortisol responses to reminders of the trauma or throughout exposure therapy (Yehuda et al., 1993b). Similarly, a helicopter paramedic studied by Bourne et al. (1968) demonstrated substantial increases of 17-OHCS after he was injured and developed infection. However, it remains unclear, whether there is a relative reduction in adrenocortical responsiveness in these cases, since cortisol levels have generally not been expressed relative to ACTH secretion. Interestingly in this regard, sexually abused children who were at high risk for PTSD and lived under conditions of ongoing stress, were reported to demonstrate increased ACTH, but normal cortisol responses in a CRF stimulation test, suggesting decreased adrenocortical reactivity (Kaufman et al., 1997).

5.1.2. CRF hypersecretion and pituitary CRF receptor down-regulation

Another mechanism that may contribute to the phenomenon of hypocortisolism may be CRF hypersecretion from the hypothalamus and an adaptive down-regulation of pituitary CRF receptors. If the adrenal gland is not hyper-responsive, as in some types of major depression, CRF receptor down-regulation should result in reduced ACTH and lower than normal cortisol levels. Accordingly, increased CSF CRF levels and blunted ACTH responses to CRF stimulation have been reported for patients with PTSD (Smith et al., 1989; Bremner et al., 1997a). Several animal studies suggest that hypothalamic CRF hypersecretion and down-regulation of pituitary CRF receptors may develop under conditions of chronic stress. Increased CRF immunoreactivity as well as increased CRF mRNA expression in the hypothalamus have been measured in rats exposed to chronic intermittent stress (Haas and George, 1988; Imaki et al., 1991; DeGoeij et al., 1992; Makino et al., 1994). After 18–48 hours of continuous stress, Hauger et al. (1988) observed a time-dependent reduction of pituitary CRF receptors, which was correlated to the decrease of CRF immunoreactivity in the median eminence. Down-regulation of pituitary CRF receptors and CRF receptor mRNA was also observed after intermittent immobilization stress (Hauger et al., 1990; Makino et al., 1994). Explanted pituitary cells of continuously stressed rats demonstrated reduced reactivity to incubation with CRF (Hauger et al., 1988). Interestingly, blunted responsiveness could be reversed by simultaneous incubation of the cells with CRF and AVP, providing a possible explanation for the observed normal or increased responsiveness to superimposed stress in animals or individuals with chronic stress or PTSD.

In human subjects, it is difficult to assess hypothalamic CRF secretion and pituitary CRF receptor status, and conclusions have to be deduced from indirect evidence. Findings regarding ACTH responses to exogenous CRF are inconclusive for PTSD and stress-related bodily disorders and, moreover, may be influenced by other mechanisms, such as feedback and biosynthesis of hormones. In the case of PTSD, increased CSF CRF concentrations and behavioral features of the disorder suggest that there may be increased central CRF activity (Bremner et al., 1997a). Central administration of CRF to animals produces many signs of stress and anxiety, which parallel many symptoms of PTSD (Heim et al., 1997b). However, there may be discrepancies in hypothalamic versus extrahypothalamic CRF activity, and novel methods have to be applied to assess hypothalamic CRF content and pituitary receptors in humans.

5.1.3. Increased feedback sensitivity

Reduced reactivity of the HPA axis in chronic stress and depression has often been attributed to negative feedback inhibition due to increased levels of circulating corticosteroids (Holsboer et al., 1985). This mechanism has no face validity in the case of decreased basal adrenal activity; however, as suggested by Yehuda et al. (1991b), increased sensitivity of the HPA axis for negative feedback may possibly be associated with the phenomenon of hypocortisolism. Based on observations regarding the time course of the development of hypocortisolism in monkeys exposed to repeated shock avoidance sessions, Mason et al. (1968) already concluded that hypocortisolism in these monkeys may not reflect adrenal exhaustion, but rather indicates the involvement of suppressive mechanisms. In support of this hypothesis, the authors observed increased ACTH responses to metyrapone in these monkeys. Similarly, reported that dominant wild baboons demonstrate low basal cortisol levels as well as a more rapid and increased suppression of cortisol by dexamethasone when compared to subordinate monkeys. Parallel findings of increased responsiveness to feedback tests have been reported for patients with PTSD and for patients with stress-related bodily disorders (Yehuda, 1997; Heim et al., 1998a). Moreover, findings of increased GR binding in lymphocytes in PTSD have been considered indicative for increased feedback sensitivity (Yehuda, 1997). However, results of cytosolic radioligand binding assays depend on prevailing cortisol levels, because the radioactive-labeled ligand binds to the unbound form of the GR in the cytosol. Therefore, increased GR binding in PTSD may reflect a higher amount of available GR due to decreased GR activation or translocation in the face of hypocortisolism, and does not necessarily reflect GR up-regulation (Heim et al., 1998b). Additionally, the interplay between mineralcorticoid receptors (MR) and GR in the regulation of the HPA axis in PTSD and other hypocortisolemic states needs further evaluation. For example, Roman rats, who are characterized by a hippocampal MR/GR-imbalance demonstrate low basal corticosterone levels and reduced reactivity of the HPA axis (Walker et al., 1989). Taken together, while intriguing, the model of increased feedback sensitivity of the HPA axis as a mechanism of hypocortisolism needs further scrutiny.

5.1.4. Morphological changes

Another factor that should be considered in association with hypocortisolism is the possible contribution of morphological changes at different levels of the HPA axis. It may well be that low adrenal activity or reactivity goes along with structural changes of the adrenal gland, such as atrophy or decreased volume. There are no studies to date assessing adrenal gland volume in patients with hypocortisolism. However, conversely, there is evidence that patients with major depression, which can be associated with hypercortisolemia, do show increased adrenal gland volumes (Nemeroff et al., 1993; Rubin et al., 1995). Although there is some controversy in clinical studies about the association of increased adrenal volumes with HPA axis hyperactivity, research from animal studies provides evidence that chronic stimulation of the adrenal gland results in increased adrenal gland volumes (Orth et al., 1992). Thus, it may be concluded that a chronic HPA axis hypoactivity is associated with a smaller adrenal volume. Reduced adrenal volume, for example, has been observed in Lewis rats with a hypoactive HPA axis (Sternberg et al., 1989a,b). Similarly, morphological changes may be present at higher levels of the HPA axis, namely the pituitary gland; however, to date it remains fairly unclear whether basal ACTH levels are normal, increased or decreased in PTSD or other stress-related disorders.

Most interestingly, however, there is accumulating evidence suggesting that patients with PTSD show decreases in the volume of the hippocampus, which is predominantly involved in the inhibitory regulation of the HPA axis (Bremner et al., 1995, 1997b; Gurvits et al., 1996; Stein et al., 1997b). The patients of the study by Stein et al. were also shown to exhibit reduced basal cortisol levels and hypersuppression of cortisol to dexamethasone (Stein et al., 1997a). In a sense, these findings represent a paradox to findings from animal studies. Sapolsky et al. (1985, 1986) demonstrated that stress-induced elevations of glucocorticoids exert toxic effects on the hippocampus resulting in neuronal cell death. The authors assume that hippocampal damage in turn promotes a disinhibition of the HPA axis resulting in further increases of glucocorticoid secretion, thus forming a feed-forward circuit. In the face of this paradox, it has been suggested that the findings of hippocampal atrophy in PTSD may reflect: (1) a preexisting vulnerability that predisposes individuals to develop PTSD; (2) a consequence of the initial trauma when cortisol levels may have been elevated; (3) a consequence of excessive HPA axis responses to multiple daily stressors; or (4) increased sensitivity of hippocampal GR enhancing the effects of low cortisol levels (Stein et al., 1997b; Yehuda, 1997). However, when discussing the findings of hippocampal atrophy in PTSD, one needs to take into account the complex regulation of hippocampal neurons. Recent research has demonstrated that hippocampal atrophy is not equivalent to neuronal cell death, but may rather reflect different types of plasticity (for review see McEwen, 1999). Thus, glucocorticoids have been shown to participate in the regulation of neurogenesis in the dentate gyrus as well as in the induction of a reversible atrophy or debranching of dendrites in the CA3 region of the hippocampus. It has been suggested that this reversible atrophy of dendrites in response to stress may be adaptive in terms of protecting hippocampal neurons from more

permanent damage (McEwen, 1999). Thus, it remains unclear whether the hippocampal atrophy observed in patients with PTSD reflects permanent neuronal damage or reversible dendritic atrophy, and the answer to this question may have important treatment implications. Moreover, recent findings temper the role of glucocorticoids in the induction of hippocampal changes, but point to the relative importance of excitatory amino acids, neurotrophins and neurotransmitter systems (for review see McEwen, 1999). The elucidation of these mechanisms may further help to understand the paradox between hypocortisolism and hippocampal atrophy in PTSD.

5.2. Determining factors

5.2.1. Stressor characteristics

The majority of studies on the differential effects of various qualities of stressors on the HPA axis have focused on animal models of habituation. It was shown that habituation of the HPA axis depends on the nature, frequency, intensity, controllability and predictability of stress exposure (Seligman, 1975; Murison et al., 1986; Natelson et al., 1988; Ottenweller et al., 1989; Orr et al., 1990). HPA axis responses are maintained in the case of a small number of previous stress exposure and high stressor intensity as well as low controllability or predictability of the stress. There is only limited evidence for associations between stress characteristics and the development of hypocortisolism. In the study by Natelson et al. (1988), baseline corticosterone in rats dropped gradually over 5 weeks of repeated stress regardless of the intensity of the stress protocol. Similarly, Mason et al. (1968) report that monkeys, who had been in the laboratory for years and had undergone many different stress experiments, developed lowest baseline 17-OHCS levels over time when exposed to repeated shock avoidance sessions. Both studies suggest that previous stress experiences may mediate basal hypocortisolism. Clinical studies suggest that the development of PTSD depends on the severity of the trauma and the number of concomitant stressors before, during or after the traumatic event (Ruch et al., 1980; Foy et al., 1987; Green and Berlin, 1987; McFarlane, 1988; Yehuda et al., 1995b,c). Neuroendocrinological studies have provided evidence that alterations in HPA axis function in PTSD patients are also related to the severity and nature of the stress experience. In one study, basal plasma cortisol levels were inversely related to the severity of combat exposure and GR number in lymphocytes was positively related to the extent of the experience of atrocities (Yehuda et al., 1991b).

5.2.2. Coping

Besides the nature of stress, the quality of behavioral responses to the stress experience may mediate the development of hypocortisolism. Findings from several studies suggest that passive coping, repression and denial of the stressful event may be related to hypocortisolism. For example, women who underwent biopsy for the diagnosis of breast cancer showed low cortisol levels, when they employed coping strategies characterized by repression (Katz et al., 1970). Similarly, in the study by

Wolff et al. (1964), those parents of fatally ill children who repressed and denied the illness showed lower than normal 17-OHCS excretion rates. Rose et al. (1968) further report that soldiers in training who were characterized by avoidance behavior exhibited decreased adrenal activity as compared to normative values. On the other hand, several other studies suggest an association between active coping and decreased adrenal activity. For example, those soldiers living in camp in Vietnam who started to actively prepare for the event of an enemy attack showed lowest 17-OHCS levels (Bourne et al., 1968). Similarly, the monkeys repeatedly exposed to shock avoidance sessions showed the lower 17-OHCS excretion rates in response to stress, the higher the number of lever responses to avoid shocks (Mason et al., 1968). A general limitation of these early findings in the human studies is a lack of psychometric assessment of coping styles. Moreover, recently, the validity of information on coping styles obtained in questionnaires has been questioned and more valid approaches are needed in the future (Stone et al., 1998).

5.3. Dispositions

5.3.1. Genetics and gender

There is only limited evidence for a genetic contribution to the development of hypocortisolism. However, it has been reported that identical twins show a higher concordance of basal cortisol levels when compared to non-identical twins, suggesting that HPA axis function generally underlies a genetic influence (Meikle et al., 1989; Kirschbaum et al., 1992a). Unfortunately, there are no direct studies on a genetic transmission of the phenomenon of hypocortisolism as manifested in stress-related disorders in humans. However, indirect evidence comes from findings of a genetic contribution to the development of PTSD and other stress-related disorders, which are characterized by hypocortisolism. One study on twin Vietnam veterans suggests that 30% of the variability of PTSD symptoms may be genetically determined (True et al., 1993). Moreover, healthy identical twins show higher concordance of startle reactions when compared to non-identical twins (Lykken et al., 1988), and increased startle responses are one key symptom of PTSD which may precede the disorder and reflect a risk factor. Relatives of Vietnam veterans with PTSD more often suffer from anxiety disorders than relatives of Vietnam veterans without PTSD (Davidson et al., 1985; Foy et al., 1987). Increased family histories of psychiatric disorders, including PTSD, have also been reported for patients with stress-related bodily disorders (Hudson and Pope, 1994). Also, there is an accumulation of stress-related bodily disorders within families (Yunus, 1994). Taken together, these findings point to a potential contribution of genetic factors to the development of hypocortisolism, which may predispose individuals to develop stress-related disorders.

Female gender has also been identified as a risk factor for both PTSD and stress-related bodily disorders, such as fibromyalgia (Hug and Gerber, 1990; Sieber et al., 1996). Although findings are not uniformly consistent, evidence from several studies suggests that there is a gender difference with respect to HPA axis function in humans. Decreased basal cortisol concentrations and enhanced suppression of

cortisol by dexamethasone have been measured in women in the follicular phase of the menstrual cycle relative to women in the luteal phase or when compared to men (Genazzani et al., 1975; Tandon et al., 1991; Tersman et al., 1991).

5.3.2. Developmental factors

Early adverse experiences induce persistent alterations of the HPA axis that show similarities to findings of hypocortisolism. The exposure of infant rats to mild stress, such as daily handling, results in decreased basal corticosterone levels, reduced adrenocortical responses to acute stressors and enhanced suppression of stress-induced HPA activation by dexamethasone in adult life. At the central level, these rats show an increased number of hippocampal GR and decreased hypothalamic CRF immunoreactivity (for review see Meaney et al., 1994). These findings compare with findings in PTSD, although in PTSD, central CRF may be hypersecreted and the stress response seems to be sensitized. Interestingly, the more intense stress of maternal separation results in increased hypothalamic CRF expression and sensitization of the ACTH response to acute stress, whereas the corticosterone response seems unaltered, suggesting a hyporesponsive adrenocortex (Ladd et al., 1996). A dissociation between central CRF secretion and adrenal activity was also observed in a study on the effect of adverse rearing conditions on non-human primates (Coplan et al., 1996). Bonnet macaques, whose mothers were confronted with variable foraging demands while rearing the infants, demonstrated increased CSF CRF and decreased CSF cortisol concentrations in adulthood when compared to primates who were reared under consistent foraging demand conditions.

Besides stress early in life, prenatal stress may induce states of persistent hypocortisolism. For example, administration of ACTH or corticosterone to pregnant rats results in decreased basal corticosterone levels, reduced adrenocortical reactivity and decreased adrenal volumes in the offspring (Catalani et al., 1993; Fameli et al., 1994). With respect to possible gender differences in the development of hypocortisolism, it is noteworthy, that female offspring was more vulnerable than male offspring to develop adrenal dysfunction (Fameli et al., 1994).

It may be assumed that stress early in life induces a vulnerability for the development of PTSD and other stress-related disorders, which is mediated via persistent neurobiological changes. In support of this hypothesis, several studies suggest a strong relationship between adverse experiences in childhood and the development of PTSD in response to combat exposure in adulthood (McCranie et al. 1992; Bremner et al. 1993; Zaidi and Foy 1994).

5.3.3. Personality

Another modulating factor in the development of hypocortisolism may be specific personality traits. Increasing evidence suggests that the personality trait of alexithymia is related to hypocortisolism. Henry et al. (1992) observed increased norepinephrine and decreased cortisol concentrations in alexithymic men, and this pattern parallels findings in PTSD (Mason et al., 1988). Increased scores in the Toronto Alexithymia Scale (Taylor et al., 1985) have been reported for Vietnam

veterans and Holocaust survivors with PTSD as well as for rape victims with and without PTSD (Zeitlin et al., 1993; Gerhards et al., 1997; Yehuda et al., 1997b). In the aforementioned study by Gerhards et al., alexithymia scores were related to abnormal cerebral laterality. Patients with alexithymia demonstrate increased numbers of bodily complaints and, conversely, high alexithymia scores were reported for patients with somatoform disorders (Cox et al., 1994). Moreover, high alexithymia scores are associated with a low tolerance to experimental painful stimulation (Nyklíček and Vingerhoets, 1996). Taken together, these findings suggest a possible relationship between stress, alexithymia, hypocortisolism and PTSD or bodily disorders. In addition to these findings, there is evidence that hypocortisolism, burnout and physical complaints are associated with low self-esteem, high external control and introversion (Pruessner et al., 1999).

In summary, there are multiple mechanisms and determinants that may be implicated in the development of hypocortisolism, and the relative contribution of these mechanisms and determinants remains a matter of speculation. The picture may even be more complicated: (1) Different mechanisms and determinants may mutually interact; for example there may be genetically determined sensitive phases which allow the induction of persistent GR up-regulation upon stress exposure. (2) The majority of the presented results are correlative findings and it remains unclear, whether abnormalities, i.e. structural changes, are antecedents or consequences of stress experience and/or pathology. (3) Some relationships may be mediated by intervening variables, such as the relationship between alexithymia and hypocortisolism could be triggered by abnormal cerebral laterality. (4) The contribution of mechanisms to hypocortisolism may change over time: for example, initially, low cortisol levels may be due to enhanced suppression of the axis, which in the long run may induce adrenocortical insufficiency and atrophy. (5) Mechanisms and determinants may not be uniform within and between groups of patients with hypocortisolism. Rather, it may be assumed that a complex and heterogeneous pattern of mechanisms may contribute to hypocortisolism in different individuals.

6. Theoretical concepts of hypocortisolism

Few authors have formulated theoretical concepts regarding the phenomenon of hypocortisolism. In these concepts, the above mechanisms and determinants have been differentially combined or emphasized, and diverse ideas on the physiological meaning of adrenal hypoactivity have been suggested.

Henry (1993) conceptualizes hypocortisolism in the context of variables that have been generally associated with the stress response, including ego involvement, perceived control, and active coping. He assumes that hypocortisolism is closely related to specific features of PTSD, such as emotional indifference or dissociation (i.e. lack of ego involvement) and repression (i.e. passive coping), and the prevention of the experience of loss of control by these features. The author further emphasizes similarities between PTSD and alexithymia, with both disorders associated with emotional indifference, denial and low adrenal activity. Based on findings

of disturbed cerebral laterality in alexithymic patients with PTSD, Henry (1993) hypothesizes that hypocortisolism in PTSD is due to repression of emotional information from the right hemisphere by a dominant left hemisphere, resulting in decreased emotional involvement.

Based on epidemiological data on the prevalence of PTSD and observations in trauma survivors without PTSD, Yehuda et al. (1993b) consider hypocortisolism as a specific correlate of the psychiatric disorder, PTSD. Importantly, PTSD and hypocortisolism are not considered as normative responses to severe stress, but are thought to represent a non-normative or maladaptive state. Based on relative solid database, the authors propose increased negative feedback inhibition as the mechanism underlying the phenomenon of hypocortisolism. Physiologically, such hyperregulation of the HPA axis would permit a maximal amplitude and fast termination of the HPA axis response to stress. With reference to findings from neonatal handling studies, the Yehuda et al. (1993b) assume a role of early life stress in the development of increased negative feedback, possibly reflecting a vulnerability factor for the development of PTSD upon trauma exposure.

The conceptualization of hypocortisolism as a phenomenon, which is linked to early developmental stress and which allows an optimal stress response, is similar to the concept of 'physiological toughness' posited by Dienstbier (1989). This author assumes that early stress experiences, but also successful coping with stress in adulthood induce a specific neuroendocrine pattern, which is characterized by decreased basal adrenal activity, increased autonomic and blunted HPA axis responses to stress and a fast termination of these stress responses. Physiologically, this pattern is thought to allow increased stress tolerance as well as better performance and optimal maintenance of physical health during stress conditions. Thus, in contrast to the above concepts, Dienstbier (1989) suggests that hypocortisolism reflects an adaptive state of stress tolerance in functional individuals.

Another theoretical approach, that comprises considerations on hypocortisolism, is the concept of 'allostatic load' posited by McEwen (1998). The author outlines a model, in which dispositions and behavioral styles influence an individual's physiological response to stress. Diverse physiological systems accommodate to changing conditions in an effort to achieve stability through change (allostasis), and are thus protective in terms of adaptation. However, over time, this accommodation may produce allostatic load. For example, chronic hyper- or hypoactivity of an allostatic system may have adverse effects on the organism. In this context, the author discusses hypocortisolism as one type of allostatic load (type 4), characterized as a lack of normal response of a generally hypoactive system, as for example seen in fibromyalgia, chronic fatigue syndrome and atopic diseases. The author emphasizes that low HPA axis responsiveness may result in increased activity of other systems, such as the immune system and may, therefore, have implications for health. Thus, in contrast to the concept of Dienstbier (1989), McEwen (1998) considers hypocortisolism as maladaptive.

Similar to the aforementioned model, Hellhammer and Wade (1993) suggest that hypocortisolism may be the consequence of both, trauma or prolonged non-traumatic stress, and that there may be a time course in the development of this

neuroendocrine abnormality. The concept is based on considerations that trauma and chronic stress may not be distinct constructs. For example, a single traumatic event may induce a prolonged stress experience, due to recurrent memories and continuous appraisals of situations as being threatening (Baum et al., 1993). In addition, chronic stress other than the traumatic event, such as daily hassles and major life events, seems to contribute to the development of PTSD (Ruch et al., 1980; Green and Berlin, 1987; McFarlane, 1988). Notably, Scott and Stradling (1994) describe PTSD-like symptoms as a consequence of chronic psychosocial stress without traumatic quality. Thus, Hellhammer and Wade (1993) assume that both trauma and chronic stress are associated with prolonged activation of hypothalamic CRF secretion and an initial pituitary–adrenal hyperactivity. As a consequence, pituitary CRF receptors may down-regulate over the course of time. The authors assume that a normalization of hypothalamic CRF secretion at this point, maybe due to a period of rest, would result in a diminished ACTH secretion, ultimately producing cortisol levels below the normal baseline.

Similar to the latter model, Wang et al. (1996) assume that adrenal activity of PTSD may change over time. In longitudinal evaluations, the authors measured low levels of urinary cortisol excretion only during certain periods of observation. Based on these findings taken together with clinical observations, the authors propose the existence of distinct stages of functioning versus decompensation in PTSD, which may be associated with differential neuroendocrine activation.

7. Implications of hypocortisolism for disease vulnerability

Traumatic or chronic stress may promote a specific dysfunction of the HPA axis, characterized by decreased adrenal activity. Several, maybe differential, mechanisms may be involved on higher levels of the axis, and central CRF secretion could be increased or decreased. Based on the physiological effects of these hormones, we suggest that the HPA axis dysfunction promoted by traumatic or chronic stress may have important implications for the vulnerability to develop stress-related bodily disorders.

First, central administration of CRF to laboratory animals produces many physiological and behavioral changes, such as increases in heart rate and mean arterial pressure, sleep disruption, reduction of food intake, inhibition of the pituitary–gonadal system, decreased reproductive behavior, and changes in gastrointestinal motility (for review see Owens and Nemeroff, 1991). Increased central CRF activity in traumatized or chronically stressed individuals may therefore promote many disorders, such as stress-related cardiovascular disease, sleep disorders, eating disorders, sexual dysfunction, infertility and irritable bowel syndrome. Through an interaction with the central noradrenergic system, CRF is also likely to regulate vigilance and arousal. Thus, reduced central CRF activity as reported for patients with chronic fatigue syndrome may be causally involved in the development of fatigue-like symptoms and exhaustion.

Second, the secretion of cortisol under stressful conditions provides a protective effect to the organism. Cortisol induces gluconeogenesis, mobilizes free fatty acids and reduces the use of amino acids for protein synthesis, and with these metabolic effects, cortisol increases the organism's energy supplies (Kaplan, 1988). Moreover, glucocorticoids exert immunosuppressive effects on many immune functions, such as lymphocyte function (Fauci, 1975, 1976), macrophage activity (Schaffner, 1985), and macrophage-induced antigen presentation and subsequent T cell proliferation (Hirschberg et al., 1982). Moreover, glucocorticoids reduce natural killer cell activity and inhibit the secretion of cytokines, such as interleukins, tumor necrosis factor and interferon (Kelso and Munck, 1984; Dupont et al., 1985; Cavallo et al., 1986; Gatti et al., 1987). These cytokines are important immune and inflammatory mediators, which are, in turn, involved in the regulation of cellular immunity (see Bateman et al., 1989 for review).

Other important mediators are leukotriens and prostaglandins, which regulate inflammatory processes, anaphylactic reactions and pain perception. Prostaglandins have been shown to increase the sensitivity of nociceptors to noxious stimuli (Handwerker, 1976; Nicol et al., 1992; Hingtgen and Vasko, 1994). Both, prostaglandins and leukotriens are derivatives of the precursor arachidonic acid, which is released by the enzyme phospholipase. For example, aspirin reduces pain perception by pharmacological inhibition of the metabolism of arachidonic acid (Allen, 1995). Interestingly, glucocorticoids have also been shown to inhibit the release of arachidonic acid by induction of an antiphospholipase protein, lipocortin (Flower and Blackwell, 1979). Animal studies have provided evidence that even subtle physiological changes of adrenal activity have a potent effect on arachidonic acid metabolism (Blackwell et al., 1982).

According to the hypothesis of Munck et al. (1984), the immunosuppressive action of cortisol prevents toxic effects of primary defensive mechanisms that are activated in response to stress. Thus, a permanent lack of the protective effects of cortisol in traumatized or chronically stressed individuals might promote a disinhibition of immune functions, resulting in an increased vulnerability for the development of autoimmune disorders, inflammation, chronic pain syndromes, allergies and asthma. This hypothesis is supported by findings of hypocortisolism in many different populations of patients with stress-related bodily disorders (vide supra). An association between hypocortisolism and increased disease vulnerability is also supported by findings from animal studies. Sternberg et al. (1989a,b) demonstrated that the difference between Lewis rats who are highly susceptible to develop arthritis in response to a streptococcal cell wall stimulus and Fischer rats who are not susceptible to develop the disease is a lack of corticosterone under stimulated conditions. Pharmacological doses of dexamethasone completely abolish the development of arthritis in Lewis rats and physiological doses of dexamethasone reduce the severity of arthritis in Lewis rats, suggesting that the lack of corticosterone is indeed causally involved in the development of arthritis in this rat strain. It should be noted that the lack of corticosterone response in Lewis rats is relative, since it is only apparent as compared to genetically comparable Fischer rats. However, corticosterone levels are similar in Lewis rats and Sprague–Dawley rats, which are

not susceptible to arthritis (Dhabhar et al., 1993). Thus, there also seems to be a genetic difference regarding the amount of corticosterone needed to regulate immune function.

It should be noted though that a number of studies suggest that stress or glucocorticoids do not solely exert immunosuppressive effects, but may also have enhancing effects on cellular immunity (for review see McEwen et al., 1997). For example, mild stress and very severe, prolonged stress have been shown to induce suppression of cellular immune responses, whereas moderate stress results in enhanced cellular immunity (Weiss et al., 1989). In another study, it has been reported that upon chronic stress exposure over 4 to 6 weeks, experimental animals demonstrate at first suppressed mitogenic responses of splenic lymphocytes, which turn into enhanced mitogenic responses over time (Monjan and Collector, 1977). Further studies should evaluate such differential stress effects under consideration of corticosterone levels. Interestingly, it has been shown that mitogenic responses of lymphocytes can be enhanced by brief exposure to low cortisol levels (Wiegers et al., 1994). Another series of studies has provided evidence for an enhancement of cell-mediated immune reactions to antigen presentation in the skin after acute stress exposure (Dhabhar and McEwen, 1996, 1997). The authors have suggested that enhancement of cellular immunity in the skin may be due to a redistribution of leukocytes from the blood to the skin in order to provide maximal defense at sites of challenge, which would be evolutionary adaptive. This redistribution appears to depend on glucocorticoid actions, since adrenalectomized rats show similar enhancement of cutaneous cellular immunity after the administration of a single dose of corticosterone mimicking acute stress exposure. In contrast, the same reaction is suppressed by glucocorticoid treatment designed to mimic chronic stress (Dhabhar and McEwen, 1999). Based on these findings, one may assume that individuals with hypocortisolism may show inadequate immune cell trafficking and may suffer from an inability to defend against pathogens, especially if exposed to them under acute stress conditions. It has actually been shown that individuals with adrenal insufficiency lack adequate trafficking of leukocytes (Thompson et al., 1980). Thus, glucocorticoids seem to shape and balance immune function and several mechanisms may contribute to maladaptive immune function in individuals with hypocortisolism.

Concordant with our hypothesis, there are several reports on elevations of immune parameters in individuals who experienced traumatic events or suffer from bodily disorders, which are associated with hypocortisolism. Bosnian prisoners of war, for example, demonstrate increases in the number and function of lymphocytes along with reduced cortisol levels (Dekaris et al., 1993). Moreover, elevated levels of IL-1β have been reported for patients with PTSD (Spivak et al., 1997). Increases in natural killer cell activity along with intrusive memories have been measured in workers recovering body parts from traumatic deaths (Delahanty et al., 1997). Sexually abused girls have been shown to demonstrate increased levels of antinuclear autoantibodies (DeBellis, 1996). Similarly, increases in antinuclear autoantibodies, thyroid autoantibodies and interleukin concentrations have been reported for patients with chronic fatigue syndrome (see Buchwald and Komaroff, 1991 for

review). Increased serum concentrations of interleukins as well as prostaglandins have been observed in patients with fibromyalgia (Hamaty et al., 1989). Interestingly, enhanced prostaglandin synthesis has long been implicated in the pathophysiology of chronic cyclic and acyclic pelvic pain syndromes (Benedetto, 1989). Unfortunately, there is virtually no evidence from experimental studies supporting a relationship between low cortisol levels, a disinhibition of immune parameters and the development of bodily disorders in humans. However, in one study, exacerbations of autoimmune thyroid dysfunction has been observed in patients who underwent unilateral adrenalectomy in cause of Cushing's syndrome (Takasu et al., 1990). In another study, spontaneous development of fibromyalgia symptoms occurred in cancer patients when treated with IL-2 (Wallace and Margolin, 1988). In healthy populations, pharmacological reduction of cortisol availability has been shown to produce decreased perception thresholds (Fehm-Wolfsdorf, 1994), and similar associations may explain low pain thresholds in chronic pain patients.

Increased vulnerability to the development of stress-related bodily disorders can also be present, if the adrenal output is normal, but the concentration of the free, biologically active fraction of cortisol is diminished due to increased concentrations of corticosteroid binding globulins (CBG). For example, chicken with a genetically determined elevation of CBG concentrations are characterized by increased cytokine activity and the occurrence of spontane autoimmune thyroiditis (Faessler et al., 1986).

8. The role of glucocorticoid receptors in mediating the effects of hypocortisolism on target cells

The protective effects of cortisol on metabolism and immune function are mediated by binding of the hormone to specific receptor proteins in target cells. According to the prevailing model of adrenal steroid action, the unbound GR, which resides in the cytoplasm, undergoes a conformational change when bound to steroid and translocates to the nucleus of the cell to affect gene transcription. The GR proteins may adapt in number and affinity to changes in physiological conditions. For example, findings of increased cytosolic GR binding in patients with PTSD have been interpreted to reflect a compensatory up-regulation of these receptors in response to low cortisol levels (Yehuda et al., 1991a,b). The ability of GR to counterbalance changes in cortisol availability may have important implications. A lack of the protective effects of cortisol on bodily function in traumatized or chronically stress individuals may be particularly expected, if low cortisol levels are not counterbalanced by a compensatory up-regulation of the receptor proteins in target cells, but rather coincide with unchanged or decreased receptor numbers. An enhancement of the adverse effects of hypocortisolism may also be expected if the affinity or function of the GR is impaired.

In fact, there are a number of studies suggesting normal or decreased GR numbers as well as impaired affinity or function of the GR in patients with several stress-related bodily disorders, which are also associated with hypocortisolism. In a

preliminary study, we observed normal to decreased numbers of GR in lymphocytes of patients with chronic pelvic pain (Heim et al., 1997a). Another recent study provided evidence for normal GR number together with decreased affinity in patients with fibromyalgia (Lentjes et al., 1998). Decreased GR number or affinity has also been observed in disorders with a more obvious pathophyisological basis, such as rheumatoid arthritis and asthma (Schlaghecke et al., 1992; Sher et al., 1994; Spahn et al., 1995). Other findings suggest impaired GR function in these disorders. For example, cultured leukocytes from patients with rheumatoid arthritis are resistant to glucocorticoid-induced activation of the antiphospholipase protein, lipocortin (Morand et al., 1994). Similarly, patients with chronic asthma show impaired inhibition of T cell proliferation by glucocorticoids (Corrigan et al., 1991). Moreover, it has been shown that allergen exposure decreases GR binding affinity and steroid responsiveness in atopic asthmatics (Nimmagadda et al., 1997). Since all of these disorders have been associated with reduced adrenal activity or reactivity, these findings may indeed reflect a lack of counter-regulation, which may enhance the adverse effects of hypocortisolism on immune function and thereby increase the risk to develop stress-related bodily disorders. Support for this assumption is also provided by observations that patients with a genetically determined glucocorticoid resistance often present with symptoms of chronic fatigue syndrome and fibromylagia (Stratakis et al., 1994). In the face of differential expression of GR in immune cells and tissues, it has also been suggested that localized GR resistance may determine the manifestation of different bodily disorders (Stratakis et al., 1994). Such localized GR resistance may also explain a dissociation between increased feedback sensitivity of the HPA axis and reduced GR number in some patients with bodily disorders (Heim et al., 1997a). Consistent with the general idea of an association between hypocortisolism, GR resistance and the development of bodily disorders, deKloet (1991) suggests that a decrease of GR relative to MR expression promotes reduced adrenal reactivity and increased vulnerability to inflammatory diseases.

Consequently, one may ask how decreased GR number, affinity or function may develop given the fact of low cortisol levels in these patients. One candidate in inducing GR resistance despite low cortisol levels may be cytokines. Increasing evidence from several studies suggests that treatment with cytokines induces decreases in GR number, affinity or function in several cells and tissues (Kam et al., 1993; Spahn et al., 1996; Verheggen et al., 1996). Interestingly, another recent in vitro study reported that treatment of L929 cells with interleukin-1α induces increased cytosolic GR binding (as found in PTSD) together with decreased steroid-induced translocation of the GR to the nucleus and inhibition of GR effects on gene transcription (Pariante et al., 1998). Thus, one may assume that excessive immune activation in response to trauma or chronic stress may add to the development of GR resistance in these individuals, despite of rather decreased adrenal activity, thereby increasing the risk for bodily disorders.

In addition, it may be fruitful to consider the role of the two different isoforms of the human GR (hGRα and hGRβ) in the development of glucocorticoid resistance and related bodily disorders. It has been shown that the hGRα isoform

is primarily involved in mediating glucocortioid effects on gene expression, whereas hGRβ appears to be a negative inhibitor of hGRα function (De Castro et al., 1996; Oakley et al., 1996). Thus, it has been suggested that abnormally low expression of hGRα (as in the above disorders) together with high expression of hGRβ may participate in the development of GR resistance and lead to the manifestation of autoimmune disorders (De Castro et al., 1996).

Finally, if a GR defect should be involved in the development of bodily disorders in individuals with hypocortisolism, one may expect that glucocorticoid treatment is ineffective in these patients. Interestingly, pharmacological normalization of glucocorticoid levels in patients with fibromyalgia (15 mg/day prednisone) has been proven ineffective (Clark et al., 1985). Treatment of patients with chronic fatigue syndrome with a hydrocortisone (16 mg/day/m^2 body surface) resulted in a modest improvement of general wellness; however, specific fatigue symptoms did not improve statistically (McKenzie et al., 1998). Another recent study reports that low doses of hydrocorticone (5 or 10 mg/day) result in symptom improvement in some, but not all patients with chronic fatigue syndrome (Cleare et al., 1999). Future studies should compare the effectiveness of different doses of glucocorticoids as well as the effectiveness of pharmacological treatments that have been shown to restore GR function, such as antidepressants (Pariante et al., 1997).

9. Conclusion and future directions

In the face of the seminal findings in patients with PTSD, the phenomenon of hypocortisolism has gained considerable attention over the past decade. However, many aspects regarding the specificity, development and physiological meaning of phenomenon of hypocortisolism remain unexplored. The present work brings together findings of basic and clinical research addressing these issues. Based on these findings, we draw the following conclusions:

1. Hypocortisolism is not a specific correlate of PTSD.
2. Hypocortisolism is also present in healthy individuals living under ongoing stress as well as in patients with stress-related bodily disorders, such as chronic fatigue syndrome, fibromyalgia, other chronic pain syndromes, rheumatoid arthritis, asthma, and allergies.
3. The mechanisms underlying the development of hypocortisolism may be complex and heterogeneous between and within patients with PTSD or stress-related bodily disorders and healthy subjects living under ongoing stress.
4. Genetic and developmental factors may contribute to hypocortisolism in some individuals, which may then be at a higher risk for the development of stress-related pathology.
5. Due to a lack of the protective properties of the hormone, sustained hypocortisolism may play a causal role in the development of stress-related bodily disorders, namely immune-related disorders and chronic pain syndromes.

The phenomenon of hypocortisolism deserves further scrutiny in future research, designed in an attempt to integrate contributions from methodological, basic and

clinical studies. The purpose of methodological studies is to define hypocortisolism in terms of absolute hormone levels in diverse body fluids under basal conditions as well as in response to challenge tests. Based on these definitions, methods that prove sensitive for the detection of hypocortisolism should be selected and used to form standardized criteria for the diagnosis of hypocortisolism. These methods should then be optimized in terms of economy and reliability, which would also involve the identification of intervening variables. For example, salivary cortisol determinations are economic, but may not be reliable indicators of adrenal activity in the face of variable CBG levels dependent on estradiol effects (Kirschbaum et al., unpublished data), and such relationships need further elaboration.

There is a multitude of questions to be answered in future clinical studies. Further scrutiny and, even more importantly, comparison of mechanisms underlying the development of hypocortisolism in diverse clinical populations is required. These studies should consider HPA axis function on all levels, interactions of the HPA axis with other hormone systems, and alterations in central neurotransmitter systems. Advanced methods, such as visualization of CRF receptors or GR using functional brain imaging or the application of more advanced methods to determine GR gene expression and nucleocytoplasmic traffic of the GR, may allow improved description of the mechanisms involved in hypocortisolism. If certain mechanisms were identified, it would be of interest to evaluate whether there are time courses in the development of these alterations.

Obviously, most individuals exposed to severe stress do not develop PTSD, whereas other individuals appear to be at risk for stress-induced psychopathology (Yehuda et al., 1998). A similar vulnerability may underlie the development of stress-related bodily disorders. Thus, the role of hypocortisolism as a pre-existing risk factor for these disorders needs to be scrutinized under consideration of genetic and developmental factors. Furthermore, some forms of hypocortisolism may affect neurobiological systems, which are involved in the modulation of behavior. There is increasing evidence that glucocorticoids differentially affect CRF pathways in the hypothalamus and the amygdala (Swanson and Simmons 1989; Makino et al. 1994), modulate CRF effects on noradrenergic neurons in the locus coeruleus (Pavcovich and Valentino, 1997) and mediate behavior, such as mood and cognitive function (Piazza and LeMoal, 1997). Thus, it would be interesting to study the effects of a lack of cortisol on neurobiological systems and behavior. It may be assumed that low cortisol levels contribute to enhanced stress reactivity (at least at the central level), cognitive impairments and personality changes seen in some patients with hypocortisolism.

Another set of studies is required to substantiate the hypothesis that hypocortisolism is causally involved in the pathophysiology of stress-related bodily disorders. Important evidence for the validity of this hypothesis could be obtained from longitudinal studies assessing HPA axis function, immunological parameters and bodily complaints in subjects before and over several years after the experience of severe stress. Moreover, experimental approaches may help verify the proposed hypothesis. For example, manipulation of cortisol levels and GR function should provoke or reduce physical symptoms or alter pain thresholds.

Similar to some findings in stress-related bodily disorders (McCain and Tilbe, 1989; Hellhammer, 1990; Crofford et al., 1994), several recent studies have found flattened diurnal cycles with a low acrocphase in the morning and relatively high cortisol levels in the evening in other clinical populations. These include patients with upper respiratory symptoms, patients with cancer and patients with metabolic syndrome and abdominal obesity (Rosmond et al., 1998; Sephton et al., 1998; Smyth et al., 1998). Patients with metabolic syndrome and abdominal obesity also showed sensitization of the HPA axis (Rosmond et al., 1998). Thus, the functional consequences of perturbations of the circadian profile with temporary phases of hypo- and hypersecretion need to be further investigated.

Future research could provide important evidence for a role of hypocortisolism in the development of stress-related pathology. Although stress has been implicated in the pathogenesis of the classic psychosomatic disorders, the pathophysiology of many of these disorders remains merely unexplained and treatment strategies are often unsuccessful. If hypocortisolism should prove to be a neurobiological mediator between stress and the manifestation of physical complaints, this pathophysiological model may open novel avenues for the prevention, diagnosis and treatment of the classic psychosomatic disorders.

Acknowledgements

The authors gratefully thank Dr. Bruce McEwen for reviewing an early version of this manuscript and for providing numerous stimulating and encouraging comments. This work was supported by grants of the Deutsche Forschungsgemeinschaft He 2561/2-1 and He 1013/13-1 and 2.

References

Ahles, T.A., Yunus, M.B., Riley, S.D., Bradley, J.M., Masi, A.T., 1984. Psychological factors associated with primary fibromyalgia syndrome. Arthritis Rheum. 24, 1102–1106.

Alfvén, G., de la Torre, B., Uvnäs-Moberg, K, 1994. Depressed concentrations of oxytocin and cortisol in children with recurrent abdominal pain of non-organic origin. Acta Paediatr. 83, 1076–1080.

Allen, K.N., 1995. Aspirin—now we can see it. Nat. Med. 1, 882–883.

Amir, M., Kaplan, Z., Neumann, L., Sharabani, R., Shani, N., Buskila, D., 1997. Posttraumatic Stess Disorder, tenderness, and fibromyalgia. J. Psychosom. Res. 42, 607–613.

Baker, D., Mendenhall, C.L., Simbratl, L.A., Magan, L.K., Steinberg, J.L., 1982. Relationship between posttraumatic stress disorder and self-reported physical symptoms in Persian gulf war veterans. Arch. Intern. Med. 157, 2076–2078.

Bateman, A., Singh, A., Kral, T., Solomon, S., 1989. The immune hypothalamic pituitary adrenal axis. Endocr. Rev. 10, 92–112.

Baum, A., Cohen, L., Hall, M., 1993. Control and intrusive memories as possible determinants of chronic stress. Psychosom. Med. 55, 274–286.

Bearn, J., Allain, T., Coskeran, P., Munro, N., Butler, J., McGregor, A., Wessely, S., 1995. Neuroendocrine responses to d-fenfluramine and insulin-onduced hypoglycemia in chronic fatigue syndrome. Biol. Psychiatry 37, 245–252.

Benedetto, C., 1989. Eicosanoids in primary dysmenorrhea, endometriosis and menstrual migraine. Gynecol. Endocrinol. 3, 71–94.

Blackwell, G.J., Carnuccio, R., DiRosa, M., et al., 1982. Glucocorticoids induce the formation and release of anti-inflammatory and anti-phospholipase proteins into the peritoneal cavity of the rat. Br. J. Pharmacol. 76, 185–194.

Boisset-Pioro, M.H., Esdaile, J.M., Fitzcharles, M.A., 1995. Sexual and physical abuse in women with fibromyalgia syndrome. Arthritis Rheum. 38, 235–241.

Boscarino, J.A., 1996. Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: Findings and clinical implications. J. Clin. Consult. Psychol. 64, 191–201.

Bourne, P.G., Rose, R.M., Mason, J.W., 1968. 17 OHCS levels in combat. Special forces 'A' team under threat of attack. Arch. Gen. Psychiatry 19, 135–140.

Bourne, P.G., Rose, R.M., Mason, J.W., 1967. Urinary 17 OHCS levels. Data on seven helicopter ambulance medics in combat. Arch. Gen. Psychiatry 17, 104–110.

Boxer, G.H., Carson, J., Miller, B.D., 1988. Neglect contributing to tertiary hospitalization in childhood asthma. Child Abuse Negl. 12, 491–501.

Bremner, J.D., Randall, P., Scott, T.M., et al., 1995. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am. J. Psychiatry 152, 973–981.

Bremner, J.D., Licino, J., Darnell, A., et al., 1997a. Elevated CSF corticotropin-releasing factor concentrations in PTSD. Am. J. Psychiatry 154, 624–629.

Bremner, J.D., Randall, P., Vermetten, E., et al., 1998b. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol. Psychiatry 41, 23–32.

Bremner, J.D., Southwick, S.M., Johnson, D.R., Yehuda, R., Charney, D.S., 1993. Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. Am. J. Psychiatry 150, 235–239.

Buchwald, D., Komaroff, A.L., 1991. Review of laboratory findings for patients with chronic fatigue syndrome. Rev. Infect. Dis. 13, 12–18.

Buske-Kirschbaum, A., Jobst, S., Wustmans, A., Kirschbaum, C., Rauh, W., Hellhammer, D.H., 1997. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom. Med. 59, 419–426.

Caplan, R.D., Cobb, S., French, J.R., 1979. White collar work load and cortisol: disruption of a circadian rhythm by job stress? J. Psychosom. Res. 23, 181–192.

Cash, J.M., Crofford, L.J., Galucci, W.T., et al., 1992. Pituitary-adrenal axis responsiveness to ovine corticotropin releasing hormone in patients with rheumatoid arthritis treated with low dose prednisone. J. Rheumatol. 19, 1692–1696.

Catalani, A., Marinelli, M., Scaccianoce, S., et al., 1993. Progeny of mothers drinking corticosterone during lactation has lower stress-induced corticosterone secretion and better cognitive performance. Brain Res. 624, 209–215.

Cavallo, R., Sartori, M.L., Gatti, G., Angeli, A., 1986. Cortisol and immune interferon can interact in the modulation of human natural killer cell activity. Experimentia 42, 177.

Chikanza, I.C., Petrou, P., Chrousos, G.P., Kingsley, G., Panayi, G.P., 1992. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheum. 35, 1281–1288.

Clark, S., Tindell, E., Bennett, R.M., 1985. A double blind crossover trial of prednisone versus placebo in the treatment of fibrositis. J. Rheumatol. 12, 980–983.

Cleare, A.J., Heap, E., Wessely, S., O'Keane, V., Miell, J., 1999. Low dose hydrocortisone in chronic fatigue syndrome: a randomized crossover trial. Lancet 353, 455–458.

Coplan, J.D., Andrews, M.W., Rosenblum, L.A., et al., 1996. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early life stressors: Implications for the pathophysiology of mood and anxiety disorders. Proc. Natl. Acad. Sci. USA 93, 1619–1623.

Corrigan, C.J., Brown, P.H., Barnes, N.C., et al., 1991. Glucocorticoid resistance in chronic asthma. Glucocorticoid pharmacokinetics, glucocorticoid receptor characteristics, and inhibition of peripheral blood T cell proliferation by glucocorticoids in vitro. Am. Rev. Respir. Dis. 144, 1016–1025.

Cox, B.J., Kuch, K., Parker, J.D.A., Shulman, I.D., Evans, R.J., 1994. Alexithymia in somatoform disorder patients with chronic pain. J. Psychosom. Res. 38, 523–527.

Crofford, L.J., Pillemer, S.R., Kalogeras, K.T., et al., 1994. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum. 37, 1583–1592.

Culclasure, T.F., Enzenauer, R.J., West, S.G., 1993. Posttraumatic stress disorder presenting as fibromyalgia. Am. J. Med. 94, 548.

Davidson, J., Swartz, M., Storck, M., Krishnan, R.R., Hammett, E., 1985. A diagnostic and family study of posttraumatic stress disorder. Am. J. Psychiatry 142, 90–93.

Davidson, J.R.T., Hughes, D., Blazer, D.G., George, L.K., 1991. Posttraumatic stress disorder in the community: an epidemiological study. Psychol. Med. 21, 713–721.

DeBellis, M.D., Chrousos, G.P., Dorn, L.D., et al., 1994. Hypothalamic pituitary adrenal axis dysregulation in sexually abused girls. J. Clin. Endocrinol. Metab. 78, 249–255.

DeBellis, M.D., 1996. Antinuclaer autoantibodies and thyroid function in sexually abused girls. J. Trauma. Stress 9, 369–378.

De Castro, M., Elliot, S., Kino, T., et al., 1996. The non-ligand binding b-isoform of the human glucocorticoid receptor (hGRb): Tissue levels, mechanism of action, and potential physiological role. Mol. Med. 2, 597–607.

DeGoeij, D.C., Jezova, D., Tilders, F.J., 1992. Repaeted stress enhances vasopression synthesis in corticotropin releasing factor neurons in the paraventricular nucleus. Brain Res. 577, 165–168.

Dekaris, D., Sabioncello, A., Mazuran, R., et al., 1993. Multiple changes of immunologic parameters in prisoners of war. J. Am. Med. Assoc. 270, 595–599.

deKloet, E.R., 1991. Brain corticosteroid receptor balance and homeostatic control. Front. Neuroendocrinol. 12, 95–164.

Delahanty, D.L., Dougall, A.L., Craig, K.J., Jemkins, F.J., Baum, A., 1997. Chronic stress and natural killer cell activity after exposure to traumatic death. Psychosom. Med. 59, 467–476.

Demitrack, M.A., Dale, J.K., Straus, S.E., et al., 1991. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J. Clin. Endocrinol. Metab. 73, 1224–1234.

Dhabhar, F.S., McEwen, B.S., Spencer, R.L., 1993. Stress response, adrenal steroid receptor levels and corticosteroid binding globulin levels—a comparison between Sprague-Dawley, Fischer 344 and Lewis rats. Brain Res. 616, 89–98.

Dhabhar, F.S., McEwen, B.S., 1996. Stress-induced enhancement of antigen-specific cell-mediated immunity. J. Immunol. 156, 2608–2615.

Dhabhar, F.S., McEwen, B.S., 1997. Acute stress enhances while chronic stress suppresses immune function in vivo: a potential role for leukocyte trafficking. Brain, Behav. Immun. 11, 286–306.

Dhabhar, F.S., McEwen, B.S., 1999. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc. Natl. Acad. Sci. USA 96, 1059–1064.

Dienstbier, R.A., 1989. Arousal and physiological toughness: implications for mental and physical health. Psycholog. Rev. 96, 84–100.

Dupont, E., Huygen, K., Schandene, L., Vandercruys, M., Palfliet, K., Wybran, J., 1985. Influence of in vivo immunosuppressive drugs on production of lymphokines. Transplantation 39, 143.

Dutton, L.M., Smolensky, M.H., Leach, C.S., Lorimor, R., Hsi, B.P., 1978. Stress levels of ambulance paramedics and fire fighters. J. Occup. Med. 20, 111–115.

Ehlert, U., Locher, P., Hanker, J.P., 1993. Psychoendokrinologische Untersuchungen bei Frauen mit chronischen Unterbauchbeschwerden. In: Kentenich, H. (Ed.), Psychosomatische Gynaekologie und Geburtshilfe. Springer, Berlin.

Elwan, O., Abdella, M., El Bayad, A.B., Hamdy, S., 1991. Hormonal changes in headache patients. J. Neurol. Sci. 106, 75–81.

Faessler, R., Schauenstein, K., Kroemer, G., Schwarz, S., Wick, G., 1986. Elevation of corticosteroid binding globulin in obese strain (OS) chickens: possible implications for the disturbed immunoregulation and the dvelopment of spontaneous autoimmune thyroiditis. J. Immunol. 136, 3657–3661.

Fameli, M., Kitraki, E., Stylianopoulou, F., 1994. Effects of hyperactivity of the maternal hypothalamic-pituitary-adrenal (HPA) axis during pregnancy on the development of the HPA axis and brain monoamiines in the offspring. Int. J. Dev. Neurosci. 12, 651–659.

Fauci, A.S., 1975. Mechanism of corticosteroid action on lymphocyte subpopulations. I. Redistribution of circulating T and B lymphocytes to the bone marrow. Immunology 28, 669.

Fauci, A.S., 1976. Mechanism of corticosteroid action on lymphocyte subpopulations. II. Differential effects of in vivo hydrocortisone, prednisone and dexamethasone on in vitro expression of lymphocyte function. Clin. Exp. Immunol. 24, 54.

Fehm-Wolfsdorf, G., 1994. Stress und Wahrnehmung. Psychobiologie der Glucocorticoide. Hans Huber, Bern.

Ferraccioli, G., Cavalieri, F., Salaffi, F., et al., 1990. Neuroendocrinologic findings in primary fibromylagia and in other chronic rheumatic conditions. J. Rheumatol. 17, 869–873.

Flower, R.J., Blackwell, G.J., 1979. Anti-inflammatory steroids induce biosynthesis of a phospholipase A_2 inhibitor which prevents prostaglandin generation. Nature 278, 456–459.

Foy, D.W., Resnick, H.S., Sipprelle, R.C., Carroll, E.M., 1987. Premilitary, military, and postmilitary factors in the development of combat-related stress disorders. Behav. Ther. 10, 3–9.

France, R.D., Krishnan, K.R., 1985. The dexamethasone suppression test as a biologic marker of depression in chronic pain. Pain 21, 49–55.

Friedman, S.B., Mason, J.W., Hanburg, D.A., 1963. Urinary 17-hydroxycorticosteroid levels in parents of children with neoplastic disease: a study of chronic psychological stress. Psychosom. Med. 25, 364–376.

Gatti, G., Cavallo, R., Sartori, M.L., et al., 1987. Inhibition by cortisol of human natural killer (NK) cell activity. J. Steroid Biochem. 26, 49–58.

Genazzani, A.R., Lemarchand-Beraud, T.H., Aubert, M.L., Felber, J.P., 1975. Pattern of plasma ACTH, hGH, and cortisol during menstrual cycle. J. Clin. Endocrinol. Metab. 41, 431–437.

Gerhards, T., Yehuda, R., Shoham, M., Hellhammer, D.H., 1997. Abnormal cerebral laterality in posttraumatic stress disorder. Ann. NY Acad. Sci. 821, 482–485.

Goenjian, A.K., Yehuda, R., Pynoos, R.S., et al., 1996. Basal cortisol and dexamethasone suppression oc cortisol among adolescents after the 1988 earthquake in Armenia. Am. J. Psychiatry 153, 929–934.

Gómez, F., Lahmame, A., de Kloet, E.R., Armario, A., 1996. Hypothalamic-pituitary-adrenal response to chronic stress in five inbred rat strains: differential responses are mainly located on the adrenocortical level. Neuroendocrinology 63, 327–337.

Green, M.A., Berlin, M.A., 1987. Five psychosocial variables related to the existence of posttraumatic stress disorder symptoms. J. Clin. Psychol. 43, 643–649.

Griep, E.N., Boersma, J.W., deKloet, E.R., 1993. Altered reactivity of the hypothalamic–pituitary–adrenal axis in the primary fibromyalgia syndrome. J. Rheumatol. 20, 469–474.

Griep, E.N., Boersma, J.W., Lentjes, E.G., Prins, P.A., van der Korst, K.K., deKloet, E.R., 1998. Function of hypothalamic–pituitary–adrenal axis in patients with fibromyalgia and low back pain. J. Rheumatol. 25, 1374–1381.

Gurvits, T.G., Shenton, M.R., Hokama, H., et al., 1996. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related psottraumatic stress disorder. Biol. Psychiatry 40, 193–199.

Haas, D.A., George, S.R., 1988. Single or repeated mild stress increases synthesis and release of hypothalamic corticotropin-releasing factor. Brain Res. 461, 230–237.

Hamaty, D., Valentine, J.L., Howard, C.W., Wakefield, V., Patten, M.S., 1989. The plasma endorphin, prostaglandin and catecholamine profile of patients with fibrositis treated with cyclobenzaprine and placebo: a 5 month study. J. Rheumatol. 19, 164–168.

Handwerker, H.O., 1976. Influences of algogenic substances and prostaglandins on the discharges of unmyelinated cutaneous nerve fibers identified as nociceptors. In: Bonica, J.J., Albe-Fessard, D. (Eds.), Advances in Pain Research and Therapy. Raven Press, New York.

Hauger, R.L., Lorang, M., Irwin, M., Aguilera, G., 1990. CRF receptor regulation and sensitization of ACTH responses to acute ether stress during chronic intermittent immobilization stress. Endocrinology 123, 396–405.

Hauger, R.L., Millan, M.A., Lorang, M., Harwood, J.P., Aguilera, G., 1988. Corticotropin-releasing factor receptors and pituitary adrenal responses during immobilization stress. Endocrinology 123, 396–405.

Hedman, M., Nilsson, E., de la Torre, B., 1992. Low blood and synovial fluid levels of sulpho-conjugated steroids in rheumatoid arthritis. Clin. Exp. Rheumatol. 10, 25–30.

Heim, C., Ehlert, U., Rexhausen, J., Hanker, J.P., Hellhammer, D.H., 1997a. Psychoendocrinological observations in women with chronic pelvic pain. Ann. NY Acad. Sci. 821, 456–458.

Heim, C., Owens, M.J., Plotsky, P.M., Nemeroff, C.B., 1997b. The role of early adverse life events in the etiology of major depression and posttraumatic stress disorder: focus on corticotropin-releasing factor. Ann. NY Acad. Sci. 821, 194–207.

Heim, C., Ehlert, U., Hanker, J.P., Hellhammer, D.H., 1998a. Abuse-related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosom. Med. 60, 309–318.

Heim, C., Pisell, T.L., Pearce, B.D., Miller, A.H., 1998b. Discrimination of activation versus down-regulaion of the glucocortical receptor using a cytosolic binding assay combined with a whole cell Western blot. Soc. Neurosci. Abstr. 27, 4901.

Heim, C., Ehlert, U., Hanker, J.P., Hellhammer, D.H., 1999. Psychological and endocrine correlates of chronic pelvic pain associated with adhesions. J. Psychosom. Obstet. Gynecol. 20, 11–20.

Hellhammer, J., 1990. Burnout bei Pflegepersonal—eine psychoendokrinologische Untersuchung. Diploma Thesis, University of Trier, Germany.

Hellhammer, D.H., Wade, S., 1993. Endocrine correlates of stress vulnerability. Psychother. Psychosom. 60, 8–17.

Henry, J.P., 1993. Psychological and physiological responses to stress: the right hemisphere and the hypothalamo-pituitary-adrenal axis. An inquiry into problems of human bonding. Integr. Physiol. Behav. Sci. 28, 368–387.

Henry, J.P., Haviland, M.G., Cummings, M.A., et al., 1992. Shared neuroendocrine patterns of post-traumatic stress disorder and alexithymia. Psychosom. Med. 54, 407–415.

Hingtgen, C.M., Vasko, M.R., 1994. Prostacyclin enhances the evoked release of substance P and calcitonin gene related peptide from rat sensory neurons. Brain Res. 655, 51–60.

Hirschberg, H., Hirschberg, T., Nousiainen, H., Braathen, L.R., Jaffe, E., 1982. The effects of corticosteroids on the antigen presenting properties of human monocytes and endothelial cells. Clin. Immunol. Immunopathol. 23, 577.

Holsboer, F., Gerken, A., Stalla, G.K., Mueller, O.A., 1985. ACTH, cortisol and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. Biol. Psychiatry 20, 276–286.

Hudson, J.I., Pope, H.G., 1994. The concept of affective spectrum disorder: releationship of fibromyalgia and other syndromes of chronic fatigue and chronic muscle pain. Bailliere's Clin. Rheumatol. 4, 839–856.

Hudson, J.I., Pliner, L.F., Hudson, M.S., Goldenberg, D.L., Melby, J.C., 1984. The dexamethasone suppression test in fibrositis. Biol. Psychiatry 19, 1489–1493.

Hug, C., Gerber, N.J., 1990. Fibromyalgiesyndrom oft verkannte Realitaet. Schweiz. Med. Wochenschr. 120, 395–401.

Imaki, T., Nahan, J.L., Rivier, C., Sawchenko, P.E., Vale, W., 1991. Differential regulation of corticotropin-releasing factor mRNA in rat brain regions by glucocorticoids and stress. J. Neurosci. 11, 585–599.

Iowa Persian Gulf Study Group, 1997. Self reported illness and health status among Gulf War veterans. A population-based study. J. Am. Med. Assoc. 277, 238–245.

Johansson, F., 1981. Differences in serum cortisol concentrations in organic and psychogenic chronic pain syndromes. J. Psychosom. Res. 26, 351–358.

Kam, J.C., Szefler, S.J., Surs, W., Sher, E.R., Leung, D.Y.M., 1993. Combination of IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. J. Immunol. 151, 3460–3466.

Kaplan, N.M., 1988. The adrenal glands. In: Griffin, J.E., Ojeda, S.R. (Eds.), Textbook of Endocrine Physiology. Oxford University Press, New York.

Katz, J.L., Weiner, H., Gallagher, T.F., Hellman, L., 1970. Stress, distress, and ego defenses. Psychoendocrine response to impending breast tumor biopsy. Arch. Gen. Psychiatry 23, 131–142.

Kaufman, J., Birmaher, B., Perel, J., et al., 1997. The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biol. Psychiatry 42, 669–679.
Kelso, A., Munck, A., 1984. Glucocorticoid inhibition of lymphokine secretion by alloreactive T-lymphocyte clones. J. Immunol. 133, 784–791.
Kirschbaum, C., Wüst, S., Faig, H.G., Hellhammer, D.H., 1992a. Heritability of cortisol responses to hCRH, ergometry, and psychological stress in humans. J. Clin. Endocrinol. Metab. 75, 1526–1530.
Kruger, U., Spiecker, H., 1994. Die Diagnostik der Nebennierenrindeninsuffizienz bei steroidpflichtigem Asthma bronchiale: Der CRH-Test im Vergleich zu Kortisol Tagesprofil im Serum und Kortisol im 24h-Urin. Pneumologie 48, 789–793.
Ladd, C.O., Owens, M.J., Nemeroff, C.B., 1996. Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. Endocrinology 137, 1212–1218.
Lentjes, E.G., Griep, E.N., Boersma, J.W., Romijn, F.P., de Kloet, E.R., 1998. Glucocorticoid receptors, fibromyalgia and low back pain. Psychoneuroendocrinology 22, 603–614.
Lykken, D.T., Iacono, K.H., Haroian, K., 1988. Habituation of the skin conductance in response to strong stimuli: a twin study. Psychophysiology 25, 4–15.
Makino, S., Gold, P.W., Schulkin, J., 1994. Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. Brain Res. 640, 105–112.
Mason, J.W., Brady, J.V., Tolliver, G.A., 1968. Plasma and urinary 17-hydroxycorticosteroid responses to 72-hr. avoidance sessions in the monkey. Psychosom. Med. 30, 608–630.
Mason, J.W., Giller, E.L., Kosten, T.R., Harkness, L., 1988. Elevation of urinary norepinephrine/cortisol ratio in posttraumatic stress disorder. J. Nerv. Ment. Dis. 176, 498–502.
Mason, J.W., Giller, E.L., Kosten, T.R., Ostroff, R.B., Podd, L., 1986. Urinary free-cortisol levels in post-traumatic stress disorder patients. J. Nerv. Ment. Dis. 174, 145–159.
McCain, G.A., Tilbe, K.S., 1989. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J. Rheumatol. 16, 154–157.
McCranie, E.W., Hyer, L.A., Boudewyns, P.A., Woods, M.G., 1992. Negative parenting behavior. Combat exposure, and PTSD sympton severity: test of a person–event interaction model. J. Nervous Mental Dis. 180, 431–438.
McEwen, B.S., Biron, C.A., Brunson, K.W., et al., 1997. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res. Rev. 23, 79–133.
McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179.
McEwen, B.S., 1999. Stress and the aging hippocampus. Front. Neuroendocrinol. 20, 1–22.
McFarlane, A.C., 1988. Posttraumatic morbidity of a disaster: a study of cases presenting for psychiatric treatment. J. Nerv. Ment. Dis. 174, 4–14.
McKenzie, R., O'Fallon, A., Dale, J., et al., 1998. Low-dose hydrocortisone for treatment of chronic fatigue syndrome. J. Am. Med. Assoc. 280, 1061–1066.
Meaney, M.J., Tannebaum, P., Francis, D., et al., 1994. Early environmental programming of hypothalamic-pituitary-adrenal responses to stress. Semin. Neurosci. 6, 247–259.
Meikle, A.W., Bishop, D.T., Stringham, J.D., Ford, M.H., West, D.W., 1989. Relationship between body mass index, cigarette smoking and plasma sex steroids in normal male twins. Genetic Epidemiol. 6, 399–412.
Monjan, A.A., Collector, M.I., 1977. Stress-induced modulation of of the immune response. Science 196, 307–308.
Morand, E.F., Jefferiss, C.M., Dixey, J., Mitra, D., Goulding, N.J., 1994. Impaired glucocorticoid induction of mononuclear leukocyte lipocortin-1 in rheumatoid arthritis. Arthritis Rheum. 37, 207–211.
Munck, A., Guyre, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr. Rev. 5, 25–44.
Murison, R., Overmier, J.B., Skoglund, E.J., 1986. Serial stressors: prior exposure to a stressor modulates its later effectiveness on gastric ulceration and corticosterone release. Behav. Neural Biol. 45, 185–195.

Natelson, B.H., Ottenweller, J.E., Cook, J.A., Pitman, D., McCarthy, R., Tapp, W.N., 1988. Effect of stressor intensity on habituation of the adrenocortical stress response. Physiol. Behav. 43, 41–46.
Neeck, G., Federlin, K, Graef, V., Rusch, D., Schmidt, K.L., 1990. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J. Rheumatol. 17, 24–29.
Neeck, G., Federlin, K, Graef, V., Rusch, D., Schmidt, K.L., 1992. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J. Rheumatol. 17, 24–29.
Nemeroff, C.B., 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol. Psychiatry 1, 336–342.
Nemeroff, C.B., Krishnan, K.R., Reed, D., Leder, R., Beam, C., Dunnick, N.R., 1993. Adrenal gland enlargement in major depression. Arch. Gen. Psychiatry 49, 384–387.
Nicol, G.D., Klingberg, D.K., Vasko, M.R., 1992. Prostaglandin E_2 increases calcium conductance and stimulates release of substance P in avian sensory neurons. J. Neurosci. 12, 1917–1927.
Nimmagadda, S.R., Szefler, S.J., Spahn, J.D., Surs, W., Leung, D.Y.M., 1997. Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics. Am. J. Resp. Crit. Care Med. 155, 87–93.
Nyklíček, M.A., Vingerhoets, A.J., 1996. Alexithymia is associated with low tolerance to experimental painful stimulation. Psychosom. Med. 58, 66.
Oakley, R.H., Sar, M., Cidlowski, J.A., 1996. The human glucocorticoid receptor b isoform. Expression, biochemical properties, and putative function. J. Biol. Chem. 271, 9550–9559.
Orr, T.E., Meyerhoff, J.L., Mougey, E.H., Bunnell, B.N., 1990. Hyperresponsiveness of the rat neuroendocrine system due to repeated exposure to stress. Psychoneuroendocrinology 15, 317–328.
Orth, D.N., Kovacs, W.J., deBold, C.R., 1992. The adrenal cortex. In: Wilson, J.D., Foster, D.W. (Eds.), Williams Textbook of Endocrinology. Saunders, Philadelphia, pp. 489–619.
Ottenweller, J.E., Natelson, B.H., Pitman, D.L., Drastal, S.D., 1989. Adrenocortical and behavioral responses to repeated stressors: toward an animal model of chronic stress and stress-related mental illness. Biol. Psychiatry 26, 829–841.
Owens, M.J., Nemeroff, C.B., 1991. Physiology and pharmacology of corticotropin-releasing factor. Pharm. Rev. 43, 425–473.
Pavcovich, L.A., Valentino, R.J., 1997. Regulation of a putative neurotransmitter effect of corticotropin-releasing factor: effects of adrenalectomy. J. Neurosci. 17, 401–408.
Pariante, C.M., Pearce, B.D., Pisell, T.L., Owens, M.J., Miller, A.H., 1997. Steroid-independent translocation of the glucocorticoid receptor by the antidepresant desipramine. Mol. Pharmacol. 52, 571–581.
Pariante, C.M., Pearce, B.D., Pisell, T.L., et al., 1997. The proinflammatory cytokine, interleukin-1 alpha, reduces glucocorticoid receptor translocation and function. Soc. Neurosci. Abstr. 24, 201.1.
Piazza, P.V., LeMoal, M., 1997. Glucocorticoids as a biological substrate for reward: Physiological and pathophysiological implications. Brain Res. Rev. 25, 359–372.
Poteliakhoff, A., 1981. Adrenocortical activity and some clinical findings in acute and chronic fatigue. J. Psychosom. Res. 25, 91–95.
Pruessner, J., Hellhammer, D.H., Kirschbaum, C., 1999. Burnout, perceived stress and salivary cortisol upon awakening. Psychosom. Med. 61, 197–294.
Rivier, C., Vale, W., 1987. Diminished responsiveness of the hypothalamic pituitary adrenal axis of the rat during exposure to prolonged stress: a pituitary mediated-mechanism. Endocrinology 121, 1320–1328.
Rose, R.M., Poe, R.O., Mason, J.W., 1968. Psychological state and body size as determinants of 17-OHLS excretion. Arch. Intern. Med. 121, 406–413.
Rosmond, R., Dallman, M.F., Bjorntorp, P., 1998. Stress-related cortisol secretion in men: Relationships between abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J. Clin. Endocrinol. Metab. 83, 1853–1859.
Rubin, R.T., Phillips, J.J., Sadow, T.F., McCracken, J.T., 1995. Adrenal gland volume in major depression: increase during depressive episode and decrease with successful treatment. Arch. Gen. Psychiatry 52, 213–218.
Ruch, L.O., Chandler, S.M., Harter, R.A., 1980. Life change and rape impact. J. Health Soc. Behav. 21, 248–260.

Rupprecht, M., Rupprecht, R., Kornhuber, J., et al., 1991. Elevated glucocorticoid receptor concentrations before and after glucocorticoid therapy in peripheral mononuclear leukocytes of patients with atopic dermatitis. Dermatologica 183, 100–105.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J. Neurosci. 5, 1222–1227.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endoc. Rev. 7, 284–301.

Schaffner, A., 1985. Therapeutic concentrations of glucocorticoids suppress the antimicrobial activity of human macrophages without impairing their responsiveness to interferon. J. Clin. Investig. 76, 1755.

Schlaghecke, R., Kornely, E., Wollenhaupt, J., Specker, C., 1992. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum. 35, 740–744.

Schmid-Ott, G., Jacobs, R., Jager, B., et al., 1998. Stress-induced endocrine and immunological changes in psoriasis patients and healthy controls. Psychother. Psychosom. 67, 37–42.

Scott, M.J., Stradling, S.G., 1994. Post traumatic stress disorder without the trauma. Br. J. Clin. Psychol. 33, 71–74.

Scott, L.V., Medbak, S., Dinan, T.G., 1998a. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. Acta Psychiatr. Scand. 97, 450–457.

Scott, L.V., Medbak, S., Dinan, T.G., 1998b. The low dose ACTH test in chronic fatigue syndrome and in health. Clin. Endocrinol. 48, 733–737.

Seligman, M.E.P., 1975. Helplessness. Freeman, San Francisco.

Selye, H., 1936. A syndrome produced by diverse noxious agents. Nature 138, 32–36.

Sephton, S.E., Sapolski, R.M., Kraemer, H.C., Spiegel, D., 1998. Absence of diurnal cortisol variation predicts early breast cancer mortality. Psychoneuroendocrinology 23, S51.

Sharav, Y., Singer, E., Schmidt, E., Dionne, R.A., Dubner, R., 1987. The analgesic effect of amitriptyline on chronic facial pain. Pain 31, 199–209.

Sher, E.R., Leung, Y.M., Surs, W., 1994. Steroid-resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. J. Clin. Investig. 93, 33–39.

Sieber, W.J., Holbrook, T., Browner, D., 1996. Predictors of PTSD in a physically traumatized population. Psychosom. Med. 58, 95.

Smith, M.A., Davidson, J., Ritchie, J.C., Kudler, H., Lipper, S., Chappell, P., Nemeroff, C.B., 1989. The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. Biol. Psychiatry 26, 349–355.

Smyth, J., Ockenfels, M.C., Porter, L., Kirschbaum, C., Hellhammer, D.H., Stone, A., 1998. Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. Psychoneuroendocrinology 23, 353–370.

Spahn, J.D., Leung, D.Y.M., Surs, W., Harbeck, R.J., Nimmagadda, S., Szefler, S.J., 1995. Reduced glucocorticoid binding affinity in asthma is related to ongoing allergic inflammation. Am. J. Resp. Crit. Care Med. 151, 1709–1714.

Spahn, J.D., Szefler, S.J., Surs, W., Doherty, D.E., Nimmagadda, S., Leung, D.Y.M., 1996. A novel action of IL-13. Induction of diminished monocyte glucocorticoid receptor-binding affinity. J. Immunol. 157, 2654–2659.

Spivak, B., Shohat, B., Mester, R., et al., 1997. Elevated levels of serum interleukin-1β in combat-related posttraumatic stress disorder. Biol. Psychiatry 42, 345–348.

Stein, M.B., Yehuda, R., Koverola, C., Hanna, C., 1997a. Enhanced dexamethasone suppression of plasma cortisol in a adult women traumatized by childhood sexual abuse. Biol. Psychiatry 42, 680–686.

Stein, M.B., Koverola, C., Hanna, C., Torchia, M.G., McClarty, B., 1997b. Hippocampal volume in women victimized by childhood sexual abuse. Psychol. Med. 27, 951–959.

Sternberg, E.M., Hill, J.M., Chrousos, G.P., et al., 1989a. Inflammatory mediator-induced hypothalamic–pituitary–adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis-rats. Proc. Natl. Acad. Sci. USA 86, 2374–2378.

Sternberg, E.M., Young, W.S., Bernardini, R., et al., 1989b. A central nervous system defect in biosynthesis of corticotropin releasing hormone is associated with susceptibility to streptococcal cell wall induced arthritis in Lewis rats. Proc. Natl. Acad. Sci. USA 86, 4771–4775.

Sternberg, E.M., 1993. Hypoimmune fatigue syndromes: diseases of the stress response? J. Rheumatol. 20, 418–421.

Stokes, P.E., Stoll, P.M., Koslow, S.H., et al., 1984. Pretreatment DST and hypothalamic pituitary adrenocortical function in depressed patients and comparison groups. A multicenter study. Arch. Gen. Psychiatry 41, 257–267.

Stone, A.A., Schwartz, J.E., Neale, J.M., et al., 1998. How accurate are current coping assessments? A comparison of momentary versus end-of-day reports of coping efforts. J. Personal. Soc. Psychol. 74, 1670–1680.

Stratakis, C.A., Karl, M., Schulte, H.M., Chrousos, G.P., 1994. Glucocorticosteroid resistance in humans. Elucidation of the molecular mechanisms and implications for pathophysiology. Ann. NY Acad. Sci. 746, 362–376.

Swanson, L.W., Simmons, O.M., 1989. Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: a hybridization histochemical study in the rat. J. Comp. Neural. 285, 413–435.

Takasu, N., Komiya, I., Nagasawa, Y., Asawa, T., Yamada, T., 1990. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome due to an adrenocortical adenoma. N. Engl. J. Med. 322, 1708–1712.

Tandon, R., Haskett, R.F., Cardona, D., Alcser, K., Greden, J.F., 1991. Menstrual cycle effects on the dexamethasone suppression test in major depression. Biol. Psychiatry 47, 512–527.

Taylor, G.J., Ryan, D.P., Bagby, R.M., 1985. Toward the development of a new self-report alexithymia-scale. Psychother. Psychosom. 44, 191–199.

Tersman, Z., Collins, A., Eneroth, P., 1991. Cardiovascular responses to psychological and physiological stressors during the menstrual cycle. Psychosom. Med. 53, 185–197.

Thompson, S.P., McMahon, L.J., Nugent, C.C., 1980. Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. Clin. Immunol. Immunopathol. 17, 506–514.

True, W.R., Rice, J., Eisen, S.A., et al., 1993. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatry 50, 257–264.

Valdés, M., Garcia, L., Treserra, J., de Pablo, J, de Flores, T., 1989. Psychogenic pain and depressive disorders: a empirical study. J. Affect. Disord. 16, 21–25.

van Denderen, J.C., Boersma, J.W., Zeinstra, P., Hollander, A.P., van Neerbos, B.R., 1992. Physiological effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS). Scand. J. Rheumatol. 21, 35–37.

Verheggen, M.M., van Hal, P.T., Adriaansen-Soeting, P.W.C., et al., 1996. Modulation of glucocorticoid receptor expression in human bronchial epithelial cell lines by IL-1β, TNF-α and LPS. Eur. Resp. J. 9, 2036–2043.

von Knorring, L., Almay, B.G.L., 1989. Neuroendocrine responses to fenfluramine in patients with idiopathic pain syndromes. Nord. Psykiatr. Tidsskr. 43, 61–65.

Walker, C.D., Rivest, R.D., Meaney, M.J., Aubert, M.L., 1989. Differential activation of the pituitary-adrenocortical axis after stress in the rat: use of two genetically selected lines (Roman low and high avoidance rats) as a model. J. Endocrinol. 123, 477–485.

Wallace, D.J., 1987. The role of stress and trauma in rheumatoid arthritis and systemic lupus erythematosus. Semin. Arthritis Rheum. 16, 153–157.

Wallace, D.J., Margolin, K., 1988. Acute onset of fibromyalgia as a complication of IL-2 therapy. Arthritis Rheum. 31, S24.

Wang, S., Wilson, J.P., Mason, J.W., 1996. Stages of decompensation in combat-related post-traumatic stress disorder: a new conceptual model. Integ. Physiol. Behav. Sci. 31, 237–253.

Waylonis, G.W., Heck, W., 1992. Fibromyalgia syndrome. New associations. Am. J. Phys. Med. Rehab. 71, 343–348.

Weiss, J.M., Sundar, S.K., Becker, K.J., Cierpal, M.A., 1989. Behavioral and neural influences on cellular immune responses: effects of stress and interleukin-1. J. Clin. Psychiatry 50, 43–53.

Wiegers, G.J., Reul, J.M.H.M., Holsboer, F., de Koet, E.R., 1994. Enhancement of rat splenic lymphocyte mitogenesis after short-term preexposure to corticosteroids in vitro. Endocrinology 135, 1257–2351.

Wolff, C.T., Hofer, M., Mason, J.W., 1964. Relationship between psychological defenses and mean urinary 17-hydroxicorticosteroid excretion rates. Methodologic and theoretical considerations. Psychosom. Med. 26, 592–609.

Yehuda, R., Southwick, S.M., Nussbaum, G., Wahby, V., Giller, E.L., Mason, J.W., 1990. Low urinary cortisol excretion in patients with post-traumatic stress disorder. J. Nerv. Ment. Dis. 178, 366–369.

Yehuda, R., Giller, E.L., Southwick, S.M., Lowy, M.T., Mason, J.W., 1991a. Hypothalamic pituitary adrenal dysfunction in posttraumatic stress disorder. Biol. Psychiatry 30, 1031–1048.

Yehuda, R., Lowy, M.T., Southwick, S.M., Shaffer, D., Giller, E.L., 1991b. Increased number of glucocorticoid receptor in posttraumatic stress disorder. Am. J. Psychiatry 148, 499–504.

Yehuda, R., Boisoneau, D., Mason, J., Giller, E.L., 1993a. Glucocorticoid receptor number and cortisol excretion in mood, anxiety, and psychotic disorders. Biol. Psychiatry 34, 18–25.

Yehuda, R., Resnick, H., Kahana, B., Giller, E.L., 1993b. Long lasting hormonal alterations to extreme stress in humans: normative or maladaptive? Psychosom. Med. 55, 287–297.

Yehuda, R., Southwick, S.M., Krystal, J.H., Bremner, D., Charney, D.S., Mason, J.W., 1993c. Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am. J. Psychiatry 150, 83–86.

Yehuda, R., Boisoneau, D., Lowy, M.T., Giller, E.L., 1995a. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch. Gen. Psychiatry 52, 538–593.

Yehuda, R., Kahana, B., Binder-Brynes, K., Southwick, S.M., Mason, J.W., Giller, E.L., 1995b. Low urinary cortisol excretion in Holocaust survivors with PTSD. Am. J. Psychiatry 152, 245–247.

Yehuda, R., Kahana, B., Schmeidler, J., Southwick, S.M., Wilson, S., Giller, E.L., 1995c. Impact of cumulative lifetime trauma and recent stress on posttraumatic stress disorder symptoms in Holocaust survivors. Am. J. Psychiatry 152, 1815–1818.

Yehuda, R., Teicher, R.L., Trestman, R., Siever, L.J., 1996. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol. Psychiatry 40, 79–88.

Yehuda, R., 1997. Sensitization of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder. Ann. NY Acad. Sci. 821, 57–75.

Yehuda, R., Levengood, J., Schmeidler, J., Wilson, S., Guo, L.S., Gerber, D., 1997a. Increased pituitary activation following metyrapone administration in PTSD. Psychoneuroendcrinology 21, 1–16.

Yehuda, R., Steiner, A., Kahana, B., et al., 1997b. Alexithymia in Holocaust survivors with and without PTSD. J. Trauma. Stress 10, 93–100.

Yehuda, R., McFarlane, A.C., Shalev, A.Y., 1998. Predicting the development of posttraumatic stress disorder from acute response to a traumtic event. Biol. Psychiatry 44, 1305–1313.

Yunus, M.B., 1994. Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. Bailliere's Clin. Rheumatol. 4, 811–837.

Zaidi, L.Y., Foy, D.W., 1994. Childhood abuse experiences and combat related PTSD. J. Trauma. Stress 7, 33–42.

Zeitlin, S.B., McNally, R.J., Cassiday, K.L., 1993. Alexithymia in victims of sexual assault: an effect of repeated traumatization? Am. J. Psychiatry 150, 661–663.