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A new view on hypocortisolism

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Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will present data on the development, mechanisms and consequences of hypocortisolism on different bodily systems. We propose that the phenomenon of hypocortisolism may occur after a prolonged period of hyperactivity of the hypothalamic–pituitary–adrenal axis due to chronic stress as illustrated in an animal model. Further evidence suggests that despite symptoms such as pain, fatigue and high stress sensitivity, hypocortisolism may also have beneficial effects on the organism. This assumption will be underlined by some studies suggesting protective effects of hypocortisolism for the individual.

1. Introduction

Since the work of Selye (1936), stress has been associated with an activation of the hypothalamic–pituitary–adrenal (HPA) axis resulting in an increased release of cortisol from the adrenal glands. In recent years, a phenomenon has been described that is characterized by a hyporesponsiveness on different levels of the HPA axis in a number of stress-related states. This phenomenon, termed 'hypocortisolism', has been reported in about 20–25% of patients with stress-related disorders such as chronic fatigue syndrome (CFS), chronic pelvic pain (CPP), fibromyalgia (FMS), post-traumatic stress disorder (PTSD), irritable bowel syndrome (IBS), low back pain (LBP), burnout, and atypical depression (Griep et al., 1998; Heim et al., 1998, 2000; Pruessner et al., 1999; Gold and Chrousos, 2002; Gur et al., 2004; Roberts et al., 2004; Rohleder et al., 2004). When hypocortisolemic, all these disorders may share affiliated syndromes characterized by a triad of enhanced stress sensitivity, pain, and fatigue.

Suggesting a common endocrinological pathway characterized by a diminished glucocorticoid efficacy in these disorders, we will discuss the development and mechanisms of hypocortisolism based on animal and human studies. In addition, consequences of a hypocortisolemic stress response on two other bodily systems, the sympathetic nervous system (SNS) and the immune system will be addressed. Finally, we will hypothesize about

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the rationale of the development of hypocortisolism and its potential protective effects.

2. The hypocortisolemic symptom triad

Stress-related disorders such as PTSD, FMS, and CFS are usually defined by accentuating one of the symptoms that constitute the symptom triad of high stress sensitivity, fatigue and pain (Heim et al., 2000). While PTSD, for example, is characterized by a high stress sensitivity together with symptoms such as intrusions, tension and increased excitability, FMS is primarily defined by the experience of widespread pain suggesting an enhanced somatosensory sensitivity. CFS, on the other hand, constitutes the best example for a disease with a primary fatigue symptomatology. However, despite different definitions we know today that there is a considerable overlap between the disorders.

In the early 1990s, Hudson and colleagues were amongst the first addressing this issue. They published a study on the comorbidity of FMS with medical and psychiatric disorders in which they reported a higher prevalence of migraine, IBS, and CFS, as well as higher lifetime rates of depression and panic disorder in patients with FMS (Hudson et al., 1992). Based on their findings, the authors suggested a common physiologic abnormality among these disorders. Since then several studies have followed supporting the assumption of a high overlap between stress-related pain and fatigue syndromes (for a comprehensive review see Clauw and Chrousos, 1997; Clauw and Crofford, 2003). In addition, epidemiologic studies provide considerable evidence for a link between traumatic events and pain and fatigue symptomatologies. Thus, numerous studies on male war veterans have reported an association between PTSD and symptoms such as fatigue, joint pain, and muscle pain (Engel et al., 2000; Ford et al., 2001). The finding of more physical complaints in veterans with PTSD has recently been confirmed for female war veterans as well (Asmundson et al., 2004; Dobie et al., 2004). Consequently, a higher prevalence of traumatic experiences such as sexual and physical abuse has been found in patients with CPP, FMS, and other chronic pain syndromes compared to the general population (Heim et al., 1998; Cohen et al., 2002; Lampe et al., 2003; Raphael et al., 2004). Interestingly, it has been observed that chronic pain patients report higher levels of pain when co-diagnosed with PTSD than pain patients without a PTSD diagnosis (Geisser et al., 1996; Sherman et al., 2000).

The striking symptom overlap in chronic pain and fatigue syndromes and an increased prevalence of these disorders in PTSD patients and vice versa give reason for the suggestion that there could be a common physiologic pathway. There is growing evidence for an altered HPA axis activity in terms of a reduced responsiveness in a subgroup of patients with the above described disorders, which could be responsible for the symptomatology.

3. Mechanisms of hypocortisolism

In all the aforementioned hypocortisolemic disorders, there are several possible patterns of hypocortisolism determined by alterations in different levels of the HPA axis. These alterations of HPA axis are determined by (1) a reduced biosynthesis or release of the respective releasing factor/hormone on different levels of the HPA axis (CRF/AVP from the hypothalamus, ACTH from the pituitary, or cortisol from the adrenal glands) accompanied by a subsequent decreased stimulation of the respective target receptors, (2) a hypersecretion of one secretagogue with a subsequent down-regulation of the respective target receptors, (3) an enhanced sensitivity to the negative feedback of glucocorticoids, (4) a decreased availability of free cortisol, and/ or (5) reduced effects of cortisol on the target tissue, describing a relative cortisol resistance (Heim et al., 2000; Raison and Miller, 2003). Regarding an increasing body of research on the above mentioned disorders, one can assume that different disorders and even different patient subgroups within one disorder are characterized by different patterns of hypocortisolism (for a comprehensive overview, see Heim et al., 2000).

4. Hypocortisolism: a developmental model

Several years ago we postulated that hypocortisolism/a hyporeactive HPA axis might develop after prolonged periods of stress together with a hyperactivity of the HPA axis and excessive glucocorticoid release (Hellhammer and Wade, 1993). This proposed time course with changes in HPA axis activity from hyper- to hypocortisolism resembles the history of patients with stress-related disorders who frequently report about the onset of 'hypocortisolemic symptoms' (fatigue, pain, stress sensitivity) after prolonged periods of stress, e.g. work stress, infection, or social stress (Buskila et al., 1998; Van Houdenhove and Egle, 2004)

The developmental model obtains support from animal data of Murison and his colleagues

(unpublished data, personal communication) who exposed rats to a prolonged period of chronic stress, namely by restraining the rats repeatedly over a period of 3 weeks. During the stressful period, the animals showed a hyperreactive HPA axis with significantly elevated corticosterone levels. Strikingly, 2 weeks after termination of the chronic stressor, the animals showed blunted corticosterone levels (hypocortisolism) compared to non-stressed control animals.

Thinking about the potential cause/reason for changes in HPA axis activity from hyper- to hypocortisolism one might consider the body's self-adjusting abilities as an important factor. Self-adjusting abilities play a significant role in survival of the organism by counteracting the enduring increased levels of glucocorticoids, and protecting the organism against the possible deleterious effects thereof. In case of the development of hypocortisolism, one may assume a failure in self-adjusting abilities ('over-adjustment'). Potential mechanisms of the 'HPA axis adjustment' are (1) the down-regulation of specific receptors on different levels of the axis (hypothalamus, pituitary, adrenals, target cells), (2) reduced biosynthesis or depletion at several levels of the HPA axis (CRF, ACTH, cortisol) and/or (3) increased negative feedback sensitivity to glucocorticoids (Hellhammer and Wade, 1993; Heim et al., 2000).

Elucidating the exact mechanisms underlying the development of hypocortisolism, recent work of Houshyar et al. (2001a,b, 2003) provides detailed information on changes of the HPA axis. Rats were exposed to chronic morphine treatment for 16 days, whereby the emerging morphine dependence is considered as a chronic stressor (Houshyar et al., 2003). In parallel to our model, prolonged elevated levels of ACTH and corticosterone during morphine withdrawal were followed by a continuous drop of corticosterone levels. As soon as 8 days after termination of morphine-treatment, animals displayed HPA axis characteristics specific for hypocortisolism: despite normal to reduced ACTH levels and normal corticosterone levels under basal conditions, animals showed a blunted ACTH and reduced (to normal) corticosterone response to restraint stress (Houshyar et al., 2001a,b, 2003). After administration of dexamethasone (max. 1 mg/kg, S.C.) prior to stress exposure, these animals showed a significantly reduced ACTH response to restraint stress ('supersuppression') compared to similarly treated non-dependent animals, while their corticosterone response was normally suppressed (Houshyar et al., 2001b). The suppressed stress response after administration of dexamethasone demonstrates an increased sensitivity to glucocorticoid negative feedback on the level of the pituitary. Considering a normal ACTH and corticosterone response to CRF stimulation, one can assume that an increased sensitivity to the negative feedback of circulating corticosterone, rather than changes of the CRF receptors on the level of the pituitary, contributes to the hyporeactive HPA axis under stressful conditions (Houshyar et al., 2001b).

Concluding, the results suggest that chronic stress will eventually result in a hypoactive HPA axis. Considering a normal HPA response to CRF administration on the one hand and an increased sensitivity to dexamethasone administration on the other hand, it seems that an enhanced pituitary feedback is the primary adaptational mechanism underlying the hypocortisolemic stress response. The duration, intensity, number and chronicity of stressors may further pronounce these effects. The low-dose dexamethasone test may be the most sensitive measure of this condition.

Regarding this conclusion with respect to the above described data from human research with reports on HPA axis deviations in CFS, FMS, PTSD and other hypocortisolemic disorders, one can assume that distinct HPA axis variations exist in different disorders and patient subgroups (Heim et al., 2000). Notably, one feature is rather consistently observed in many studies: increased sensitivity to glucocorticoid negative feedback as indicated by cortisol supersuppression in the dexamethasone suppression test (DST). This might be the most common feature in hypocortisolemic disorders.

5. Hypocortisolism: effects on the sympathetic nervous system and the immune system

5.1. Hypocortisolism and the sympathetic nervous system

The HPA axis plays an important role in the regulation of the SNS. CRF seems to increase the spontaneous discharge rate of locus coeruleus (LC) neurons and enhances norepinephrine (NE) release in the prefrontal cortex (Valentino, 1988; Valentino et al., 1993; Smagin et al., 1995), whereas glucocorticoids seem to exert more inhibitory effects on NE release. Results from animal studies with adrenalectomized (ADX) rats have indicated that endogenous glucocorticoids restrain responses such as catecholamine turnover, synthesis, and release in sympathetic nerves during

immobilization stress (Kvetnansky et al., 1993; Pacak et al., 1993). In addition, findings of enhanced tonic and stress-induced CRF release within the LC in ADX rats might imply that CRF, which activates the LC, is negatively regulated by circulating glucocorticoids (Pavcovich and Valentino, 1997). Studies in humans have also shown an association between glucocorticoid concentrations and SNS responses. For example, a 1-week treatment with 20 mg prednisone reduced SNS activity and plasma NE levels in healthy subjects (Golczynska et al., 1995).

Interestingly, increased catecholamine concentrations have been reported in patients with stress-related disorders characterized by hypocortisolemic stress responses. In PTSD, for example, augmented norepinephrine levels in cerebrospinal fluid have been found in patients under basal conditions (Geracioti et al., 2001). Liberzon et al. (1999) reported higher plasma catecholamine levels in war veterans with PTSD during experimental exposure to combat sounds compared to veterans without PTSD. Fibromyalgia constitutes another stress-related disorder with hypocortisolemic features, which seems to be accompanied by an increased sympathetic activity (see Martinez-Lavin, 2004). In one study, FMS patients displayed higher basal plasma NE levels as well as exaggerated NE responses to interleukin (IL)-6 injection (Torpy et al., 2000). These results indicate that hypocortisolemic features, as observed in a subgroup of patients with stress-related disorders, might result in reduced inhibitory feedback activities of cortisol on catecholamine release and synthesis.

5.2. Hypocortisolism and the immune system

Glucocorticoids are the most potent anti-inflammatory hormones in the body. They act on the immune system by both suppressing and stimulating pro- and anti-inflammatory mediators. While they promote Th2 development, for example by enhancing interleukin (IL)-4 and (IL)-10 secretion by macrophages and Th2 cells (Ramierz et al., 1996), they inhibit inflammatory responses and suppress the production and release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), IL-1 and IL-6 (see Franchimont et al., 2003). During virtually all forms of stress including infections, physical trauma, or psychological insults, the immune system becomes activated, resulting in a release of cytokines (Maier and Watkins, 1998). An important role of glucocorticoids during stress is to suppress the production and activity of pro-inflammatory cytokines, thus restraining the inflammatory reaction and preventing tissue destruction (see McEwen et al., 1997; Ruzek et al., 1999; Franchimont et al., 2003). Accordingly, stress-induced increases in glucocorticoid levels seem to prevent bodily responses from overshooting and threatening homeostasis, as was first assumed by Munck and colleagues 20 years ago (Munck et al., 1984).

Alterations in HPA axis function may have enduring immune effects considering the modulating role of glucocorticoids on the immune system. Therefore, a hypocortisolemic stress response, as observed in patients with stress-related disorders, may result in an overactivity of the immune system in terms of increased inflammatory responses due to impaired suppressive effects of low cortisol levels (see Heim et al., 2000; Rohleder et al., 2004). This assumption is supported by studies reporting elevated levels of pro-inflammatory cytokines in patients with stress-related disorders such as PTSD, CFS, and FMS (Maes et al., 1999; Patarca-Montero et al., 2001; Thompson and Barkhuizen, 2003; Rohleder et al., 2004). Further evidence for an immune activation in those patients is provided by observations of increased numbers of natural killer (NK) cells and activated T lymphocytes (Laudenslager et al., 1998; Patarca, 2001). It should be noted that data on immune system functioning in stress-related disorders are quite ambiguous, since other studies have reported unchanged cytokine levels and lower NK cell and T lymphocyte activity, respectively (Kawamura et al., 2001; Amel Kashipaz et al., 2003). Based on the literature, one may preliminarily suggest that early innate and inflammatory immune responses may be overactive, whereas adaptive immunity seems to be unchanged or depressed (see Raison and Miller, 2003; Rohleder et al., 2004).

6. Hypocortisolism: protective effects?

Beside the above described negative symptoms associated with hypocortisolism (high stress sensitivity, pain, and fatigue), there is evidence that hypocortisolism may also have protective consequences for the organism. Subsequently, we will illustrate potential beneficial effects of hypocortisolism by giving some examples concerning protection of the mother and the fetus during pregnancy, adaption in order to allow immunologic responses, and prevention from high allostatic load scores.

Assessing the cortisol awakening response in pregnant women, preliminary results from our laboratory suggest that women with higher daily

stress load showed lower cortisol levels in the morning compared to women with normal to low daily stress load. This result suggests a possible prevention of harmful stimulatory effects of maternal cortisol on placental CRF, which plays a major role in the initiation of delivery (Rieger, 2005).

Several studies have addressed a link between stress-related pain and fatigue syndromes and underlying infections. For example, the prevalence of FMS in patients with chronic hepatitis C virus infection is about 15–16%, a rate significantly higher compared to the general population (Rivera et al., 1997; Buskila et al., 1998; Thompson and Barkhuizen, 2003). In CFS, high prevalences of infections such as mycoplasmal infections have been reported (Nasralla et al., 1999; Nijs et al., 2002). Based on the reports of a reduced HPA activity in combination with higher cytokine levels and increased prevalences of infections in stress-related disorders, Raison and Miller (2003) assume that prolonged or repeated exposure to immune stimuli might predispose an individual to reduced glucocorticoid signaling as a means of freeing bodily defenses from inhibitory control in the face of an ongoing infectious threat. Thus, an enhanced release of inflammatory compounds may be adaptive under conditions in which recurrent infection is likely and immune readiness is an attendant requirement. Van Hoof et al. (2003) even hypothesize that atypical depression as one of the most common affective disorders in CFS patients is not an affective disorder but constitutes the symptom of sickness response. The term 'sickness response' refers to non-specific symptoms such as fatigue, increased pain sensitivity, depressed activity, concentration difficulties, and anorexia that accompany the response to infection (Hart, 1988; Maier and Watkins, 1998). Sickness behavior at the behavioral level appears to be the expression of a central motivational state that reorganizes the organism's priority to cope with infectious pathogens (Hart, 1988). Therefore, Van Hoof et al. (2003) argue that the state of atypical depression or chronic fatigue is essentially characterized by a decrease in energy consumption during periods of sickness or injury to promote subsequent recuperation. Thus, the disease may be adaptive to conserve energy during threats beyond the organism's ability to cope and thereby serving an important function for survival. A link between diseases such as FMS and the sickness response has also been suggested (Van Houdenhove and Egle, 2004). This is not surprising considering that symptoms such as pain, fatigue, concentration difficulties and flu-like symptoms are part of both the stress-related disorders and the sickness response.

Further evidence for the protective effects of the development of a hypocortisolism refers to the allostatic load index. The term 'allostatic load' was firstly introduced by McEwen and Stellar (1993) describing the wear and tear of the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge. Allostatic load results when the allostatic systems (e.g. the HPA axis) are either overworked or fail to shut off after the stressful event is over or when these systems fail to respond adequately to the initial challenge, leading other systems to overreact (McEwen, 1998). In this context, results of Hellhammer et al. (2004) demonstrate a significantly higher allostatic load index in older compared to younger subjects with the exception of hypocortisolemic elderly who had a comparable allostatic load to young people even though they scored far higher on perceived stress scales. Considering the fact that allostatic load has been associated with a higher risk for mortality, these data suggest that a hypocortisolemic response to stress may rather be protective than damaging.

All these examples demonstrate that reduced HPA axis reactivity with low cortisol levels is not only maladaptive but, contrarily, may have even beneficial and advantageous effects for the organism's survival. Low cortisol levels in the case of pregnant women may protect the mother and the child against the risk of pre-term birth, which could be harmful for both of them. Similarly, low cortisol levels in those individuals who are repeatedly or continuously exposed to intense immune stimuli may be beneficial for health and survival. Most strikingly, the demonstration of a low allostatic load index in hypocortisolemic subjects suggests that a down-regulation of the HPA axis in chronically stressed subjects protects those subjects against the harmful effects of a high allostatic load index.

Based on these results we propose that hypocortisolism is a protective response dampening chronic HPA axis activity and thereby reducing the damaging effects of the glucocorticoid response to daily hassles at the expense of symptoms such as high stress sensitivity, pain, and fatigue.

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