



The role of glucocorticoids and corticotropin-releasing hormone regulation on anxiety symptoms and response to treatment

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Abstract

The stress response has been linked to the expression of anxiety and depression, but the mechanisms for these connections are under continued consideration. The activation and expression of glucocorticoids and CRH are variable and may hold important clues to individual experiences of mood disorders. This paper explores the interactions of glucocorticoids and CRH in the presentation of anxiety and depressive disorders in an effort to better describe their differing roles in each of these clinical presentations. In addition, it focuses on ways in which extra-hypothalamic glucocorticoids and CRH, often overlooked, may play important roles in the presentation of clinical disorders.

Key Words

- ▶ glucocorticoids
- ▶ CRH
- ▶ anxiety
- ▶ PTSD
- ▶ depression

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Introduction

Stress reactions are by no means universal, and the activation of ‘stress hormones’, such as glucocorticoids or corticotropin-releasing hormone (CRH), is not necessarily the mark of a stress response (1). Some individuals have lower-than-usual release of glucocorticoids in fearful situations, whereas others have higher release (2), and glucocorticoid release has differential effects and antecedents depending on an individual’s history and development (3, 4). The roles of these hormones are nonetheless crucial to our understanding of both resilience and pathology.

Glucocorticoid levels have been strongly linked to many pathological conditions (3). In particular, they have been strongly, and differentially, tied to generalized anxiety and depressive disorders, posttraumatic stress disorder (PTSD) and social anxiety. Each of these areas of research has implicated glucocorticoid levels, either high or low, in the presentation of variable symptoms

of anxiety (3). Despite the seeming ties between these areas of research, little information exists to bridge the gap of understanding between the fields, and many discrepancies exist within each of the studies. It is important to note therefore that although each of these concerns focuses on the presentation of anxiety-like symptoms, the underlying glucocorticoid activities, as well as the presenting symptoms, are varied.

Although studies have reliably demonstrated the negative impacts of consistently high circulating glucocorticoids, high glucocorticoid levels by itself is not necessarily problematic. Rather, this may simply be an indicator of high energy and activity in some cases (3, 5). In some, this may reveal that the person is highly engaged in high-energy endeavors, whereas in others, it shows a potentially pathological response to stressors. Of particular concern are high levels of glucocorticoids with regulatory dysfunction such that the feedback system



does not shut off glucocorticoid release. In these cases, long-term exposure to heightened glucocorticoid levels can have damaging impacts (1, 3).

Glucocorticoids are responsible for upregulating CRH in the amygdala, frontal cortex, and bed nucleus of the stria terminalis (6, 7, 8, 9), whereas they down-regulate hypothalamic CRH (5). Given this site-specific relationship, it is possible that, when we observe glucocorticoid levels in a vacuum, we are actually looking at very different events with very different consequences due to the brain region upon which the glucocorticoids are acting (5, 10, 11). Levels of circulating CRH can have long-lasting expression independent of concurrent glucocorticoid levels. Both CRH levels and the site of activation, however, are important to the presentation of anxiety symptoms, such that noting CRH levels alone is also insufficient to understand the response (6).

By better understanding how glucocorticoid and CRH functioning in different contexts can lead to variable symptomatology, researchers may be better equipped to develop treatment strategies involving glucocorticoids for generalized anxiety and depressive disorders, PTSD, social anxiety and other conditions. The purpose of this paper is to explore the interactions of glucocorticoids and CRH in the presentation of anxiety and depressive disorders in an effort to better describe their differing roles in each of these clinical presentations. In addition, we describe ways in which extra-hypothalamic glucocorticoids and CRH, often overlooked, may play important roles in the presentation of clinical disorders.

Depression and anxiety

Although diagnostic criteria for anxiety and depressive disorders such as generalized anxiety disorder and major depressive disorder are unique and diverse, they are generally typified by heightened negative affect (or lowered positive affect), vegetative symptoms (e.g., sleep changes, appetite/weight changes) and thoughts that are hard to control (e.g., rumination, worry, guilt) (12). Underlying mechanisms for anxiety and depressive disorders may be similar, as evidenced by overlapping symptoms (e.g., irritability, high negative affect) and treatments (e.g., selective serotonin reuptake inhibitors (SSRIs), cognitive behavioral therapy) (3). Depression and anxiety can be temporary states based on an individual's adjustment to a life circumstance, but often occur chronically over a person's lifetime. These disorders can significantly inhibit functioning, and major depression itself has been linked

to significantly reduced well-being and productivity (e.g., Stewart *et al.* 2003) (13).

Symptoms of anxiety and depressive disorders have been linked to hypersecretion of corticotropin-releasing hormone (CRH), leading to high levels of circulating glucocorticoids (5, 14, 15). This is supported by the fact that individuals with depression have increased startle response and may have enhanced anxious anticipation (16). In addition, some forms of psychosis such as schizophrenia and delusional disorders are associated with higher circulating glucocorticoids and high levels of CRH. Risks of developing symptoms of anxiety, mania and psychosis are also higher among individuals who have been prescribed glucocorticoid medications (17). Some have suggested that the link between glucocorticoids and depression may stem from overexposure to glucocorticoids early in life, for example, due to exposure to chronic stress (e.g., abuse) and the subsequent reduction of synaptic potentiation (10, 18). This overexposure may lead to a hyper-anxious state, producing vulnerability to exhaustion and possible depression (19). Certain CRH receptors such as CRH1 may also be linked to the development of depression after early stressful experiences (20), but trials with CRH1 antagonists are few, and findings do not strongly support their efficacy (21, 22).

Given the findings suggesting a link between high glucocorticoids and symptoms of mental illness, it is not surprising that inhibitors of glucocorticoids have been studied as a possible intervention for mental illness including depression. Although further study is necessary, it appears that corticosteroid synthesis inhibitors (CSIs) may show some efficacy in treating individuals with intractable depression (23). Kling and coworkers (23) propose that the mechanism of action is through a reduction in the expression of extra-hypothalamic CRH, rather than in a decrease in corticosteroids themselves (24). To achieve this, CSIs may reduce glucocorticoid enhancement of CRH in extra-hypothalamic regions (23). It has been postulated that these treatments may be best used as adjunctive treatments and have shown some success in studies (21). Interestingly, at least one case has been reported in which the administration of a corticosteroid (prednisone) reduced depression symptoms (24).

Ruthenium (Ru) compounds block glucocorticoids generally. Some studies have looked into giving Ru compounds to mental health patients to reduce glucocorticoid expression with the idea that high glucocorticoids were driving symptom expression.

Ru compounds such as mifepristone (RU486) have been shown to have efficacy in reducing psychotic symptoms in individuals with psychotic depression, though they may not be effective in reducing depression symptoms themselves (22).

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) has been classified as an anxiety disorder and occurs in individuals who have been exposed to a traumatic event or events. This exposure can be a direct experience (e.g., experiencing or witnessing an event), by proxy (e.g., the event happens to a close friend or family member), or may be characterized by repeated exposure to the details through images or other means (25). PTSD is characterized by re-experiencing (e.g., nightmares, flashbacks), avoidance (i.e., of situations that may elicit memories), negative cognitions and mood (e.g., depression, anxiety), and arousal (e.g., hyper-responsiveness to stressors) (12). Symptoms of PTSD can present along a spectrum of severity and can have long-lasting effects. Although PTSD is often linked to military or combat situations, traumatic events occur in a range of circumstances and situations and may affect anyone (25).

In a phenomenon originally described by Mason and coworkers, individuals with PTSD surprisingly tend to have lower glucocorticoid levels than people without PTSD (Table 1) (26). This finding was initially controversial, given the seemingly strong link between glucocorticoid levels and high anxiety. Despite this, individuals with PTSD also have higher levels of CRH in the cerebral spinal fluid (27) and appear to have similar cortisol reactivity to individuals without the disorder (28). Based on these findings, it is apparent that multiple processes must be at play in order for opposing glucocorticoid profiles to create symptoms that appear, on the surface, to be similar. Several studies have shown that low levels of glucocorticoids are particularly prevalent among individuals with PTSD who have also experienced early life stressors such as long-term abuse or complex trauma. This indicates that a lifetime of adversity can lead to blunted stress reactivity, and can reduce the effectiveness of the stress response system.

In several studies of specific groups (e.g., Holocaust survivors, rape survivors), individuals who experience symptoms of PTSD have lower glucocorticoid levels than individuals without PTSD (29). This has led to the theory that the symptoms of PTSD may be treatable through

Table 1 Selection of studies showing low glucocorticoid levels in individuals with PTSD.

PTSD publications	Main findings related to glucocorticoids
Mason <i>et al.</i> (1986) (26)	Shows lower cort levels in patients with PTSD
Mason <i>et al.</i> (1988) (44)	Shows lower glucocorticoid levels in patients with PTSD
Yehuda <i>et al.</i> (1990) (29)	Low urinary glucocorticoid levels in individuals with PTSD
Yehuda <i>et al.</i> (1995) (45)	Shows lower glucocorticoid levels in Holocaust survivors with PTSD
Yehuda <i>et al.</i> (2000) (46)	Shows that offspring of individuals with PTSD are also at increased risk for PTSD and have low glucocorticoid levels
Yehuda <i>et al.</i> (2002) (47)	Shows that lower glucocorticoid levels are associated with more severe PTSD symptoms
Glover & Poland (2002) (48)	Shows lower glucocorticoid levels in mothers with PTSD
Yehuda <i>et al.</i> (2005) (49)	Shows lower glucocorticoid levels of women with PTSD exposed to trauma during pregnancy, and in their children
Neylan <i>et al.</i> (2005) (50)	Shows that lower basal glucocorticoid levels predict severity of PTSD symptoms in police officers
Wessa <i>et al.</i> (2006) (51)	Shows lower glucocorticoid levels in patients with PTSD
Meewisse <i>et al.</i> (2007) (52)	Review showing low glucocorticoid levels in adults with PTSD
Yehuda <i>et al.</i> (2007) (53)	Shows that offspring of individuals with PTSD are also at increased risk for PTSD and have low glucocorticoid levels
Gill <i>et al.</i> (2008) (54)	Low glucocorticoid levels in women with PTSD

PTSD, posttraumatic stress disorder.

infusions of glucocorticoids, particularly temporally with the traumatic event. Findings for this research, however, have been mixed.

Treatment with glucocorticoid medication has been suggested as a possible intervention to reduce the presentation of PTSD symptoms in individuals at risk. In animal models for instance, the administration of a steroidogenesis inhibitor has been shown to prevent the onset of posttraumatic anxiety in some rats (30). However, glucocorticoids have also shown promise as prophylactic treatments for humans experiencing trauma: patients with critical illnesses (31), and other individuals with PTSD and phobias (32, 33). These studies introduce the exciting idea that pharmacotherapy, when timed and

dosed appropriately, may help to reduce the presentation of anxiety symptoms after individuals experience trauma.

It should be noted that medically prescribed glucocorticoids are not without risks. Treatment with glucocorticoids can have significant and long-lasting physical and psychological impacts on patients and has been reported to lead to debilitating psychological conditions in some cases (17). Several studies have found, however, that treatment with low doses of glucocorticoids can reduce symptoms of PTSD and particularly avoidance symptoms, as well as improving symptoms of specific phobias (32). These findings indicate that glucocorticoids at an appropriate level may be crucial to the formation and integration of memories related to traumatic events. Based on these findings, glucocorticoids may be a helpful intervention, but must be treated with some caution and may not be appropriate for the treatment of all individuals with risk factors for PTSD.

Social anxiety

Social anxiety is a biological phenomenon with underlying environmental influences, similar to PTSD or anxiety and depression. Correlates of social anxiety have been studied in macaques showing that temperament influences how individuals respond to the presence of stressors (34). Individuals with social anxiety may be framed as suffering from an acute version of a common state in children called shyness. Social anxiety, or the fear of judgement from others in social situations, may result in avoidant behaviors, heightened anxiety responses and potentially panic-like symptoms (35). Adults with social anxiety are more likely than non-socially-anxious adults to have been 'shy' as children (36), and exhibit many similar behavioral patterns including withdrawal and avoidance (36).

Although shy and fearful children tend to have high cortisol levels and high reactivity to stress when they are young (Fig. 1) (37, 38, 39), in later life, socially anxious individuals may develop a different pattern with reduced glucocorticoid levels and decreased reactivity (Figs 2 and 3) (40). As adolescents and adults, these children enter a hypo-arousal phase, notable due to 'shutting down'. This hypo-arousal phase is marked by decreased energy, decreased reported anxiety, and reduced glucocorticoid levels (40). This could be an expression of a sort of learned hopelessness resulting in declining glucocorticoid expression.

This pattern of low glucocorticoids is similar to that seen among individuals with PTSD and may indicate a

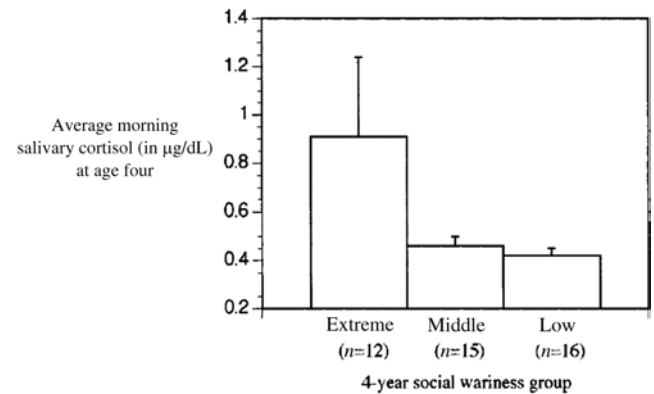


Figure 1

Differences among the three 4-year social wariness groups on morning salivary cortisol at age 4. (Note: This analysis is based on natural log-transformed cortisol values; values have been reconverted for presentation.) Reprinted from *Developmental Psychobiology*, Vol 30, Schmidt LA, Fox NA, Rubin KH, Sternberg EM, Gold PW, Smith CC & Schulkin J, Behavioral and neuroendocrine responses in shy children, Pages 127–140, Copyright (1998), with permission from John Wiley and Sons.

similar behavioral pattern related to avoidance. Also similar to individuals with PTSD, low doses of glucocorticoids administered during exposure for social anxiety have been shown to decrease the anxiety response (32). Studies indicate that chronic social stress, such as that which a shy or fearful child might experience, influences

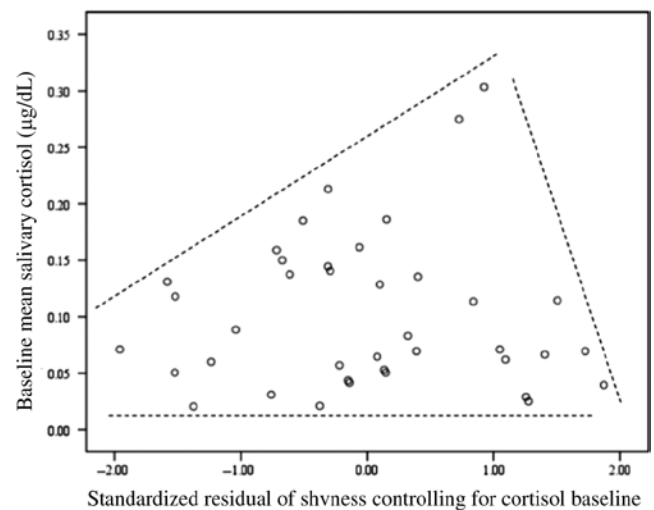
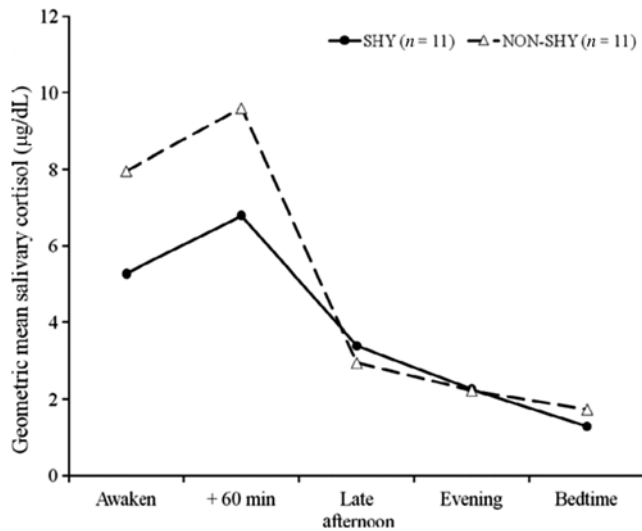


Figure 2

Scatterplot of the relation between the standardized residual of shyness controlling for baseline salivary cortisol and log transformed baseline mean salivary cortisol in 10-year-old children. (Note: Dashed lines are intended to illustrate outline of triangular shape of scatterplot.) Reprinted from *Personality and Individual Differences*, Vol 43/6, Schmidt LA, Santesso DL, Schulkin J & Segalowitz SJ, Shyness is a necessary but not sufficient condition for high salivary cortisol in typically developing 10 year-old children, Pages 1541–1551, Copyright (2007), with permission from Elsevier.

**Figure 3**

Three-day average of daily salivary cortisol output from awakening until bedtime in shy and non-shy young adults. Reprinted from *Personality and Individual Differences*, Vol 55/6, Beaton EA, Schmidt LA, Schulkin J & Hall GB, Repeated measurement of salivary cortisol within and across days among shy young adults, Pages 705–710, Copyright (2013), with permission from Elsevier.

the expression of CRH in both the amygdala and the hypothalamic–pituitary–adrenal (HPA) axis in rats (41, 42).

Conclusion

Glucocorticoids are not just related to stress, but rather to energy levels as well. Accordingly, it is not just the presence or the absence of glucocorticoids that is important, but rather the ability to appropriately regulate these chemicals in a changing environment. This seems to be part of the key to resilience and overall health (1). In addition, the complex relationship between glucocorticoids and the experience of anxiety indicates that therapy to either reduce or increase glucocorticoid levels may be important in the treatment of various

conditions including depression/anxiety, PTSD and social anxiety (Table 2). Additional research is needed in the area of how psychotherapy and other alternative treatments may affect glucocorticoid levels and change patterns of reactivity.

Glucocorticoids importantly influence the expression of CRH such that high glucocorticoids and high CRH are present in trait fearfulness. This raises the question, however, of what would happen, and whether it is possible, in the case of high glucocorticoids and low CRH. Could this potentially be a protective hormonal milieu that might reduce the expression of deleterious anxiety responses? Further, it is important to understand the complex relationship between glucocorticoids and CRH as they relate to the symptoms experienced by individuals with anxiety or depression, PTSD and social anxiety. These interactions may help to understand the differential expression of symptoms, as well as the underlying chemical influences. Glucocorticoids and CRH influence each other, as well as fear and anxiety responses, in different ways depending on their location and levels. The interactions of these two systems and others contribute to the presentation of symptomatology in several conditions and may also lead to a reduction in the body's abilities to cope with stressful situations (1, 43).

As noted, CRH is differentially expressed throughout the brain. Differential expression of brain circuits such as in the amygdala may lead to differential expression of cortisol and CRH or may contribute to anxiety symptoms being expressed differently. Placental CRH is also being explored as a possible source of predispositions toward anxiety symptoms and high levels of circulating glucocorticoids. Fundamentally, the impact of glucocorticoids is to affect how a person responds to adversity over a lifetime, and it is within that frame that we may begin to target important areas for the treatment of anxiety conditions using novel glucocorticoid therapies in conjunction with more traditional medicines and therapies.

The literatures addressing each of these disorders, glucocorticoids and CRH are each vast in and of themselves. It is beyond the scope of this paper to comprehensively review each of these areas of work. The aim of this paper is rather to suggest that glucocorticoids and CRH, including within and outside of the HPA axis, are vital to the presentation of a variety of symptom profiles that differ based on localization of activation among other factors. In doing so, many valuable, relevant, and important studies may have been neglected, but the hope is that this

Table 2 Three clinical conditions and their relative levels of CRH and glucocorticoids.

Anxiety/depression	Posttraumatic stress disorder	Social anxiety
High CRH High circulating glucocorticoids	High CRH Low circulating glucocorticoids	High CRH High circulating glucocorticoids when young; low levels when older

paper will spur others to action and encourage further research in these areas.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

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