The Interface of Stress and the HPA Axis in Behavioural Phenotypes of Mental Illness

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Abstract Abnormalities of hypothalamic-pituitary-adrenal (HPA) axis function are one of the most consistent biological findings across several mental disorders, but many of the mechanisms underlying this abnormality as well as the potential contribution to behavioural phenotypes remain only partially understood. Interestingly, evidence suggests a U-curve, with dysregulation of the HPA axis towards both hyper- or hypoactivity manifesting as a risk to mental wellbeing. This review will elaborate on both the clinical and molecular role of the neuroendocrine stress system in depressive, psychotic and post-traumatic stress disorders and present some of the most recent findings that have shed light on the complex interface between environmental stressors, molecular mechanisms and clinical presentation. Crucially, plasticity of the HPA axis confers both vulnerability to adverse events, particularly so in early developmental stages, as well as hope for the treatment of mental disorder, as evidenced by changes in HPA functioning associated with remission of symptoms.

Keywords Stress · Cortisol · HPA axis · Depression · Psychosis · PTSD

Contents

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1 Overview of HPA Axis Functioning

Activity of the HPA axis, the neuroendocrine stress system, is governed by the secretion of corticotrophin-releasing factor (CRF) and vasopressin (AVP) from the hypothalamus, which in turn activate the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. This finally stimulates the secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex, which then interact with their cognate receptors in multiple target tissues. Glucocorticoids have widespread regulatory roles as part of the stress response, both in peripheral functions such as immunity and metabolism as well as in the central nervous system (CNS). In the CNS, glucocorticoids moderate neuronal survival, neurogenesis, long-term potentiation and dendritic growth as well as atrophy in complex anatomical structures extensively implicated in psychopathology, particularly the hippocampus and amygdala [reviewed in Herbert et al. (2006)]. Notably, the HPA axis is embedded in bidirectional relationships to other allosteric systems that have been implicated in psychopathology, such as the inflammatory (Dantzer et al. 2008) and monoaminergic systems (Gotlib et al. 2008), and thus some of the behavioural effects of HPA functioning may be mediated by interaction with these systems.

In the HPA axis, glucocorticoids are responsible for feedback inhibition both on CRF and AVP from the hypothalamus and directly on secretion of ACTH from pituitary corticotropes. Endogenous glucocorticoids regulate release of CRF in the paraventricular nucleus and ACTH in the pituitary via activation of their cognate receptors—the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). MR has a high affinity for endogenous glucocorticoids, whilst the GR has a lower affinity, suggesting the GR is more important in the regulation of the stress response, i.e. an acute elevation in glucocorticoids, whereas the high affinity of the MR tends to be tonically activated at most times of the day. The assertion that the GR modulates HPA function during stress is supported by research utilising the GR-selective synthetic glucocorticoid dexamethasone as a pharmacological challenge—which, in healthy individuals, is associated with a reduction in cortisol levels for up to 24 h, demonstrating GR mediated negative feedback within the HPA axis. Recent research also suggests MR can regulate fast feedback inhibition (Atkinson et al. 2008).

2 HPA Function in Unipolar and Bipolar Depression

Considering its role at the interface between stress and brain function, it is perhaps not surprising that the HPA axis has been found abnormal in many psychiatric disorders, albeit with idiosyncratic presentation. In depression, it appears clinical abnormalities of HPA function are, at least in part, related to reduced feedback inhibition by endogenous glucocorticoids, leading to hyperactivity of the axis [reviewed in Pariante (2006)]. Indicative of this hyperactivity, a significant percentage of depressed patients have increased levels of cortisol in the saliva, plasma and urine, and increased size (as well as activity) of the pituitary and adrenal glands [Reviewed in Nemeroff and Vale (2005)]. Recent research developments have utilised hair cortisol as a long-term measure of HPA functioning, and have confirmed elevated cortisol hair levels in depression, suggesting persistent HPA hyperactivity [reviewed in Staufenbiel et al. (2013)]. Depressed patients also show an increased HPA response to psychosocial stressors (Pariante and Lightman 2008) and are more likely to report daily events as stressful (Bylsma et al. 2011). Depression is also associated with an elevated cortisol response to awakening, a phenomenon that persists even after recovery (Bhagwagar et al. 2003, 2005; Vreeburg et al. 2009). Further, recent evidence suggests that unaffected individuals with a parental history of depression show a similarly augmented cortisol awakening response (Vreeburg et al. 2010). Interestingly, individuals at risk for depression show elevated waking cortisol levels similar to depressed patients, but their HPA axes recover more rapidly from psychosocial stress exposure (Dienes et al. 2012). This hyperactivity is likely to relate to impaired functioning of GR, reducing the ability of the HPA axis to feedback and inhibit its own activity. Studies have shown changes in both function and expression of GR in patients in major depression: non-suppression of cortisol secretion following administration of dexamethasone; impaired GR function in peripheral blood mononuclear cells isolated and cultivated in vitro, or in peripheral cells examined in vivo using metabolic or vascular indices; and reduced GR expression in neuropathological studies of post-mortem human brains [reviewed in (Pariante 2006; Pariante and Lightman 2008; Pariante and Miller 2001)].

Interestingly, evidence not only suggests idiosyncratic HPA activity depending on clinical status, but also variations depending on clinical subtypes. A recent review spanning four decades of HPA research found that whilst depression was generally associated with increased cortisol and ACTH but not CRH levels, individual subtypes differed: atypical depression was associated with a third of a standard deviation (SD) lower, melancholic depression a quarter of an SD higher, and psychotic depression nearly half an SD higher cortisol levels (Stetler and Miller 2011). Interestingly, it appears that melancholic depression is associated with greater cortisol awakening response and diurnal cortisol slope, whereas atypical depression appears to be more closely linked to elevation of inflammatory as well as metabolic markers (Lamers et al. 2012).

Similar to depression, bipolar disorder is associated with blunted response to dexamethasone challenge (Daban et al. 2005) and there is evidence of elevated baseline cortisol levels both during manic and depressive phases (Duffy et al. 2012). Bipolar patients also show an enhanced cortisol awakening response (Deshauer et al. 2003), and there is some evidence suggesting altered HPA function in the offspring of bipolar parents (Ellenbogen et al. 2010). Elevated hair cortisol has also been reported bipolar patients, but only when age of onset was older than 30 (Manenschijn et al. 2012). Moreover, manic episodes appear to be preceded by elevations of both cortisol and ACTH, suggesting relevance to the pathogenesis of bipolar disorder, rather than altered HPA functioning being a relict of depressive symptoms. In line with this, evidence obtained from post-mortem investigation of GR expression showed increased expression in both amygdalar neurons and astrocytes for unipolar, but not bipolar depressed patients or healthy controls (Wang et al. 2013).

3 HPA Function in Psychosis

The HPA axis has also been shown to be functionally altered in psychosis, with a high degree of similarities to depressive disorders: first episode psychosis patients show elevated baseline levels of HPA activity as well as blunted response to dexamethasone challenge in the context of elevated diurnal cortisol levels, the latter of which appears to be normalised by antipsychotic medications, as well as potentially enlarged size of the pituitary gland (Borges et al. 2013). A recent meta-analysis showed an increased pituitary volume of non-significant magnitude in first episode psychosis as well as a significant increase in individuals at ultra-high risk of psychosis who transitioned (Nordholm et al. 2013) and further evidence has shown similar pituitary volume elevations in non-affected relatives of patients with schizophrenia (Mondelli et al. 2008). Interestingly, patients who received medication had significantly larger pituitary glands compared to drug-naïve patients, possibly due to the effects of antipsychotics on prolactin production. Clinical high risk for psychosis in medication-free individuals is also associated with elevated basal salivary cortisol (Sugranyes et al. 2012).

Unlike depressed patients however, first episode patients show a significantly lower awakening cortisol response when compared to healthy controls (Mondelli et al. 2010). Interestingly, blunted cortisol response to awakening in schizophrenia patients predicts worse cognitive functioning (Aas et al. 2010), and is positively correlated with and predicted by the severity of positive symptoms in schizophrenia patients (Belvederi Murri et al. 2011). Schizophrenia patients further show a tendency towards attenuated cortisol response to psychosocial stress, however in the context of increased activity of the sympathetic nervous system as indicated by elevated heart rate and blood pressure (Brenner et al. 2009) and individuals at ultra-high risk for psychosis exhibit a significantly attenuated cortisol response to psychosocial stress compared to healthy controls (Brenner et al. 2009; Pruessner

et al. 2013). Patients with psychosis also show a greater emotional reactivity to daily life stress (Myin-Germeys et al. 2005). Interestingly however, Pruessner et al. (2013) found that lower cortisol output in response to psychosocial stress in patients with psychosis is correlated with higher levels of self-reported stress during the preceding year.

4 HPA Function in PTSD

Perhaps the most mixed findings on HPA function have been obtained in individuals with post-traumatic stress disorder (PTSD). A meta-analysis on both basal as well as dynamic HPA functioning found no differences in PTSD patients, trauma-exposed (TE) and non-exposed (NE) individuals in terms of basal cortisol levels, consistent across saliva, urine and plasma sampling, although reductions in baseline cortisol have been reported in individual studies (Klaassens et al. 2011). Whilst exposure to trauma in adulthood had no significant overall impact on basal cortisol levels it was associated with enhanced cortisol suppression in response to dexamethasone. Conversely, some studies on hair cortisol in PTSD have reported elevated cortisol levels (Steudte et al. 2011; Luo et al. 2012), whilst others have not (Steudte et al. 2013), potentially due to the different kinds of trauma exposure in the respective samples.

Interestingly, evidence reviewed by de Kloet et al. (2006) showed that whilst PTSD is associated with enhanced inhibitory feedback in response to dexamethasone challenge, indicative of increased functioning of the GR, individuals with PTSD show augmented cortisol responses to psychosocial stress tests. In line with these findings, de Kloet et al. (2012) recently reported that cognitive challenge was rated as more stressful by and led to elevated ACTH but not noradrenaline responses in PTSD patients, but research utilising dexamethasone challenge found opposing effects, i.e., enhanced suppression of ACTH (Yehuda et al. 2004; Golier et al. 2006).

A recent meta-analysis comparing PTSD to PTSD comorbid with depression (PTSD + MDD) showed further interesting subtleties in differential HPA function: PTSD, PTSD + MDD and TE groups exhibited attenuated morning cortisol compared to NE groups, but whilst PTSD and TE groups showed similar patterns in afternoon cortisol levels, comorbid depression was associated with significant elevations compared to NE controls (Morris et al. 2012). Furthermore, PTSD, PTSD + MDD and TE groups all showed augmented cortisol suppression in response to dexamethasone, with no significant effect size differences between the groups. Interestingly, these findings were observed in the context of overall diminished daily output of cortisol in PTSD and PTSD + MDD patients but not TE individuals. However, some of this evidence remains mixed, as there have also been reports of elevated afternoon cortisol levels in patients with PTSD in another meta-analysis (Miller et al. 2007) (Table 1).

Table 1 Cortisol characteristics associated with disorders and adversity-exposure

Cortisol measure	Depression	Bipolar Disorder	Psychosis	PTSD	Childhood adversity	Adulthood adversity
Awakening response	↑	↑	↓	↓	Mixed evidence	↕[a]
Afternoon	↑	↑	↑	=	–	↑
Daily output	↑	↑	↑	↓[b]	↑	↑
Hair	↑	↑[c]	–	Mixed evidence	↓	–
Post-DST	↑	↑	↑	↓	↑	↓
Post-psychosocial stress test	↑	?	↓[b]	↑	↓	–

[a] Context-dependent increases or decreases
[b] Tendency
[c] Only when onset-age <30

5 The Impact of Stress in Early Life

Evidence over the last decades has provided evidence suggesting that HPA axis dysfunction is not a simple consequence or an epiphenomenon of mental disorder, but on the contrary it is a risk factor predisposing to the development of psychopathological behaviour, brought about by early life experiences programming molecular changes as well as by biological vulnerability to stress. Perhaps the most striking development in this field has been the realisation that abnormal functioning of the HPA axis may reflect a susceptibility that can be programmed through early life events—starting even as early as in prenatal development [reviewed in (Cottrell and Seckl 2009)]. Clinical studies have shown that women who are sexually or physically abused in childhood exhibit a markedly enhanced activation of the HPA axis as adults. Even if not currently depressed they exhibit enhanced ACTH and heart rate responses when exposed to psychosocial stress; and if they are currently depressed they exhibit the largest increase in ACTH secretion and heart rate, as well as a very large increases in cortisol secretion (Heim and Nemeroff 2002). Moreover, research using dexamethasone has also found persistent HPA axis hyperactivity in men with early life trauma (Heim et al. 2008). Notably however, evidence on associations of childhood trauma with awakening cortisol response has been inconsistent, with reports of both augmentation and attenuation of the awakening cortisol response (Lu et al. 2013; Mangold et al. 2010).

Research attempting to establish associations of HPA functioning profiles with psychopathological behaviours needs to control for the mediating effects of childhood trauma, as childhood trauma itself has been shown to be associated with a variety of adult mental disorder, including depression, bipolar disorder, psychosis and PTSD (Putnam et al. 2013; Varese et al. 2012; Subica 2013; Edwards et al. 2003). Interestingly, a recent study demonstrated that when participants meeting

criteria for MDD were matched to healthy controls with no lifetime history of depression based on age, sex and experience of childhood adversity, using the dexamethasone/CRH test failed to distinguish depressed from non-depressed participants (Carpenter et al. 2009). Conversely, depressed individuals with a history of childhood trauma, as opposed to depressed patients without this type of early experience, show decreased cortisol hair levels (Hinkelmann et al. 2013).

One of the most frequently proposed mechanisms through which early life experiences may impact on the HPA axis is epigenetic programming. Indeed, there is evidence for greater methylation of the GR in hippocampal regions of suicide completers who had been subjected to childhood abuse compared to suicide completers without a history of childhood trauma (McGowan et al. 2009). Similarly, Tyrka et al. (2012) recently reported that a history of childhood adversity in healthy adults was associated with increased methylation of a promoter region of the GR gene in leukocyte DNA. Moreover, this methylation was associated with an attenuated response to the dexamethasone/CRH test. In line with this evidence, childhood trauma induces demethylation of glucocorticoid response elements of the gene coding for the GR-associated heat shock protein FKBP5, which normally inhibits the ability of the ligand to bind cytosolic GR and subsequently translocate to the cell nucleus, where it can increase FKBP5 transcription which in turn reduces GR activity. Individuals with a functional polymorphism of this gene are at greater risk of PTSD, depression and suicide (Klengel et al. 2012). Interestingly, polymorphisms of the FKBP5 gene associated with greater expression of the chaperone protein are also associated with prolonged elevation of cortisol levels following psychosocial stress exposure (Ising et al. 2008). Although most research has focused on the effects of early life events on programming changes in the HPA axis itself concentrating on epigenetic modifications of glucocorticoid receptor genes, it is important to emphasise that there are many other closely related systems that may be susceptible to programming. For example, a recent study showed increased methylation of the serotonin transporter gene (SERT) in bullied children when compared to their discordant mono-zygotic co-twins, which was associated with blunted cortisol response to the TSST (Ouellet-Morin et al. 2012).

6 The HPA-Stress Interface in Late Adolescence and Adulthood

The 3-hit model of vulnerability and resilience recently proposed by Daskalakis et al. (2013) suggests that the interaction of genetic predisposition with early life experience sets the course of neuroendocrine alterations in neural development via epigenetic programming towards an adult phenotype vulnerable to environmental stressors. Indeed, stressful life events in adulthood such as trauma or exposure to chronic stress may precipitate the onset of a range of disorders and can facilitate relapse in existing disorders (Melchior et al. 2007; Stilo et al. 2012; Bebbington

et al. 1993; Francis et al. 2012; Lethbridge and Allen 2008). Interestingly, the type of stress one is exposed to appears to be associated with differential patterns of HPA response and subsequent vulnerability to specific psychopathological syndromes. There is evidence that the immediate response of the HPA axis to trauma (i.e. within 24 h of exposure) can predict the development of PTSD: several studies suggest that lower cortisol levels in the peritraumatic period are associated with a higher risk of subsequent PTSD, and there is evidence of enhanced cortisol suppression in response to dexamethasone in trauma-exposed individuals who go on to develop PTSD (Morris and Rao 2013). Furthermore, PTSD-specific HPA functioning in the form of diminished morning but elevated afternoon cortisol levels within a week of exposure are also linked with the subsequent development of the disorder (Aardal-Eriksson et al. 2001).

Marin et al. (2007) assessed life stress and HPA functioning in healthy women between the ages of 15 and 19, and found that exposure to episodic stressors in the context of high chronic stress led to increased cortisol release, both upon awakening and overall daily output, as well as reduced GR mRNA. However, exposure to episodic stressors in the context of low chronic stress led to decreased cortisol release and enhanced GR mRNA. In the context of medium chronic stress, the level of exposure to episodic events had no impact on either cortisol or GR levels. A meta-analysis by Miller et al. (2007) further showed that idiosyncratic stress signatures can differentially impact on HPA function: for example, the awakening cortisol response increases in response to significant stressors that pose a threat to the social self, but decreases when the stressor poses threat to physical integrity, involves a loss and/or is perceived as uncontrollable. Similarly, some stressor types only impact on certain HPA measures but not others, e.g. whilst stressors that pose a threat to the social self appear to increase afternoon cortisol levels, they do not impact on overall daily cortisol output or response to dexamethasone challenge.

7 Conclusion

The findings discussed in the present review show that specific HPA axis profiles appear to be characteristic of different disorders and syndromes. The high degree of neuroplasticity during early developmental stages acts as a window of sensitivity, allowing childhood adversity to convey vulnerability to mental illness in later life, which, even in the absence of the development of psychopathological behaviours, is associated with highly complex effects on measures of HPA function. Taken together, HPA axis dysfunction in mental disorders as described above may not be the consequence of these ailments per se, but rather the manifestation of persistent neurobiological abnormalities that predispose to their development dependent on specific combinations and characteristics of idiosyncratic stress exposure. As such, on-going disruption of HPA homeostasis, be it towards hyper- or hypoactivity, can have adverse impacts on mental and physical wellbeing. Due

to its unique position at the interface between biological systems and adversity, the HPA axis not only presents as one of the most interesting examples of molecular interplay of the individual with their environment over the course of a lifetime, but also as one of the most challenging areas of mental health research.

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