Hypothalamic–Pituitary–Adrenocortical Axis Function in Attention-Deficit Hyperactivity Disorder

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Contents

Abstract The hypothalamic–pituitary–adrenocortical axis plays a critical role in mediating the physiological response to the imposition of stress. There are theoretical reasons to expect reduced basal cortisol secretion and cortisol hyporeactivity in hyperactive/impulsive or combined type attention-deficit hyperactivity disorder (ADHD). Early studies reported profound abnormalities in the diurnal rhythm of cortisol secretion or the cortisol response to stress in children with severe or persistent ADHD. However, subsequent work using larger samples or improved methods has not provided convincing evidence for changes in basal cortisol secretion in non-comorbid forms of ADHD. In contrast, children with ADHD and

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comorbid oppositional defiant disorder show lower basal cortisol concentrations and a blunted cortisol awakening response. With respect to cortisol reactivity to stress in ADHD, recent evidence has been mixed, with some studies reporting normal cortisol responses and others showing blunted cortisol responses in non-comorbid ADHD. Again, it appears important to consider whether comorbid disorders are present, because children with ADHD and comorbid disruptive behavior disorders exhibit blunted cortisol responses, whereas those with comorbid anxiety disorders show enhanced cortisol responses to stress. Longitudinal studies are required to investigate whether abnormalities in cortisol secretion play a causal role in the etiology of ADHD and related disruptive behavior disorders.

Keywords ADHD · Cortisol · Disruptive behavior disorder · Neuroendocrinology · Stress

Abbreviations

ACTH	Adrenocorticotropic hormone
AVP	Arginine vasopressin
BAS	Behavioral activation system
BIS	Behavioral inhibition system
CAR	Cortisol awakening response
CBG	Cortisol-binding globulin
CD	Conduct disorder
CRH	Corticotropin-releasing hormone
DBD	Disruptive behavior disorders
HPA	Hypothalamic–pituitary–adrenal (axis)
ODD	Oppositional defiant disorder
PVN	Paraventricular nucleus
SCID	Structured clinical interview for DSM-IV
TSST-C	Trier social stress test for children

1 Introduction

This chapter will consider the relationship between attention-deficit hyperactivity disorder (ADHD) and the hypothalamic–pituitary–adrenocortical (HPA) axis, a critical physiological system that mediates responses to stress. Stress can be defined as the imposition or perception of an environmental change or challenge, which could be positive or negative in valence but, in either case, requires an adaptive

response by the organism (Herman and Cullinan 1997). The secretion of glucocorticoid hormones, principally cortisol in humans, is a key component of this adaptive response that alerts the organism to environmental or physiological changes and promotes the recovery of homeostasis. Dysregulation of HPA axis responses can have a detrimental effect on health and well being. For example, prolonged hypersecretion of glucocorticoids can impair psychological functioning and damage vulnerable brain structures, such as the hippocampus (Herbert et al. 2006). Although not a consistent observation, major depressive disorder is frequently associated with glucocorticoid hypersecretion, together with deficits in the negative feedback mechanisms that normally terminate HPA axis activity (Burke et al. 2005; Holsboer 2000).

Conversely, insufficient cortisol secretion may be harmful to health and psychological functioning (Heim et al. 2000a). Such a deficit has been linked with a compromised immune system and increased risk for physical illnesses (e.g., arthritis) and psychiatric disorders (e.g., chronic fatigue syndrome, post-traumatic stress disorder) (Cleare 2003; Yehuda et al. 2005; Yehuda et al. 1995). The main objective of this chapter is to review evidence linking ADHD with abnormalities in HPA axis activity and to explain what this can tell us about the pathophysiology of the disorder. Comorbid disorders will also be considered because they may moderate the relationship between ADHD and HPA axis dysfunction. The chapter will end with a discussion of gaps in our knowledge base and offer a number of recommendations for future research in this area.

2 The Hypothalamic–Pituitary–Adrenocortical Axis

Information about stressors in the environment is relayed from limbic brain regions, such as the amygdala and prefrontal cortex, to the paraventricular nucleus (PVN) of the hypothalamus. A population of neurons in this latter region responds to stress by releasing adrenocorticotropic hormone (ACTH) secretagogues, such as corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), into the pituitary portal circulation. CRH and AVP interact with receptors on corticotropic cells of the anterior pituitary to cause secretion of ACTH into the bloodstream. ACTH subsequently binds with receptors in the adrenal cortex to induce synthesis and secretion of cortisol.

Cortisol targets many organs and tissues and has effects on metabolism, such as promoting glycolysis. It also crosses the blood–brain barrier to act centrally and to regulate HPA axis activity by activating negative feedback mechanisms: effectively, cortisol inhibits its own production. Through its actions at glucocorticoid (GR) and mineralocorticoid (MR) receptors, particularly those expressed in limbic structures (such as the amygdala and hippocampus), cortisol is capable of modulating a range of psychological processes relating to learning and memory (de Quervain et al. 2009; Roozendaal 2000). CRH also plays a role in coordinating the adaptive response to stress through its effects on central structures such as the

amygdala (Kalin et al. 1989; Kalin and Takahashi 1990; Swiergiel et al. 1993). CRH has anxiogenic properties, promoting vigilance and context-dependent motor responses, such as fight, flight, or freezing. All of these peptide- and steroid-based effects facilitate adaptive responses to stress in the short-term and help the organism to maintain or recover homeostasis.

As well as functioning as an alarm system at times of environmental challenge, the HPA axis exhibits a marked diurnal (or circadian) rhythm in humans. Cortisol secretion is highest in the morning, at the start of the activity cycle, and lowest immediately before or during sleep (Deuschle et al. 1997; Netherton et al. 2004; Rosmalen et al. 2005; Weber et al. 2000). Superimposed upon the early part of the rhythm is a characteristic increase in cortisol secretion within 1 h of waking (Clow et al. 2004; Pruessner et al. 1997): the cortisol awakening response (CAR). The suprachiasmatic nucleus of the hypothalamus is implicated in the initiation of the CAR (Clow et al. 2004, 2010), but different mechanisms may regulate the CAR relative to other components of the cortisol diurnal rhythm. In addition, genetic influences appear to be greater on cortisol concentrations measured in the morning, compared to the evening (Bartels et al. 2003; Wust et al. 2000). Of interest, the CAR may be less pronounced, or even absent, in childhood (Freitag et al. 2009; O'Connor et al. 2005), whereas many studies have observed an intact CAR in healthy adolescent populations (Fairchild et al. 2008; Oskis et al. 2009; Rosmalen et al. 2005).

3 What Is the Theoretical Basis for Investigating the Relationship Between ADHD and HPA Axis Abnormalities?

Gray (1982) proposed the existence of three interrelated neuropsychological systems subserving, respectively: fight or flight, reward sensitivity (mediated by the "behavioral activation system" or BAS), and punishment sensitivity (mediated by the "behavioral inhibition system" or BIS). According to this model, individuals differ in terms of the relative activity of these systems: some are particularly prone to seek out rewards (high BAS), while others are strongly motivated to avoid punishing stimuli (high BIS). Individuals with psychopathological conditions may represent the extreme end of the spectrum on either of these continua (e.g., anxiety disorders may be the result of excessive BIS activity) or a functional imbalance between these systems. Gray argued that the BIS responds to conditioned stimuli (signals) for punishment and nonreward so as to induce passive avoidance and extinction of behavior. BIS output causes the cessation of ongoing behaviors, focuses the organism's attention on environmental cues, and increases nonspecific physiological arousal (the most relevant feature for the present chapter).

Gray originally argued that the functions of the BIS were mediated by the septo-hippocampal system and its connections to the prefrontal cortex. Following early suggestions by Quay (1997) and Barkley (1997), a great deal of work in the field has been directed at trying to understand ADHD as a consequence of functional

impairment of the BIS. Such impairment is argued to give rise to the hyperactive/impulsive symptoms of ADHD as well as neurocognitive impairments in visual and verbal working memory, emotion regulation, and motor fluency (Barkley 1997). As implied by its hypothetical role in increasing arousal levels, an underactive BIS may lead to reduced cortisol levels both at baseline, and particularly under conditions of psychological challenge, in ADHD. It is *critical* to distinguish between cortisol levels measured under resting conditions (referred to as 'basal' cortisol) and cortisol measures under psychological or physical stress (referred to as 'cortisol reactivity' or 'cortisol responses to stress'). Given that impaired BIS activity is suggested to be relatively specific to the combined or predominantly hyperactive/impulsive types of ADHD (Barkley 1997; Quay 1997), one prediction arising from this theory is that abnormalities in HPA axis activity should be observed in these two subtypes but not in the predominantly inattentive type of ADHD.

4 Basal Cortisol Secretion in ADHD and Related Disorders

This review of empirical findings will start by considering studies that have investigated basal or resting cortisol levels in ADHD.

An early study measured the diurnal rhythm of cortisol secretion in a group of 30 children with ADHD, comparing their results with those of a control group of adults and a psychiatric control group (21 children with autism). Saliva samples were collected at 2-h intervals in the morning. Further samples were obtained in the afternoon and evening to characterize the diurnal profile. Absolute cortisol levels were not reported and so it is not possible to tell whether ADHD was associated with abnormally low or high levels relative to the other groups. Nevertheless, the authors found that a majority (57%) of the children with ADHD failed to show a normal diurnal rhythm, whereas only 20% of the autistic subjects and 10% of the adult controls exhibited abnormalities in diurnal rhythm (Kaneko et al. 1993). When the results for the ADHD group were subdivided in terms of severity of hyperactivity, dysregulation of the cortisol rhythm was more common in those with moderate-to-severe hyperactivity, relative to those with mild hyperactivity.

The authors also used the Dexamethasone Suppression Test, which involves giving subjects a synthetic glucocorticoid in the evening and then measuring plasma cortisol concentrations the following morning. Due to the negative feedback effects of glucocorticoid administration on HPA axis activity, most subjects show suppression of cortisol secretion in the morning after dexamethasone administration. Kaneko et al. (1993) found that cortisol nonsuppression was significantly more common in the children with ADHD, relative to adult controls, implying that HPA axis negative feedback mechanisms function less effectively in ADHD. Again, HPA axis abnormalities were more common in those with severe hyperactivity: 78% of subjects in this subgroup showed cortisol nonsuppression, compared with only 20% of the mild hyperactivity ADHD subgroup.

Although these results are certainly interesting, the authors' failure to report absolute cortisol concentrations makes this study difficult to interpret. It would have been preferable to include a group of healthy children, rather than using adult controls. There were also differences in terms of procedure between the adults and the children, with adults taking a higher dose of dexamethasone closer in time to the morning cortisol assessment, and sex differences between the clinical and control groups. It is unclear whether ADHD participants were assessed for comorbid disorders that could have impacted upon HPA axis activity, such as disruptive behavior disorders (DBDs), anxiety, or depression. Finally, the absence of a normal cortisol diurnal rhythm has not been replicated in subsequent studies (see below), and it seems unlikely that such marked disturbances in the pattern of cortisol secretion are characteristic of most individuals with ADHD.

A study that compared patients with ADHD and comorbid oppositional defiant disorder (ODD; $n = 32$) and healthy control subjects ($n = 25$) found lower basal cortisol levels in the ADHD plus ODD group (Kariyawasam et al. 2002). A post hoc examination of the effects of psychostimulant administration showed that reductions in cortisol concentration were specific to the ADHD plus ODD subjects who were not taking methylphenidate or amphetamine: this finding implies that psychostimulants increase cortisol secretion. It would have been helpful to have included a non-comorbid ADHD group to determine whether it was ADHD or ODD that was driving these results and to provide further data on the effects of psychostimulants. Another limitation of this study is that cortisol concentration was measured at a single time-point only, which may have occurred at a different point in the diurnal rhythm of the two groups (although all samples were collected in the afternoon). An observation of consistently lower levels across the diurnal cycle would have been more convincing.

Methodological improvements in cortisol assessment were implemented in a small-scale study of 18 children with ADHD and 71 healthy controls that found normal waking cortisol levels and an intact CAR in the ADHD group, overall (Blomqvist et al. 2007). However, a post hoc comparison of 13 participants with high levels of hyperactivity/impulsivity ADHD symptoms and the healthy control group showed that the hyperactive ADHD subgroup (who met criteria for combined type ADHD) did not show a rise in cortisol levels in the 30 min after waking. This finding is broadly consistent with the results described above showing that HPA axis function is more aberrant in subjects with moderate-to-severe forms of hyperactivity. Limitations of this study included the use of a small ADHD group, the apparent lack of assessment for comorbid psychiatric illnesses, and lack of matching for gender.

A recent study that also used up-to-date saliva collection methodology found a normal CAR in children with ADHD alone or ADHD plus conduct disorder (CD), but a reduced CAR in those with ADHD and comorbid ODD (Freitag et al. 2009). This finding appeared to be driven by a general reduction in cortisol secretion in the latter group, rather than a specific effect on the awakening response, since they showed lower cortisol levels both at waking and +30 min after waking. This observation of a blunted CAR, specifically in those with ADHD plus comorbid

ODD, illustrates the importance of collecting information about comorbid disorders, a point which will be discussed in more detail below. The study also showed that increases in cortisol concentrations, from waking to +30 min postawakening, were smaller in participants who had experienced higher levels of psychosocial adversity.

A large ($n = 1{,}768$) general population study assessing the CAR and evening cortisol levels in preadolescent children found only a weak (positive) association between self-reported ADHD symptoms and evening cortisol (Sondeijker et al. 2007). There was no relationship between cortisol concentrations and parent-reported ADHD symptoms, arguably a more meaningful and reliable measure of psychopathology than self-reported symptoms. Moreover, the magnitude of the CAR was not related to symptoms of ODD or CD. One possibility is that these null findings reflect the limited variance in externalizing symptomatology that occurs in general population samples: the situation may have differed if a clinical sample had been used. However, given the statistical power provided by such a large sample, the most parsimonious interpretation of these results is that ADHD symptoms are not associated with clinically significant changes in *basal* cortisol secretion, except perhaps in extreme samples.

This conclusion is further reinforced by a recent study that characterized the diurnal profile of cortisol secretion in 28 adults with ADHD (mainly the combined type) and 28 healthy control subjects. Saliva samples were collected directly after waking and +30 min postawakening to assess the CAR. Further samples were obtained at 1700 and 2300 h to provide information about the diurnal rhythm. The results showed almost identical cortisol diurnal profiles in the ADHD and control groups (Hirvikoski et al. 2009), with both groups exhibiting a pronounced cortisol rhythm and a normal CAR. However, this study was limited by a high incidence of comorbid disorders in the ADHD group, with many participants meeting current or past criteria for major depressive disorder, generalized anxiety disorder, or borderline personality disorder.

In addition to research focusing specifically on aspects of basal cortisol secretion, such as the diurnal cortisol rhythm or the CAR, a large number of studies have reported data relevant to the issue of altered basal cortisol secretion in ADHD. These experiments assessed prestress or baseline cortisol levels before stress induction (and therefore under relatively controlled conditions). The majority of these earlier experiments found no differences between ADHD participants and healthy controls in baseline cortisol levels (Blomqvist et al. 2007; Hirvikoski et al. 2009; Lackschewitz et al. 2008; Luby et al. 2003; Randazzo et al. 2008; Snoek et al. 2004). An exception was a study that observed slightly lower prestress cortisol levels in children with combined type ADHD (van West et al. 2009).

To summarize these results: although a number of early studies provided evidence for reduced or dysregulated basal cortisol in ADHD (particularly in its persistent form or when it involves severe hyperactivity), the methodologically strongest or largest studies have not demonstrated abnormalities in basal cortisol secretion. Furthermore, studies that collected data on cortisol secretion before stress

induction largely failed to show alterations in prestress cortisol levels in ADHD, regardless of subtype. While the literature does provide tentative evidence that combined type ADHD, or particularly ADHD with comorbid ODD, may be associated with slightly lower basal cortisol levels, or a blunted CAR, it is unclear whether these reductions are of clinical or prognostic significance. In addition, some of the studies purporting to have measured "basal" cortisol may have inadvertently assessed stress-induced cortisol levels, particularly if they only obtained one saliva sample in a setting that was novel to the child (e.g., a laboratory or a psychiatric clinic). It is partly for this reason that most current studies of basal cortisol secretion typically involve collecting multiple samples across the day while the participants are going about their normal routines (i.e., in naturalistic conditions). In the next section, studies that assessed cortisol reactivity during stress in ADHD will be reviewed and evaluated.

5 Is ADHD Associated with Cortisol Hyporeactivity?

An early study reported that children with persistent ADHD were characterized by reduced cortisol reactivity during performance of a neuropsychological test battery, relative to those who showed a remission of their ADHD (King et al. 1998). Baseline cortisol levels before neurocognitive testing were also slightly lower in the group with persistent ADHD compared to those who would subsequently remit. Limitations of this study included a small sample size, the lack of a matched control group, and incomplete characterization of participants. In addition, only one poststress saliva sample was obtained, leaving open the possibility that the groups differed in the latency of their stress response. From what we now know about factors determining whether a cortisol response occurs (see below), it is surprising that such large increases in cortisol were seen in the nonpersistent ADHD group when performing a battery of neurocognitive tasks. In fact, the children with nonpersistent ADHD may have been the group showing an abnormal pattern of cortisol reactivity, rather than the group with persistent ADHD.

Another study used separation from the caregiver and a play task, involving induction of mild frustration, as separate psychosocial stressors, in a cohort of preschool children. Although the focus of the study was major depressive disorder, it is relevant to the current review because a psychiatric control group of children with ADHD or ODD was included, together with a healthy control group. No differences were found between subjects with ADHD or ODD and healthy controls in salivary cortisol responses to caregiver separation (cortisol went down in both groups). Cortisol increased in both groups following performance of the frustrating task (Luby et al. 2003). In contrast, the depressed group showed a weak increase in cortisol during caregiver separation and a further increase during the frustration task.

Cortisol levels were also assessed on three consecutive evenings: analysis of these data revealed no group differences in evening basal cortisol. As will be

discussed in a later section, it is not ideal to collapse across the diagnoses of ADHD and ODD and, as such, the results of this study are difficult to interpret. However, they do not provide evidence for disrupted HPA axis activity in either of these externalizing disorders because their pattern of reactivity was similar to that of healthy controls. A further limitation of the study was that participants were given a snack by the experimenters up to 30 min before baseline cortisol assessment. This may have increased cortisol levels and made it difficult to demonstrate effects of caregiver separation, since "prestress" levels were already relatively high. Nevertheless, work of this nature is important because little is known about associations between cortisol secretion and ADHD or ODD in younger age groups.

More recently, researchers have used standardized psychosocial stressors, such as the Trier Social Stress Test (TSST), to assess cortisol reactivity in clinical groups. This test involves giving a public speech in front of audience, and typically also a video camera, to induce the feeling of being socially evaluated (Kirschbaum et al. 1993). The advantage of using standardized tests of this kind is that the results can be compared to those generated by other research groups, and the stressor is more likely to be effective than those generated on an ad hoc basis. Relevant to this point, many everyday experiences that might be considered stressful do not appear to elicit cortisol responses in the majority of children or adolescents (Gunnar et al. 2009). For example, discussing conflictual topics with parents did not elicit increased cortisol secretion in a majority of healthy adolescents (Klimes-Dougan et al. 2001). In addition, even in children who report high levels of dental anxiety, cortisol levels typically did not increase during dental examinations (Blomqvist et al. 2007).

A recent meta-analytic review of 208 studies of stress reactivity in adults found that, to elicit cortisol or ACTH increases, stressors must threaten the individual's goals (Dickerson and Kemeny 2004). These might include not only the goal of physical self-preservation but also the goal of preserving the "social self." Thus, tasks that threaten the social self, such as being socially evaluated while giving a speech in front of a panel of judges, reliably increase HPA axis activity. Tasks that require intense mental effort but which do not involve threat to the social self, such as challenging neurocognitive tasks or mental arithmetic, were far less effective in provoking cortisol responses. The meta-analysis also found that uncontrollability and unpredictability were important components of effective stressors and, that these factors acted synergistically to enhance the effects of threatening the individual's central goals (Dickerson and Kemeny 2004). The TSST encompasses many of these elements, including social evaluation, achievement stress, and loss of control, and thus represents an effective psychological stressor in its original format or in the version modified for children (Foley and Kirschbaum 2010).

The question of whether patterns of cortisol reactivity differ between ADHD subtypes was addressed in a study that compared children with predominantly inattentive versus combined types of ADHD (van West et al. 2009). They used the modified Trier Social Stress Test for Children (TSST-C) to induce psychological stress in their participants. Children with combined type ADHD showed blunted cortisol responses during the test, relative to control subjects and those with

predominantly inattentive type ADHD, whereas the latter two groups did not differ. Baseline cortisol levels were also slightly lower in children with combined type ADHD compared to healthy controls. These results therefore support the distinction made in the DSM-IV between predominantly inattentive and combined types of ADHD, and the suggestions that these forms of ADHD constitute qualitatively distinct and unrelated disorders (Barkley 1997; Diamond 2005). They are also in line with theoretical proposals described in an earlier section, which hold that attenuated cortisol responses are a consequence of an underactive BIS. As noted above, this underactivity is suggested to be specific to predominantly hyperactive/impulsive or combined types of ADHD.

One point of note is that although ADHD subjects with comorbid disorders were excluded from the study, the combined type ADHD group had significantly higher scores on the delinquency and aggression subscales of the Teacher Report Form and Child Behavior Checklist compared to the other two groups: this subthreshold externalizing comorbidity could have influenced the results. In addition, it seems likely that many of the subjects are at high risk for developing CD/ODD in the future, even though they did not meet full DSM-IV criteria at the time of assessment at age 6–12 years. Although the authors were not able to recruit a predominantly hyperactive/impulsive type ADHD group, which would have provided stronger evidence for a link between cortisol hyporeactivity and the hyperactive/impulsive cluster of ADHD symptoms, this study had several strengths, including the use of a standardized stressor; a comprehensive psychiatric assessment; a reasonably large sample size; and group matching for age, gender, socioeconomic status, and IQ.

Another study that investigated cortisol reactivity to the TSST-C, specifically in children with predominantly inattentive type ADHD, reported blunted cortisol responses to stress. This pattern was observed in subjects meeting diagnostic criteria for ADHD, relative to both healthy controls and those with subthreshold levels of predominantly inattentive type ADHD symptoms (Randazzo et al. 2008). These findings are clearly at variance with those reported above by van West et al. (2009), showing normal stress reactivity to the TSST-C in children with predominantly inattentive type ADHD. Of possible relevance in this respect is that the sample size used in the Randazzo et al. (2008) study was small: only seven participants met full criteria for predominantly inattentive type ADHD.

A recent study examined cortisol and cardiovascular responses to psychological stress in adults with ADHD compared to control subjects (Lackschewitz et al. 2008). Although cardiovascular responses were blunted during stress in the ADHD group, there were no group differences in cortisol reactivity. There was, however, a trend toward lower cortisol levels at baseline and throughout the procedure in the ADHD group. Interestingly, the ADHD participants reported experiencing greater subjective stress than control subjects, suggesting a discrepancy between emotional and physiological components of the stress response. A potential limitation of this study was that one-third of the ADHD subjects had comorbid depression/anxiety disorders, which may enhance cortisol responses. In addition, although all ADHD subjects were assessed for current comorbid

psychiatric disorders, using the structured clinical interview for DSM-IV (SCID), it is unclear whether they were screened for, or met, lifetime criteria for DBDs such as ODD or CD. This could be problematic because cortisol hyporeactivity may be a trait abnormality even in subjects with remission of DBD symptoms.

Snoek et al. (2004) assessed cortisol reactivity in children with ADHD alone, ADHD plus comorbid ODD, or ODD alone to examine whether reduced cortisol reactivity was specific to DBD, such as ODD or CD, or whether this pattern extended to externalizing disorders in general. Compared with healthy controls, children with ODD alone, or ADHD plus ODD, showed blunted cortisol responses, whereas those with ADHD alone exhibited a normal pattern of cortisol reactivity. Group differences were evident only under stressful conditions: there were no differences in baseline cortisol in the early afternoon. These data indicate that cortisol reactivity is normal in non-comorbid ADHD, but reactivity may be blunted in individuals with a comorbid DBD.

This study had a number of limitations, including relatively high rates of comorbid anxiety disorder in all three clinical groups. Also, many of the subjects with ADHD or ADHD plus ODD were taking methylphenidate on the day of testing. However, it is worth noting that chronic use of psychostimulant medication is reported to have no detectable effects on serum cortisol levels (Weizman et al. 1987). Furthermore, the presence of comorbid anxiety disorders should have affected all three clinical groups to an equal extent. Thus, neither of these factors appears to be a plausible explanation for differences between the "ADHD alone" and the ODD groups.

Further evidence that comorbid disorders may play an important role in influencing cortisol reactivity comes from a large study of clinic-referred ADHD patients who underwent venipuncture to provide blood samples for genotyping (Hastings et al. 2009). This relatively naturalistic stressor appeared effective in eliciting cortisol responses, and the researchers subsequently examined whether comorbid anxiety or DBD influenced stress reactivity. They hypothesized that these conditions would have opposing effects on cortisol secretion. They also investigated whether there were differences in cortisol reactivity between ADHD subtypes. As predicted, children with ADHD and a comorbid anxiety disorder displayed larger cortisol responses, whereas those with ADHD and comorbid DBD showed blunted cortisol responses to stress. Children with ADHD alone and those with ADHD and comorbid anxiety plus DBD formed intermediate groups between those with either internalizing or externalizing comorbidity, only. Unfortunately, this study did not include a healthy control group; hence, it is unclear whether the children with pure ADHD exhibited a normal or a blunted cortisol response relative to those without any psychiatric disorder. The results of the analyses comparing ADHD subtypes did not reveal differences in baseline or stress-induced cortisol. However, the effect of DBD comorbidity on cortisol reactivity appeared to differ according to ADHD subtype: there were no differences between combined type ADHD without DBD and combined type ADHD with DBD, whereas comorbid DBD led to lower cortisol reactivity in those with predominantly inattentive or predominantly hyperactive–impulsive types of ADHD.

In summary, findings on cortisol reactivity in ADHD have been mixed, with several studies providing convincing evidence for blunted cortisol responses to psychosocial stress in ADHD (particularly combined type ADHD), but a similar number of experiments revealing normal patterns of cortisol reactivity in ADHD. In fact, studies using almost identical methodology and clinical samples with the same presenting diagnosis (e.g., predominantly inattentive type ADHD) have reported entirely conflicting results (cf., Randazzo et al. 2008; van West et al. 2009).

One way of reconciling some of these discrepancies may be to consider the prevalence of comorbid DBD symptoms or diagnoses in the ADHD participants, since ODD and CD have repeatedly been shown to be associated with cortisol hyporeactivity during psychosocial stress (Fairchild et al. 2008; Popma et al. 2006; van Goozen et al. 1998, 2000). The importance of assessing for comorbid DBDs in patients with ADHD is shown most clearly in studies that have explicitly compared subjects with ADHD alone, versus those with ADHD and comorbid ODD or ODD alone. Cortisol responses were normal in those with pure ADHD but blunted in subjects with ODD (with or without ADHD) (Snoek et al. 2004). This position is broadly supported by a study explicitly investigating the impact of comorbid internalizing and externalizing disorders on cortisol reactivity in ADHD (Hastings et al. 2009), which found that subjects with ADHD and comorbid DBD showed weaker cortisol responses to stress than those with pure ADHD. The authors also found that subjects with ADHD and comorbid anxiety disorders displayed larger cortisol responses during stress than those with ADHD alone. Thus, in general, cortisol reactivity is increased in individuals with internalizing disorders and reduced in those with externalizing disorders such as ODD and CD. When these forms of comorbidity occur together, they appear to cancel each other out in terms of their effects on cortisol reactivity.

6 Recommendations for Future Research on HPA Activity in ADHD and Related Disorders

6.1 Assess Cortisol in Relation to Waking Time

A key point of this review has been that the HPA axis is a dynamic system that not only responds to psychological and physical stress but also exhibits a marked diurnal rhythm and a CAR close to the start of the activity cycle. As a consequence, in studies of basal cortisol secretion in psychiatric disorders, it is critical to assess cortisol levels in relation to the waking time of the individual being assessed. This is particularly important when morning cortisol levels are being measured because subtle group differences in waking time could create the erroneous impression that there are group differences in cortisol secretion (when, in fact, the CAR is simply occurring at a different time in the clinical group). Thus, measuring cortisol levels at waking and +30 min after waking and recording the time of awakening are

strongly advised. As well as increasing the validity and reliability of group comparisons of morning cortisol secretion, assessment of the CAR means that researchers obtain a sensitive measure of physiological reactivity. Additional measurements at +45 and +60 min are desirable since they permit enhanced characterization of the latency and profile of the CAR and may provide information about efficacy of negative feedback mechanisms. However, it is also important to use protocols that most participants can implement in their everyday lives and to consider that it may not be practical to collect these extra morning samples when studying young children. Furthermore, because afternoon and evening cortisol levels may be more readily influenced by the effects of psychopathology, subjective mood states, and environmental factors, it is advisable to collect additional samples during these periods to enable characterization of the diurnal cortisol profile. Finally, wherever feasible, cortisol levels should be assessed across two or more days to assess reliability and stability of group differences in cortisol secretion or dysregulation of the cortisol diurnal profile.

6.2 *Advantages of Assessing Cortisol Levels in Saliva*

Undergoing venipuncture can be stressful (Hastings et al. 2009), and so measuring cortisol levels in saliva rather than serum is usually preferable because it avoids this confound. In addition, salivary cortisol is a better measure of biologically available (so-called free) cortisol levels: much of the cortisol measured in serum is bound to cortisol-binding globulin (CBG) and unable to act at corticosteroid receptors. A further advantage is that most participants regard provision of saliva samples as more acceptable than giving blood samples. Thus, researchers maximize the number of individuals willing to take part in their studies by adopting the former method. Clearly, if cortisol is being measured under naturalistic conditions (i.e., in the participants' homes), then obtaining saliva is the only practical method of doing this. Electronic devices can be used to monitor subject compliance with saliva collection protocols (Broderick et al. 2004), but this may not be economically feasible in large population-level studies. An alternative approach is to ask participants to record their saliva collection times in a "diary"; they can also use this to make a note of potential confounds that may influence cortisol levels, such as taking exercise, using caffeinated drinks, or smoking cigarettes before saliva collection.

6.3 *Appropriate Conditions, Ethical Issues, and Sample Sizes in Psychoneuroendocrine Research*

Several studies have shown that the incremental increase in cortisol levels during stress is broadly similar whether the stressor is applied in the morning or in the afternoon (Kudielka et al. 2004). Nevertheless, it is recommended that researchers

restrict their testing to a set period in the day (e.g., mid- to late-afternoon). This should improve detection of increases in cortisol levels following stress and provide other advantages, such as making group differences in baseline levels more interpretable. As noted above, the use of a standardized stressor and acclimatization to the laboratory setting are also highly desirable in terms of achieving increases in cortisol levels in most control participants. Many studies of stress reactivity in children have failed to meet these criteria, largely due to the use of weak psychological stressors (Gunnar et al. 2009). Of course, this issue has an ethical dimension because researchers should not seek to induce intensely negative emotional states and they have a duty to protect their participants – particularly when working with children. However, to elicit measurable and robust cortisol responses, it is necessary to temporarily threaten the individual's "social self" by making them feel as though they are being negatively socially evaluated and that they have lost control of the situation in some way (Dickerson and Kemeny 2004).

In addition, the tests need to be adequately powered, and so sample sizes need to be relatively large in stress reactivity research because there is considerable inter-individual variability in cortisol responses to psychological stress. Even in typically developing adolescents, when using a standardized stressor, cortisol levels may drop in some individuals and rise by 400–500% in others. As a consequence, it is difficult to demonstrate significant group differences if sample sizes are small.

7 What Do We Need to Know About the Relationship Between ADHD and HPA Axis Activity?

Several important issues remain unresolved. First, does cortisol hyporeactivity play a causal role in the etiology of either ADHD or common comorbid disorders such as ODD, or are any changes in cortisol secretion a consequence of these disorders? Related to this is another question: does cortisol hyporeactivity reflect a state-like effect or does it represent a trait-like vulnerability factor that increases risk for developing ADHD or ODD/CD in a probabilistic fashion? Furthermore, is such a deficit present before development of the full ADHD syndrome or even after remission of symptoms? Longitudinal studies are required to answer these questions since, to date, almost all research in this area has been cross-sectional in basis (i.e., the studies have made comparisons between cases and control subjects at a specific point in time). Second, what neurobiological mechanisms are responsible for the pattern of cortisol hyporeactivity observed in ADHD and related externalizing disorders, such as ODD? For example, are there fundamental deficits in the hypothalamic–pituitary–adrenal axis (such as reduced pituitary size or adrenal insensitivity to ACTH) in individuals with ADHD/ODD? Or, as seems more likely, is there some impairment of "processive" aspects of the stress response, mediated by dysfunction in limbic circuits that convey information about stressors in the environment to the hypothalamus? Accordingly, it may be

informative to relate volumes in key brain structures that influence HPA axis activity (such as amygdala and hippocampus) and patterns of cortisol secretion in disorders such as ADHD.

Third, if individuals with ADHD, or related externalizing disorders, retain a normal pattern of cortisol reactivity, does this act as a protective factor and is it predictive of better outcomes? Preliminary findings in children with ODD suggest that cortisol hyporeactivity during stress is a potential biomarker for a poor response to psychological treatment (van de Wiel et al. 2004). This could be a worthwhile issue to investigate in relation to psychological (or possibly pharmacological) treatments for ADHD.

Fourth, does cortisol hyporeactivity reflect a general deficit in physiological arousal, or an adaptation to prenatal or early life stress, in those with ADHD? Studies in animals and humans have demonstrated that prenatal stress can exert a programming effect on the HPA axis (Glover et al. 2010; Lupien et al. 2009). For example, fetal exposure to elevated glucocorticoid concentrations at certain periods during gestation permanently alters HPA axis activity in rodents (Kapoor et al. 2006). Although the evidence for similar programming effects in humans is sparse, recent studies have reported elevated basal cortisol in children whose mothers experienced prenatal anxiety late in pregnancy (Huizink et al. 2008; O'Connor et al. 2005), although another study found the largest effects if prenatal anxiety occurred early in gestation (Van den Bergh et al. 2008). In contrast to these results, a study investigating the impact of adverse life events during pregnancy upon cortisol secretion in offspring (tested in adulthood) found normal basal cortisol secretion and exaggerated responses to the TSST in those exposed to prenatal stress (Entringer et al. 2009). These findings, which provide suggestive evidence for fetal programming of the HPA axis in humans, may be relevant, given that prenatal anxiety also appears to act as a risk factor for the development of ADHD symptoms and externalizing symptoms (O'Connor et al. 2003; Van den Bergh and Marcoen 2004).

Since it is well established that environmental adversity is linked with ADHD (Biederman et al. 2002), it may also be instructive to consider the consequences of early life or chronic psychosocial adversity. Findings on the long-term impact of early life stress and maltreatment on cortisol reactivity are mixed: some studies show heightened cortisol responses in adult survivors of sexual abuse (Heim et al. 2000b), but others show blunted cortisol responses in victims of physical abuse and maltreatment (Carpenter et al. 2007, 2009; Elzinga et al. 2008). In relation to the consequences of chronic adversity, a number of studies have revealed hypocortisolism in healthy individuals living under conditions of ongoing stress, or patients living with chronic pain or physical illness (Heim et al. 2000a). These studies illustrate the potential importance of studying early experiences that may have a programming effect on the HPA axis and measuring current exposure to everyday stressors. This is because both factors may impact upon basal cortisol secretion and cortisol reactivity. In addition, measuring these factors may enhance our understanding of the mechanisms underlying alterations in HPA axis activity in ADHD and related externalizing disorders such as ODD and CD.

8 Conclusions

The HPA axis is a key physiological system, which mediates responses to stress and also exhibits a diurnal rhythm and a response to awakening. There are theoretical reasons to expect an association between hyperactive/impulsive forms of ADHD and reduced cortisol secretion, particularly under conditions of stress. Although early studies reported provocative results on cortisol secretion in ADHD, suggesting marked dysregulation of the HPA axis, more recent work has provided little convincing evidence for alterations in basal (resting) cortisol secretion in non-comorbid forms of ADHD. Where ADHD occurs together with ODD, there may be a moderate reduction in basal cortisol secretion or the magnitude of the CAR. The results of studies assessing cortisol reactivity during stress in ADHD do not show a consistent pattern, although blunted cortisol responses are more commonly reported in combined type relative to predominantly inattentive type ADHD. Again, the presence or absence of comorbid illnesses may be important, with cortisol hyporeactivity typically observed in those with ADHD plus ODD or CD and exaggerated cortisol responses seen in those with comorbid internalizing disorders such as generalized anxiety disorder.

The vast majority of studies on basal cortisol secretion or cortisol reactivity in ADHD have been cross-sectional in design and, as a consequence, little is known about the prognostic value of measuring HPA axis activity. It is also not known whether abnormalities in cortisol secretion play a causal role in the etiology of ADHD, or are merely a consequence of living with ADHD [which may be accompanied by higher levels of perceived stress in everyday life (Hirvikoski et al. 2009)]. Evidently, longitudinal research in this area is merited and may be highly informative.

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