Child maltreatment and the developing HPA axis

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Abstract

The developing HPA axis is under strong social regulation in infancy and early childhood and is vulnerable to perturbation in the absence of sensitive, responsive caregiving. Child maltreatment has complex, long-term influences both on basal cortisol levels and on HPA responsivity to pharmacological and psychological stressors, depending on current psychiatric status, current life adversity, age, and most likely, genetic factors. Among the more consistent findings, maltreated children with internalizing problems have elevated basal cortisol most often detected in early AM concentrations, whereas adults maltreated as children often exhibit low basal cortisol levels and elevated ACTH response to psychological stressors. To disentangle these complicated interactions, future research must take the above qualifiers into account, study the transition to puberty, explore the moderating role of candidate genes, and utilize animal models and pharmacological challenges, when ethical, to localize changes in the HPA axis. Post-institutionalized children may provide a model to separate early adverse care histories from current adversity.

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Everyday life involves managing stressors of varying degrees of severity, and the body must respond to these environmental stressors with physiological adaptations to restore homeostasis. The hypothalamic–pituitary–adrenal (HPA) system constitutes one of the principle pathways of the mammalian stress response, in which a cascade of events leads to elevations in glucocorticoid hormones. In response to a stressor, the hypothalamus increases the amount of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) that it produces and releases into the anterior pituitary gland, which responds by producing and releasing adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal gland to produce cortisol, a steroid hormone with the brain as the principle target organ. Cortisol is necessary for survival, but when cortisol is chronically elevated or poorly regulated, it can have deleterious impacts on health (Sapolsky et al., 2000). The HPA system is not fully mature at birth. There are manifest developmental changes throughout childhood in both basal HPA activity and cortisol reactivity (Gunnar and Donzella, 2001). During this extended period of development, experiences play a role in shaping the basal rhythms and reactivity of the HPA system.

The current article explores the impact of adverse early experiences on the developing HPA axis. We begin by tracing postnatal development of the HPA axis and establishing that the HPA axis is under strong social regulation during the first few years of life. We then review the literature on the response to pharmacological and psychological stressors among adults maltreated as children, stress response in maltreated children, basal cortisol levels in maltreated children and adults, developmental changes in HPA function, post-institutionalized children as a special population to differentiate early maltreatment from current life stress, and the potential moderating role of candidate genes.

Healthy human newborns exhibit robust increases in cortisol in response to aversive stimulation such as physical examinations or childhood inoculations (for a review, see Gunnar, 1992). Over the first year of life, while infants continue to show behavioral distress upon encountering these stressors, there is a marked decrease in the responsiveness of the HPA axis (Gunnar et al., 1996a; Larson et al., 1998; Lewis and Ramsay, 1995). Indeed, as shown in Fig. 1, by the end of the first year of life, one no longer observes increases in cortisol to stressors...
such as a doctor’s exam followed by two injections given as part of the childhood series of inoculations. The decrease in responsiveness of the HPA system to stressors over the course of the first year appears to persist throughout the toddler and preschool years. On average, toddlers and preschoolers do not elevate cortisol in response to mildly threatening situations that elicit distress, wariness, and inhibition of approach, such as encountering a clown or attending the first day of nursery school (De Haan et al., 1998; Gunnar et al., 1997; Nachmias et al., 1996; Spangler and Schieche, 1998). This pattern of hyporesponsing may be functionally equivalent to a period in rats that has been termed the relative “stress hyporesponsive period” or SHRP. In the rat, from postnatal days 4–14, it is difficult to elevate corticosterone (the rodent equivalent of cortisol) and ACTH to stressors that after day 14 will readily activate the HPA system. It is hypothesized that the SHRP protects the brain from the potentially deleterious impact of elevated adrenocortical hormones.

In both rats and humans, parental caregiving mediates the SHRP. For rats, when parental care is sufficiently disrupted, the HPA system of the infant rat is no longer buffered and large increases in corticosterone are observed (Suchecki et al., 1993). In human infants and toddlers, sensitive, responsive parental caregiving has an equivalent role in buffering the HPA system. For example, toddlers who were fearful at the approach of a live clown did not show elevations in cortisol if they were with a parent who responded sensitively to them (Nachmias et al., 1996). Likewise, when 9-month-olds were provided with a babysitter during a 30-min separation, no increases in cortisol to separation were observed when the babysitter was instructed to respond sensitively to the infants’ signals, but significant elevations were noted when the babysitter was instructed to be cold, distant and perfunctory (Gunnar et al., 1992). Similarly, preschoolers in day care with low responsive, stimulating care providers showed a rise in cortisol over the day, but those with highly responsive, stimulating care providers did not (Dettling et al., 2000). Sensitive, responsive caregiving by the attachment figure is presumed to lead to secure attachment formation (Sroufe, 1983), and toddlers who are securely attached do not show elevations in cortisol when the attachment figure is present (Ahnert et al., 2004; Gunnar et al., 1996b; Nachmias et al., 1996; Spangler and Grossman, 1993; Spangler and Schieche, 1998). In the absence of a responsive caregiver, however, toddlers are just as prone to cortisol elevations as are younger infants (Gunnar and Donzella, 2001).

Thus, despite resistance to cortisol elevation at the group level, we might expect individual toddlers with a history of insensitive, unresponsive care to be susceptible to cortisol elevation following stressful events. Toddlers with a history of maltreatment are at increased risk for a disorganized/disoriented attachment status, i.e., an observed pattern of behavior toward a primary caregiver in which the child shows conflicting patterns of avoidance and approach (Main and Solomon, 1990). In cases of maltreatment, the caregiver is simultaneously a threat and a biologically based, expected source of comfort. Due to this paradox, under stress the disorganized/disoriented toddler may display proximity-seeking behavior suddenly followed by avoidant behavior, freezing, or stereotypies. It has been hypothesized that these disorganized/disoriented toddlers, unable to effectively use their caregivers as a coping resource, may be particularly stress vulnerable. Initial support for this hypothesis comes from several studies that report high cortisol levels among children with disordered/disoriented attachment status following Ainsworth’s Strange Situation, a stressful procedure in which the attachment system is challenged by repeated maternal separations (Hertsgaard et al., 1995; Spangler and Grossman, 1993; but see Spangler and Schieche, 1998). In contrast, none of these studies found high post-test cortisol levels among securely attached children in response to the strange situation.

As further evidence that activity of the HPA system in early human development is under strong social regulation, children in deprived rearing environments show marked disturbances in diurnal cortisol rhythms. The normal diurnal rhythm is characterized by a peak in cortisol levels 30 min after waking, followed by a gradual decrease over the course of the day. Several studies indicate that toddlers living in orphanages in Russia and Romania have blunted early morning cortisol levels and no systematic decrease in levels over the course of the day (Carlson and Earls, 1997; Kroupina et al., 1997). This is clearly shown in Fig. 2, which depicts cortisol levels among a number of young children living in a Russian orphanage (Kroupina et al., 1997). Similarly, among preschoolers in foster care, approximately 35% entering a new foster placement exhibit a blunted diurnal rhythm (Bruce et al., in preparation; Fisher et al., 2004; Gunnar et al., 1996b; Nachmias et al., 1996; Spangler and Schieche, 1998).
al., 2000). Low early morning cortisol levels among these children corresponded to the degree of neglect the children experienced prior to being removed from their families. Thus, it appears that being deprived of an evolutionarily expectable level of care, i.e., the species-typical family rearing environment, is associated with dysregulation of the HPA diurnal rhythm in young children, particularly blunting of the early morning peak in cortisol production. These findings are consistent with the animal literature, in which blunted morning cortisol and lack of diurnal variation in rhesus monkey infants have been associated with chronic stress and caregiving disruptions (Boyce et al., 1995; McCormack et al., 2003; see Sanchez, this volume). Relatedly, monkey infants who are abused or harshly treated demonstrate high cortisol reactivity in response to stressors, even in the mother’s presence (Dettling et al., 1998; McCormack et al., 2003), indicating that abusive monkey mothers do not serve the stress buffering function of typical monkey mothers.

To date, much of the human literature on maltreatment and HPA function has focused on stress reactivity among adults who were maltreated as children. Results vary depending both on current psychiatric diagnoses and on the methodology used—pharmacological challenge versus psychological stressor. Pharmacological challenge involves exogenous administration of one of the hormones involved in the HPA axis, such as ACTH or CRH. The system’s response to this probe can then be measured, allowing for localization of functional changes at various levels of the HPA axis. A psychological stressor, on the other hand, is a situation such as public speaking that is likely to naturally provoke a stress response. For maltreated women who had no current psychiatric diagnoses, CRH challenge and a psychological stressor each provoked an elevated ACTH response but normal cortisol response. ACTH challenge for this sample confirmed the relative insensitivity of the adrenal to ACTH (Heim et al., 2000, 2001). Similarly, maltreated women with borderline personality disorder exhibited an elevated ACTH response to CRH challenge compared to non-maltreated women with similar diagnoses (Rinne et al., 2002). Depressed women with a history of maltreatment had an elevated ACTH response to a psychological stressor, the Trier Social Stress Test (TSST), but their cortisol output was also elevated compared to a non-maltreated depressed group. In contrast to the TSST psychological stressor, CRH challenge yielded a blunted ACTH response in depressed maltreated women compared to the non-maltreated depressed group (Heim et al., 2000; Heim and Nemeroff, 2001). This blunting presumably reflects chronic CRH drive resulting in down-regulation of the ACTH response to CRH (Heim et al., 2004). Maltreated men and women with PTSD both had an elevated cortisol response to a social stressor, and men with PTSD also had highly elevated cortisol in response to a cognitive stressor (Bremer et al., 2003). This gender difference suggests that more studies are needed that include men who were maltreated as children. Many of these studies did not account for current life stress, nor did they differentiate based on type of maltreatment experienced (Gunnar and Vazquez, 2006). It will be important for future research to take these variables into account, as well as psychiatric diagnosis, gender, and type of stressor (pharmacological vs. psychological), to replicate and continue to clarify this complex set of findings. Based on the existing evidence, the most consistent finding appears to be that childhood maltreatment is associated with elevated ACTH response to psychological stressors in adulthood. If there is no current psychiatric diagnosis, the adrenal apparently is less responsive to this excess of ACTH, with the result that the cortisol response is normal. In contrast, those who are currently diagnosed with depression or PTSD seem to lack this compensatory mechanism, at least in response to psychological stressors—they show not only an elevated ACTH response but also an elevated cortisol response.

In contrast to the studies of adults with a history of childhood maltreatment, few studies of maltreated children have been able to use pharmacological challenge tests to localize changes in HPA function. One study of sexually abused girls showed a blunted ACTH response to CRH challenge but a normal cortisol response (De Bellis et al., 1994). In contrast, Kaufman et al. (1997) noted ACTH hyperresponding to CRH, but only among depressed, maltreated children who were still living under conditions of intense family disruption and emotional abuse. In the animal literature, blunting of ACTH in response to CRH has been found in infant monkeys reared by abusive mothers (see Sanchez, this volume), consistent with the blunting observed in maltreated adults as noted above (Heim et al., 2004). Unfortunately, studies of maltreated children’s response to psychological stressors are also noticeably lacking, although Hart et al. (1995) noted cortisol suppression among maltreated preschoolers on the days when they required gentle physical restraint to control their aggressive behavior.

Most of the research on HPA activity in maltreated children has focused on basal levels rather than stress reactivity. Perhaps because of this dearth of studies on stress reactivity, and because the HPA system is able to adapt to chronic stress, the human literature on activity of the HPA axis in maltreated children is complex and the findings are inconsistent. Some studies find elevations in basal cortisol levels (Carrion et al., 2002; Cicchetti and Rogosch, 2001a,b; De Bellis et al., 1999), others find rises from morning to afternoon (Hart et al., 1996; Kaufman, 1991), and still others find no difference in basal levels (Hart et al., 1995). As in the adult literature, the picture becomes somewhat clearer if these seemingly contradictory findings are parsed according to current psychiatric status. Maltreated children with internalizing disorders, i.e., depressive and anxiety disorders, tend to have elevated basal cortisol (Gunnar and Vazquez, 2006). Two studies at day camps have observed a significant rise in cortisol levels across the day for depressed maltreated children, as shown in Fig. 3 (Hart et al., 1996; Kaufman, 1991). Non-depressed maltreated children and normal controls did not exhibit this rise. Dysthymic sexually abused girls aged 7–15, nearly half of whom had a history of attempting suicide, had slightly elevated basal cortisol across the day (De Bellis et al., 1994). In a study of pre-pubertal maltreated children with chronic PTSD, 24-h urinary-free cortisol (UFC) concentrations were elevated compared to normal controls (De Bellis et al., 1999). UFC levels correlated positively with the duration of...
with internalizing problems alone. Cicchetti and Rogosch (2001b) found that 24-h UFC levels of maltreated children with PTSD did not differ significantly from UFC levels of non-maltreated clinically anxious children.

Baseline cortisol levels of maltreated children with externalizing disorders, i.e., “acting-out” or aggressive disorders such as conduct disorder, have not been shown to differ from those of normal controls (Cicchetti and Rogosch, 2001b; Hart et al., 1995). This null result does not necessarily indicate that the HPA system is functioning normally. Non-maltreated children with pure externalizing disorders (i.e., without comorbid internalizing problems) tend to have lower basal cortisol levels than normal controls (Hardie et al., 2002; King, 1998; McBurnett et al., 1991, 2000; Moss et al., 1995). Externalizing problems and maltreatment status may have opposing influences on HPA activity. In that case, we might expect that maltreated externalizing children would not differ from normal controls in basal cortisol but would have higher basal cortisol than non-maltreated externalizing children (Gunnar and Vazquez, 2006). Indeed, Cicchetti and Rogosch (2001b) obtained this pattern of results for externalizing maltreated boys, though not for girls.

It is somewhat difficult to reconcile the literature on HPA function in maltreated children versus in adults with a history of maltreatment because, as mentioned above, most studies of maltreated children have focused on basal cortisol whereas most studies of adults have focused on stress reactivity. Although maltreated children with PTSD have basal cortisol levels equal to or higher than normal controls, some evidence suggests that adults with PTSD who were physically or emotionally abused as children have low basal cortisol (Roy, 2002; Yehuda et al., 2001). This transition from hypercortisolism in maltreated children to low basal cortisol levels and reduced stress reactivity at the level of the adrenal in adulthood is particularly interesting in light of a normative developmental change in basal cortisol levels. In typically developing children, basal cortisol levels, particularly morning values, increase from childhood through adolescence, and the timing of this increase has been linked to pubertal status (Halligan et al., 2004; Netherton et al., 2004). It may be that HPA function remains under social regulation to some extent throughout childhood, and that puberty signals the end of the human stress hyporesponsive period and the full maturation of the diurnal rhythm. This hypothesis would be consistent with the findings of hypercortisolism in maltreated children, who are likely to have inadequate social supports. A longitudinal study of sexually abused girls has documented this transition from hypercortisolism to hypocortisolism, reporting elevated basal morning levels at around age 11 (De Bellis and Putnam, 1994) and low basal levels at around age 18 (Putnam, 2003). Additional longitudinal studies are needed to trace the impact of early maltreatment on HPA function from childhood through the pubertal transition. Such research may help us begin to integrate the child and adult literatures on maltreatment and HPA function.

One limitation on interpretation of the existing literature on child maltreatment and HPA function is that the effects of early maltreatment are powerfully confounded with current life stress and current degree of social support (see Kaufman et al., 1997). When alterations in HPA function are observed, do they reflect the adversity and lack of sensitive, responsive care in early childhood, or current adversity and current lack of sensitive, responsive social supports, or an interaction of these experiences? Longitudinal studies could begin to address this confound by at least measuring current life stress and social supports. To isolate the effects of early neglect or maltreatment, however, there is a need for data on children who experienced a circumscribed period of early deprivation followed by a transition to an adequate environment where chronic adversity is less likely. Internationally adopted, post-institutionalized children may be a good model, at least of a circumscribed period of neglect. These children were reared in orphanages prior to adoption, and while institutionalized, they lacked a stable caregiver and may also have been deprived of adequate nutrition, medical care, and cognitive stimulation (Gunnar et al., 2000; Johnson, 2000). Following adoption, physical growth and behavioral development improve rapidly and dramatically, suggesting that the period of deprivation has ended (Johnson, 2000; Rutter et al., 1999; Ames, 1997).

As noted, institutionalized toddlers in Russia and Eastern Europe have blunted early morning cortisol levels and no consistent change in cortisol levels over the course of the day.
(Carlson et al., 1995; Carlson and Earls, 1997; Kroupina et al., 1997). This distortion does not appear to be permanent; however, Fig. 4 illustrates that following adoption, HPA function appears to rebound as well. Post-institutionalized children eventually establish a fairly normal diurnal cortisol rhythm (Gunnar et al., 2001; Kertes et al., in press). Limited data suggest that children who experienced the most severe early deprivation while institutionalized show slightly higher early morning cortisol levels and/or slightly elevated cortisol at some point during the day (Gunnar et al., 2001; Kertes et al., in press). As shown in Fig. 5, children whose orphanage care resulted in more severe growth delay had significantly higher early morning cortisol levels an average of 7 years after adoption than did those whose care resulted in more typical growth patterns (Kertes et al., in press). Based on the animal literature, we would expect that, despite only small changes in basal cortisol activity, early deprivation might produce larger or more prolonged cortisol increases to psychologically stressful events. As yet, there is no data on HPA response to psychological stressors among post-institutionalized children.

Another emerging body of research focuses on candidate genes that may help account for the observed heterogeneity in behavioral outcomes of maltreatment. Studies of risk and resilience note the many psychosocial factors that influence outcomes of maltreatment (Masten et al., 1990). Genetics undoubtedly plays a role as well. Childhood abuse survivors appear to be less likely to develop depression if they carry the long version of the serotonin transporter (SERT) gene than if they carry the short version (Caspi et al., 2003; Kaufman et al., 2004). Similarly, childhood abuse survivors appear to be less likely to develop antisocial behavior problems if they carry a version of the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) gene permitting high levels of MAOA expression appear to be less likely to develop antisocial behavior problems than if they carry a version of the gene associated with low levels of MAOA expression (Caspi et al., 2002). These studies illustrate an interaction between environmental and genetic risk factors in the etiology of psychiatric disorders. Some of the candidate genes that appear to moderate the impact of childhood maltreatment on risk for psychiatric disorders may operate, at least in part, by influencing the sensitivity of the HPA axis to early stressful life events. Peer-reared rhesus macaques have smaller ACTH responses to separation if they carry two copies of the long SERT allele (Barr et al., 2004). In addition, rhesus infants who experience repeated, unpredictable separations exhibit smaller HPA responses to separation if they carry two copies of the long SERT allele (Sanchez et al., 2005). Buffering of the HPA response to stressors among offspring with the long SERT gene may help explain their protection from developing internalizing-type behavior problems. If these findings can be replicated in the human maltreatment literature, it would also help to explain why the effect of maltreatment on HPA function varies according to psychiatric diagnosis.

Child maltreatment clearly has complex, long-term effects on HPA function, which likely have deleterious implications for physical and mental health. There are two glucocorticoid receptors in the brain with opposing effects, and optimal HPA function is thought to depend on the ratio of activation of these two receptors (De Kloet, 1991). Mineralocorticoid receptors (MRs), which have a higher affinity for cortisol (bind more readily) and are 80–90% occupied at basal levels of cortisol, maintain the HPA circadian rhythm, blood pressure, cerebral glucose availability, and neuronal responsivity, keeping the body ready to mount an effective fight-or-flight response when needed. Glucocorticoid receptors (GRs), which have a lower affinity for cortisol and are typically only occupied at the morning peak of the HPA circadian rhythm or during a stress response, mediate most of the stress effects of cortisol (Sapolsky et al., 2000). If basal levels of cortisol are chronically high, as has been observed in maltreated children, GRs will be chronically occupied, which can result in immune suppression, reduced synaptic plasticity, and other deleterious effects (Sapolsky et al., 2000). Moreover, chronically elevated cortisol and CRH during development, when brain circuits are still
maturing, appears to shape the way these circuits interpret environmental threat and the magnitude and duration of stress responses in the future, which can result in increased vulnerability to stress and increased risk of developing mood or anxiety disorders (Heim and Nemeroff, 2001). On the other hand, chronically low levels of basal cortisol, such as those observed in some adults with a history of child maltreatment, can also have deleterious effects on health and behavior because not enough MRs are occupied and thus the body is not as prepared to cope effectively with stressors (De Kloet, 1991; Sapolsky et al., 2000).

Even though the alterations in HPA function associated with child maltreatment are likely detrimental in the long term, they were initially adaptive responses. For a maltreated child, chronically elevated cortisol levels and a heightened state of vigilance may well be adaptive in the context of coping with the chronically stressful situation of having a maltreating caregiver. The difficulty is that because the HPA system is immature at birth and the developing brain circuits are shaped by early experience (Gunnar and Vazquez, 2006), the adaptive response to the maltreating context has long-term effects on how the brain will respond to stress, a response pattern that may be much less adaptive outside of the maltreating context. Some individuals become more vulnerable to future life stresses, developing a lower threshold of perceiving stress and an exaggerated stress response. This stress vulnerability may leave individuals at greater risk of developing mood or anxiety disorders (Heim and Nemeroff, 2001), although the hypothesis that disturbances in CRH and cortisol during development are critically important to probe the HPA axis in ways not ethically provoking an HPA response in children, animal models are needed. Studies spanning the pubertal transition are particularly needed, along with studies of the role of candidate genes in moderating HPA responses and research on the effectiveness of environmental interventions. Further, because of the difficulty of ethically provoking an HPA response in children, animal models are critically important to probe the HPA axis in ways not possible with children, and thereby to help explicate mechanisms and inform future clinical research. Ongoing coordination between animal research and clinical research will be crucial.

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