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Association of Post-Traumatic Stress Disorder (PTSD) in Children and HPA Axis Regulation

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ABSTRACT

Over the past decades, numerous findings have shown that exposure to stress or trauma during the critical period of early development can elicit adverse impacts on the psychological processes and physiological functioning of the body. Precisely, early life stress is associated with a greater risk of developing mental disorders or physical conditions later in life. Accordingly, early life adversity may alter children's regulation of secretion of neurobiological substrates, as well as influence the sensitivity of their response to stimuli such as stressors. Children who encountered a traumatic event, such as natural disasters, sexual or physical abuse, may develop post-traumatic stress disorder (PTSD), which may in turn disturbed the development of HPA axis and other neuroendocrinal systems which regulate the body's response to stressors. However, the degree and manner of which childhood stress impacts the regulation of the HPA axis remain unclear and conflicted. Several studies have reported that abused children demonstrated substantially higher morning cortisol levels, which is regulated by the HPA axis, than non abused children. Other studies, however, have shown contradicting results

Keywords: Adolescent, childhood trauma, corticotropins, cortisol, HPA axis regulation, post-traumatic stress disorder

INTRODUCTION

The term "stress" is used to define any stimulus that disrupts homeostasis, or challenges the body psychologically and emotionally(1). Childhood maltreatment, neglect, or early life stress can result in adverse health conditions, including disorders of heart and blood vessels, abnormal immune regulation, and neurological disorders, including major depressive disorder (MDD)(2-4). When the hypothalamus encounters a "stressor", corticotropin-releasing hormone (CRH) and vasopressin are released(4). The anterior pituitary gland is stimulated by CRH to release corticotropin and corticotropin, which activates the adrenal cortex to produce glucocorticoids (GCs)(5). The main function of glucocorticoids is to restore the body's balance after being stimulated(6, 7). This review aims to determine the effects childhood trauma and post-traumatic stress disorder (PTSD) in children have on the regulation of HPA axis.

Post-traumatic stress disorder (PTSD)

People who have experienced a severely damaging or disturbing event may develop post-traumatic stress disorder (PTSD), which is related to the dysfunction of the hypothalamic- pituitary-adrenocortical (HPA) axis(8). The hyper-activity of the neurobiological system that responds to threat (the sympathetic nervous system), and the hypo-activity of the HPA axis is hypothesized to be a risk factor of PTSD development, due to the failure to synchronize with other neurobiological systems(7,9). In adults, being exposed to trauma can increase the risk of PTSD and the possibility of a blunted response to cortisol. In addition, children who experience trauma are also critically at risk of PTSD(10). However, studies show that childhood trauma includes different kinds of

abuse, ranging from sexual to emotional abuse, which is less explicit(11). Additionally, the animal models designated to reinforce the theory that childhood abuse results in higher vulnerability to PTSD do not prove childhood abuse to be the essential leading factor(12). On the contrary, the significant factor that alters the development of the HPA axis and systems involved in trauma response is the absence of parental stimulation(13,14).

Development of HPA activity during childhood

At birth, the HPA axis has already become greatly responsive towards stressors, and its responses can be observed as early as 18-20 of pregnancy (15,16). Eighty percent of circulating cortisol in adults is considered inactive as it is bound to corticosteroid-binding globulin (CBG) (5,17). In newborns, however, CBG levels are lower and do not rise up to adult's level until six months(18). Therefore, newborns' plasma cortisol's level is low, then increases over the first few months after birth(19). Their free cortisol, however, is higher than the levels observed in older children(20, 21). Furthermore, measures of salivary cortisol display elevations of cortisol levels in response to even slight disturbances (20, 22,23). At the age of six months, the HPA axis can be considered somewhat matured(24,25).

At one year of age, infants' HPA axis gradually becomes less responsive, and can hardly be stimulated to elevate the cortisol level (26,27). This hypoactive regulation of the HPA axis reflects that during the first years of life, children's reactivity to stress is buffered by the presence of their parents (13,28). Children may show small elevations in cortisol level in response to stressors, but only a few cases of children display these shifts(29,30).

Data has suggested that the increase of reactivity in the HPA axis and neurobiological systems in adolescence may result in an enhanced sensitivity to stressors(6, 24). Evidence now shows that the basal cortisol level rises as children transition into adolescence, which may correlate with puberty (29,31,32). Additionally, a recent study suggests that teenagers with higher pubertal development reflect a higher overall diurnal cortisol level throughout a day (24,29,33). During puberty, the HPA system matures and its responses to stimulus becomes more adult-like(24). Conclusively, the influence of early-life parental care on the HPA axis and cortisol regulation may not be apparent until puberty (30,31).

The Stress Response of the HPA axis and cortisol

Cortisol, the HPA axis's final output, can be evaluated noninvasively with three methods that reflect distinct hidden mechanisms: the cortisol awakening response (CAR), daily patterns, and response to laboratory stressors(23, 34). CAR is a term which refers to an increase in cortisol that arises naturally simultaneous with waking up (21,35). Furthermore, it can be disturbed by various factors such as sleep and day-to-day distress(36, 37). Cortisol levels decrease throughout the day due to the time-dependent regulation of the suprachiasmatic nucleus (SCN) of the hypothalamus, so a decreasing slope of cortisol level throughout the day indicates a healthy and flawlessly functioning system(38). Finally, measuring the body's reactivity to an acute stressor can indicate the pace or intensity with which the hypothalamus initiates the HPA axis(15). In contrast, cortisol level's restoration from acute stress may reflect the effectiveness of cortisol's negative feedback on the axis(39). Cortisol, produced and released diurnally by the adrenal cortex, is a critical catabolic hormone, peaking to promote waking in the morning and gradually dropping thereafter(39,40). Cortisol maintains blood glucose levels and, with the purpose to preserve and provide energy to the brain and the neuromuscular system, the hormone suppresses non-vital organ systems(41,42). Moreover, cortisol has an

anti-inflammatory effect which prevents damage caused by inflammation to linger and spread among tissues and nerves (43, 44). Besides serving a critical role in everyday operation of the body, cortisol acts as a vital component of stress response(45). When confronted with a threat, whether physical or psychological, cortisol levels rise, providing the abilities and substances required to deal with stressful stimuli or to flee(46). While increasing the rate of cortisol secretion is a short-term response to stimuli, it is possible that the body's physical and psychological health reaches an adverse condition if the secretion of cortisol is prolonged or excessive(47-49).

To be expected, the HPA axis receives the most significant amount of repercussions in comparison to other neuroendocrine systems adversely affected by childhood stress(13,31). The harmful impacts of stress on the HPA axis function during critical developmental stages may jeopardize normal development and may extend into adulthood(50-52). Numerous studies have demonstrated a positive correlation between early-life stress and abnormally active HPA axis in healthy adults and those diagnosed with depression or PTSD(9,31). This hyperactivity of the HPA axis is evaluated by the substantial increase in levels of peripheral cortisol and cortisol awakening response, as well as higher response of adrenocorticotropic hormone and cortisol to stressful events(6, 51). In contrast, several other studies using comparable scope of populations and designs have shown a contradicting result reflecting a positive correlation between early-life stress and abnormally slowed and deficient activity or hypoactivity of the HPA axis, whose consequences are decreased peripheral cortisol levels and blunted cortisol responses to psychosocial stressors(9,29,39). Other studies found no effect of early-life stress influence on cortisol awakening response or CAR, as well as the absence of correlation between early-life stress and HPA axis reactivity to acute stressors(10,34).

A study has found a correlation between physical neglect as a child and lower hair cortisol concentrations in some individuals (53,54). Ultimately, a statistical analysis that combines multiple studies on the relationship between early-life stress and cortisol has presented an informative outcome(21). There were no significant relationships between early-life stress and CAR, baseline or reactive cortisol level, or cortisol reactivity (10,55). In spite of that, when blood samples were collected from individuals who had experienced early-life stress, namely, sexual, physical, or emotional abuse, an increased in CAR was detected(23,56,57). In addition, early-life stress was discovered to be related to a blunting effect of cortisol (45,58). Different search results may consequence from various factors, including different definitions of early-life stress, which may be sexual, physical, or emotional abuse or even neglect, the number of episodes having occurred, and the duration of adverse events which have accumulated, as well as different ages at which abuse occurred, as well as the presence or absence of psychosocial support, and genetic and epigenetic influences(2,59).

The precise timing of early-life stress, however, is likely to be the most critical factor in later life HPA axis modulation(39,60). More precisely, the period ranging from infancy to early childhood, or zero to five years of age, are critical stages of brain development. After an initial period of hyper-responsiveness, the HPA axis may transition to a hyporesponsive stress state of decreased CAR, basal cortisol, and reactive cortisol level (61,62). Numerous studies that repeatedly observe the same individuals have demonstrated that stress responsiveness may decrease with age throughout early childhood (31,63). The transition, as mentioned earlier, from a hyper-responsive to a hyporesponsive HPA axis during the first five years of life is a crucial mechanism for HPA axis development(64). Being exposed to early-

life stress during the first two years of life may result in prolonged cortisol response to an acute stress during adolescence(31). Therefore, the co-occurrence of early-life stress and raised glucocorticoids levels during the hypo-responsive period may result in progressive glucocorticoid receptor insensitivity, impairing the development of HPA axis (59,65). Additionally, adolescence is a susceptible developmental stage. During adolescence, the HPA axis alters to become more responsive, as evidenced by progressive increases in basal and reactive cortisol levels (11,20). The correlation between early-life stress and the HPA axis modulation during adolescence have been hypothesized to be the opposite of that in childhood, as evidenced by decreases in baseline cortisol level and blunted cortisol responses to social stressors (64). These age-dependent influences of childhood stress on HPA axis modulation are thought to contribute to specific mental disorders during late-life(66,67). If a child experiences trauma, the risk of the child developing a major depressive disorder or post-traumatic stress disorder (PTSD) later in life is equal(60). If, on the other hand, the trauma occurs during adolescence, the risk of developing PTSD is greater than the risk of developing depression(68, 69).

The HPA Axis - Pediatric PTSD relationship

The distinction between long-term (chronic stressors), for example, child neglect, sexual abuse, exploitation, maltreatment, and short-term (acute stressors), for example, serious accidents, injuries, or natural disasters, may cause the symptoms and alterations in the neural and endocrine system to be different (12,70). Child neglect and maltreatment frequently occurs in conjunction with the parent's abnormal mental states, which may suggest the presence of innate biological risk factors or social risk factors such as poverty, drugs or alcoholism (1,71). Additionally, apparent dissociation is hypothesized to be associated with recurring trauma instead of a single trauma experience (72-74). In fact, studies have shown associations that are independent between a single type of childhood trauma and the quality of mental health conditions in adulthood(75). However, different types of childhood trauma have a cumulative adverse effect on the symptoms of PTSD and depression in adults, scaling with different degrees of exposure(75).

Various studies have been conducted to determine alterations in the neuroendocrine system of adults with PTSD (31). Most of them have shown decreased cortisol levels throughout 24 hours, elevated basal corticotropin-releasing hormone levels in cerebrospinal fluid, along with decreased cortisol levels throughout 24 hours, and decreased salivary or urinary cortisol concentrations(8,48). Nonetheless, other studies have revealed contradictory findings; individuals with PTSD demonstrated elevated urinary cortisol excretions or concentrations which are equivalent to individuals who do not suffer PTSD(76). Concerning the sympathetic nervous system, catecholamine levels in the urine, plasma, and CSF have consistently been elevated in adults with PTSD. However, children may respond physiologically to acute or chronic stressors differently from adults(77). To be more precise, a study has shown that sexually abused girls demonstrated significantly higher day-and-night catecholamine and metabolite urinal concentrations than non-abused girls(78). Additionally, they had lower basal and lower stimulated plasma adrenocorticotropic hormone levels in the evening, in contrast, their plasma cortisol response to corticotropin-releasing hormone injection and that of non-abused girls were equivalent(65). Furthermore, a day camp research program performed a test on children who experienced a range of maltreatments, which included child neglect, abuse, and various disruptions of caregiving (13,79). The findings suggested a noticeable difference in average cortisol concentrations, from morning to afternoon,

depending on the types of trauma the children encountered(79). To be exact, morning salivary cortisol levels were remarkably higher in a group of children who had been subjected to both physical and sexual abuse, as well as another group who experienced both neglect or mental abused(56). However, a subgroup of children who had only experienced physical abuse demonstrated lower morning cortisol levels and showed less morning-to-afternoon drop in cortisol concentration(80). This result is supported by another research program which suggested that foster children subjected to adverse childhood experiences were significantly more likely to have lower morning cortisol levels than children who were not maltreated (13,80). Moreover, lower morning cortisol levels are associated with higher severity of physical neglect in foster children. In contrast, higher morning cortisol levels reflect more severe emotional abuse(13).

Even though the studies above present contradictory results, altogether, the findings support the concept that cortisol regulation patterns and the functioning of the hypothalamic pituitary adrenocortical system vary according to specific types of childhood stress or adverse experiences(31). Concerning the dysregulation of the autonomic nervous system in abused adolescents, an imbalance between salivary alpha-amylase concentrations, which indicates the activity of the sympathetic nervous system, and cortisol responses to a social stressor has been detected (81-83). The researchers concluded that childhood stress from being maltreated might disturb the synchronization between the asymmetry between the sympathetic nervous system and the HPA axis, or reduce the intensity of one system's response but not the others. Furthermore, a study of abused girls ranging from 12 to 16 years of age found that the abused group exhibited a blunted HPA axis response to the Trier Social Stress Test (TSST)(37). On the other hand, the non-abused girls, or the control group, demonstrated an increase in cortisol levels following the TSST, which gradually dropped back to non-stress level over time(25). Nonetheless, the maltreated youth who demonstrated blunted HPA axis reactivity was not associated with depression or symptoms of PTSD(84). Moreover, long-term repeated observations examining non-stress cortisol levels in mistreated girls at six points in time from age 6 to 30 year old have provided evidence which supports the concept that an abnormal reduction in cortisol secretion may occur after a duration of increased cortisol secretion in abused victims (13,21,85).

CONCLUSION

In conclusion, children who lack adequate parenting and experience trauma or abuse demonstrate that the HPA axis is strongly regulated early in life. Variations in parental care have significant and various effects on the axis's concurrent regulation. Social regulation failures of the HPA axis in young children due to insufficient or abusive care may result adversely in systems involved in processing traumatic experiences. Ultimately, exposure to early-life stress during vulnerable periods of HPA axis development significantly increases the danger of developing PTSD or psychiatric disorders later in life. Therefore, adequate and effective parenting is extremely crucial and required for a child to develop a healthy mental and physical health when progressing into adolescence and adulthood.

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