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The influences of genes and early life stress on the HPA axis regulation

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ABSTRACT

Stress is considered as an uncontrollable and/or unpredictable cognitive perception expressed in physiological and behavioral responses, causing adverse emotional reactions and life events if not handled appropriately. HPA axis as a key regulator for adaptation to social and physical stressors, which is more sensitive to the adverse effects of life events during early childhood and adolescence periods. This may result in alterations in adult behavior and physiology as well as in individual differences in response to later stress exposure. The enduring effects of early life stress on gene expression may cause impaired HPA axis functioning, resulting in behavior and physiological alternation. This thesis will focus on the effects of early life stress on HPA axis regulation and genes which mediate the effects of ELS on risk for physiological disorder development by regulating or interfering with the HPA axis.

CONTENTS

Introduction

Stress is considered as the cognitive perception of an uncontrollable and/or unpredictable situation expressed in physiological and behavioral responses (Koolhaas et al., 2011), and can be characterized by the absence of an anticipatory response or a reduced recovery of the neuroendocrine reaction (Koolhaas et al., 2011). These stressors refer to unpredictable or uncontrollable situations that exceed the natural regulatory capacity of an organism (Koolhaas et al., 2011). In addition, organisms also feel stress under the situations that threaten their security and evoke the classical fight-or-flight response (McEwen, 2016). The ability to respond and adapt to stress differs from person to person. Individuals who are able to handle stress may eventually go through tremendous suffering and keep moving forward. While others, easily beaten by stress, may thus get stuck into depression and develop stress-induced disorders over time. Thus it is worth considering what are the factors that cause this difference.

It is now well-accepted that genetic factors and environmental influences across the lifespan together likely underlie stress vulnerability. Early life stress (ELS) refers to a wide range of adverse and stressful experiences (such as sexual abuse, physical abuse, extreme poverty, parental loss, domestic or school violence) during the first few months of life, early and late childhood and adolescence (Shonkoff et al., 2009; McEwen, 2016). It plays an essential role in the development of brain structure and neurological capacity associated with the determination of physiological and pathological onset later in life, and ELS have occurred in childhood period is considered as a risk factor of stress-induced disorders. On the other hand, multiple genetic factors were reported to associate with individuals' response and adaptation to stress. Thus, the interaction of genes and ELS might be a key factor that affects the alternation of the response system.

In this essay, I would like to discuss the following three aspects. Firstly, understanding and defining the dynamic concept of stress and response system. Secondly, clarifying sensitive periods when the ELS affects individual response and adaptation to stress. Thirdly, identifying several important genetic variations involved in the stress response system and their interaction with ELS, which mediates long-lasting alternations in the response and adaptation to stress.

Understanding of stress and response system

The brain is organizing response and adaptation to physical and social stressors (McEwen, 2007), playing a vital role in recognizing perceptual information as potential stressors and initiating physiological and/or psychological responses (McEwen, 2016). It regulates and directs peripheral systems, including endocrine, metabolic, cardiovascular, immune systems which are needed to successfully adapt to the stressor (McEwen, 2016; McEwen, 2006). Thus, it is essential to understand how the brain and body handle stress and maintain homeostasis. In this case, the term allostasis is introduced to refer to an active process of adaptive bodily responses to stressors for maintaining homeostasis, following the changes in “set-points” and other boundaries of control (McEwen et al., 2003). This can be carried out by means of alternation in hypothalamic-pituitary-adrenal (HPA) axis hormones, the autonomic nervous system (ANS), and a wide range of other systems to adapt to stress in the short term (McEwen et al., 2003). During the process of allostasis, the activity levels of primary mediators are altered and sustained in response to physical and social stressors (McEwen et al., 2003). However, sustained or inadequate allostasis can lead to disease, in which case allostatic load is introduced (McEwen et al., 2003). Allostatic load refers to the wear and tear

that occurs when organisms fail to shut off the stress response when no longer needed (McEwen et al., 2006). In this case, energy supply exceeds demands while the organism continues to take in and store as much energy than it needs. Another type of allostatic load involves not turning on sufficient stress response due to inadequate energy income (McEwen et al., 2003). In this case, energy demands exceed energy income, resulting in the induction of overreacted glucocorticosteroids' (GCs) secretion and other mediators' activity (McEwen et al., 2016). Thus the allostatic load is a process of chronic elevation of the allostatic changes in same mediators producing chronic wear and tear, which accumulates repeated chronic physiological and psychological consequences, leading to pathological conditions (McEwen et al., 2006; Heim et al., 2009).

Hypothalamic-pituitary-adrenal (HPA) axis is the main regulator of stress

The primary physiological role of the central nervous system (CNS) is to sense the external environment and assess its impact on the fitness of the organism (McEwen, 2007). CNS modulates the internal physiological activities to adapt to the external environment optimally (McEwen, 2007). In response to the threats of the environment, the CNS signaling occurs through the release of noradrenaline from nerves of the sympathetic nervous system (SNS) or GCs (cortisol in primates and corticosterone in other mammals) from the HPA axis (McEwen, 2007). Noradrenaline responds quickly and it just takes few seconds to release when the body needs the most energy to adapt to acute threat (for example, fight-or-flight stress responses) (Granger et al., 2007). On the other hand, GCs responds slowly and reaches a peak at around 20 min after a stressor's onset (Nicolson, 2008). Therefore, GCs are mostly used to measure enduring stress rather than a short stressor (Sumter et al., 2010). From the perspective of individual survival and health, the HPA axis plays a critical role in mediating the metabolic and cardiovascular function that restores homeostasis while facing acute or chronic stressors by provoking the systemic release of GCs. (Sapolsky et al., 2000). The paraventricular nucleus (PVN) of the hypothalamus is the area with the highest concentration of CRH (Swanson et al., 1983). The PVN also synthesize and secrete vasopressin, which interacts with CRH to regulate the pituitary gland and stimulate the release of adrenocorticotropic hormone (ACTH)(Shekhar et al., 2005; Jacobson et al., 1991). ACTH then stimulates the adrenal cortex to produce and secrete GCs (Nemeroff, 1996). GCs, which serve as the critical end product of the HPA axis, in turn, act on almost all cells in the body and have a negative feedback on the production of CRF and ACTH by stimulation of glucocorticoids receptor (GR) in the hypothalamus and pituitary (Nemeroff, 1996; Jacobson et al., 1991). These suppressive GC actions prevent the excessive release of GCs, so the stress response is inhibited and return to baseline conditions (Sapolsky et al., 2000).

On the other hand, recurrent or persistent activation of the HPA axis leads to chronic dysregulation of the HPA axis, which is associated with the pathophysiology of stress-related diseases (Arnett et al., 2006). For example, studies in human have demonstrated that dysregulation in cortisol reactivity is a prominent neuroendocrine feature in patients with mood and anxiety disorders (Heim et al., 2008). Chronic hyperactivation of the stress system is related to an increased secretion of CRH and arginine vasopressin (AVP) expression by the hypothalamus and ACTH hypersecretion by the pituitary (Herman et al., 1995; Makino et al., 1995). This will lead to higher circulating cortisol levels and HPA axis hyperactivation over time(Herman, 2013), resulting in insensitive negative GCs feedback of the HPA axis loop (Stetler et al., 2011). The chronic HPA axis hyperactivation is widely reported in major depression and also found in some anxiety disorders (Charmandari et al., 2005). HPA axis hypoactivation is another type of HPA axis

dysregulation that has been found associated with psychological disorders. HPA axis hypoactivation is characterized by lower circulating cortisol levels and blunted cortisol stress responses (Carpenter et al., 2011; Suzuki et al., 2014). Exposure to an acute stressor cause HPA activation resulting in an increased cortisol output, but if the stressor persists for a prolonged period of time, the negative feedback loop of HPA axis can mount a long-term counter-regulatory response, leading to a sustained and lower cortisol output (Gunnar & Quevedo, 2007). This diminished activity could be related to a negative feedback hypersensitivity of GC through the up-regulation of GC-receptor (GR) number and sensitivity (Heim et al., 2001; Heim et al., 2008; de Kloet et al., 2007) The typical example of hypoactivation of the HPA axis is post-traumatic stress disorder (PTSD) (Rohleder et al., 2010). These results indicate that GC signaling has a particularly important role in the pathophysiology of excessive stress exposure. Impaired GC signaling, which caused by hyper- or hypoactivation of the HPA axis, could lead to allostatic load that has debilitating effects on physiological development and have close association to chronic physical and mental disease (Yehuda et al., 2011; Carpenter et al., 2011; Suzuki et al., 2014; Rohleder et al., 2010).

Early life stress (ELS)

Excessive stress exposure, especially in stress-sensitive developmental stages of higher brain plasticity, may oversensitized or undersensitized HPA responses to stress, leading to allostatic load with profound and detrimental effects on the physiology of the organism, as seen in the development of stress-related disorders (Heim et al., 2001; Lupien et al., 2009; Koolhaas et al., 2011). The term early life stress (ELS) describes a wide range of adverse and stressful experiences (such as sexual abuse, physical abuse, extreme poverty, parental loss, domestic or school violence) during the first few months of life, early and late childhood and adolescence (Shonkoff et al., 2009; McEwen, 2016). ELS could contribute to prolonged psychoneurobiological alterations, which is characterized by an increased risk factor of disease development in later life (Agorastos et al., 2019). Emerging scientific studies indicated that adult stress-related disorder is related to adverse experiences occurring during the early life period (Shonkoff et al., 2009; McEwen, 2016). A 5-fold increase in the risk of attempted suicide in adulthood has been reported in people who have experienced any childhood adversity (Dube et al., 2001). Increased risk for depressive disorders has been found in the population who have suffered parental loss or separation (Agid et al., 1999). Those children who experienced evaluated parental neglect and emotional abuse have been found to have lower stress management abilities and higher levels of anxiety (Heim et al., 2009). While not all individuals exposed to ELS go on to develop stress-related disorders and adapt to subsequent stress in adulthood (Heim and Binder, 2012). It is worth noting that what factors may play roles in outcome variability in the effects of ELS. The severity of physical and psychological consequences may be associated with the specific timing of ELS could have enduring effects on downstream biological pathways. Furthermore, the interaction of stress-related gene expression and ELS could influence the secretion and action of GCs in the brain and explain inter-individual variation in vulnerability to stress response and later behavior.

Sensitive periods for the effects of ELS

Experiences of early life affect the developing nervous system, leading to individual differences in physiological stress responses and variations in later behavior. The main reason for the strong association between various forms of early life stress and depressive symptoms or disorders is that ELS has different

impacts on HPA axis activity depending on the sensitive developmental period of exposure (Heim et al., 2001). Critical periods refer to time windows where expected experiences are necessary for HPA axis function to develop normally. The HPA axis appears to progress rapidly during early childhood and adolescence, which may provide periods of vulnerability. Although the prenatal period is a critical period during which the brain regions involved in HPA axis regulation, such as hippocampus, frontal cortex and amygdala start to develop (Lupien et al., 2009), the maturation rates and extent of brain plasticity across development drastically differ during early childhood and adolescence (Lupien et al., 2009). Therefore, the HPA axis may be particularly sensitive to environmental factors, positive experiences as well as the negative experiences, during these sensitive periods.

Early childhood

Early childhood (0-5 years) represent one of the most vulnerable periods in HPA axis functioning (Gunnar and Donzella, 2002; Kuhlman et al., 2017; Tallot et al., 2016). Early childhood is a period of rapid growth and development of the HPA axis, and excessive cortisol can have detrimental effects on development (Kuhlman et al., 2017). In the first two to three months after birth, the HPA-axis exhibits hyperactivity and hyperresponsivity to stress response with higher cortisol levels (Gunnar et al., 2009a; Larson et al., 1998), and may later transition into a stress hyporesponsive period, which is characterized by lower basal cortisol levels and blunted cortisol reactivity (Daskalakis et al., 2013; Kuhlman et al., 2017; Tallot et al., 2016). The shift from a hyper- to a hyporesponsive stress axis in the first five years in life may represent a particularly important stress-sensitive period (Daskalakis et al., 2013). Particularly, ELS exposure during this period may interfere in the normal development of a hyporesponsive HPA-axis, resulting in higher basal cortisol and enhanced cortisol responses to stress. Several studies have shown that cortisol level at baseline and response to stress increased in infants and children with ELS exposure. For example, higher baseline cortisol has been found in infants whose mothers have depression history (Brand et al., 2010), potentially because depressed mothers hardly provide attentive and attached parenting (Lovejoy et al., 2000; Pereira et al., 2012). Similarly, maternal emotional withdrawal also has been associated with elevated basal cortisol level among 18 months old children(Bugental et al., 2003). More direct evidence of the continuous impact of ELS on the HPA axis hyporesponsive period comes from a study focusing on the developmental trajectory of stress response of HPA axis from infancy to early childhood (Hibel et al., 2009). In this study, a trajectory of increased cortisol response against 7 to 24 months challenge task has been reported among children who have witnessed interparental violence, while their non-exposed counterparts showed a trajectory of decreased cortisol response (Hibel et al., 2009). Kuhlman et al. showed that children who are exposed with ELS in the first year in life showed a prolonged cortisol reactivity to acute social stressors in their adolescent period (Kuhlman et al., 2015). Adversity exposure during early childhood may also result in elevated cortisol (Bair-Merritt et al., 2012; Bush et al., 2011). In cross-sectional analyses, higher levels of total cortisol output have been found among 5-year-old children who are exposed to inter-parental violence during the last 12 months, accompanying with various family adversity such as financial stress, parenting overload, maternal depression, and harsh parenting (Bair-Merritt et al., 2012; Bush et al., 2011). Additionally, adversity exposure during infancy is associated with flattened diurnal cortisol slopes and higher cortisol levels (Kuhlman et al., 2017). While, nurturing caregiving is believed to play an important role in keeping cortisol at relatively low levels by blunted cortisol responses, which have social buffering effects on optimal development (Kuhlman et al., 2017). The cortisol levels have been tested in infancy and children who received nurturing caregiving during ELS exposure: a blunted cortisol responses during

maternal separation with the responsive caregiver was observed in 9 months old infants (Gunnar et al., 1992). Bernard et al. reported that 13-month old previously maltreated children who were placed in foster care (a kind of environmental regulation) with the protection services exhibited steeper diurnal cortisol slopes compared to those who remain with their parents with potential maltreatment (Bernard et al., 2010). Therefore, environmental regulation which may have compensatory effects, as a social buffer, so that the HPA axis works in a resembling way that steeper diurnal cortisol slopes (Bernard et al., 2010). While, if lack social buffering, ELS could possibly lead to increased and prolonged cortisol levels (Kuhlman et al., 2017), subsequently, contributes to GR insensitivity and thus altering the physiological of HPA axis development (Kuhlman et al., 2017; Cohen et al., 2012). This could be speculated that GR insensitivity may cause a disruption of HPA axis feedback loop regulation, leading to continued heightened basal cortisol and delayed recovery from later stress exposure (Kuhlman et al., 2017).

In sum, the shift from a hyperresponsive to hyporesponsive of the HPA axis in the first five years in life may represent a particularly crucial sensitive period to stress exposure (Gunnar and Donzella, 2002; Daskalakis et al., 2013). Nurturing caregiving, which has social buffering effects on optimal HPA axis development, plays an important role in keeping cortisol at relatively low levels by blunted cortisol responses (Kuhlman et al., 2017; Tallot et al., 2015). However, ELS during this first sensitive period may lead to a hyperactivity and hyperresponsiveness of HPA axis with higher cortisol levels at baseline and in response to stress, which cause excessive cortisol and may have detrimental effects on development (Gunnar et al., 2009; Larson et al., 1998; Kuhlman et al., 2017).

Role of puberty/adolescence

The age of human adolescent development is roughly between 10 and 18 years old (Eiland and Romeo, 2013). In mice and rodents, the puberty refers to the postnatal period ranging from weaning to puberty (ranging from 30 to 60 days of age) (Eiland and Romeo, 2013). The developmental stage of puberty/adolescence is a second sensitive and vulnerable period that causes functioning changes in HPA axis activity (Somerville et al., 2010). From childhood to adolescence, the HPA axis shifts from hyporesponsivity to hyperresponsivity with higher basal and reactive cortisol levels (Gunnar et al., 2009). Puberty is marked by fundamental modifications in both the hypothalamic-pituitary-gonadal (HPG) and HPA axis (Romeo, 2005), which result in very different levels of gonadal and adrenal steroid hormones (Ernst and Mueller, 2008). During puberty, the adrenal glands begin to secrete increasing amounts of gonadal steroids and adrenals, and both are the primary sources of corticosteroids (Ernst and Mueller, 2008). Although there is a slight increase in the secretion of corticosteroids during puberty, a dramatic increase in the release of corticosteroids is typically observed following a stressor in both human and animal studies (Sapolsky et al., 2000). The nervous system is exposed to significant and sustained increases in gonadal steroids during puberty, which could affect the stress response on the HPA axis (Ernst and Mueller, 2008). The emerging literature indicates that ELS exposure during pubertal development can lead to both short- and long-term changes in HPA reactivity. Also, the magnitude and duration differences in stress cause a dramatic change in corticosteroid response. Adults rats show habituated stress response to repeated same stressor exposure (Romeo, 2010; Romeo et al., 2013). In contrast, prepubertal rats (25–30 days of age) exhibit prolonged corticosterone responses to the same stressor compared to adults (>65 days of age), particularly in response to both physical and psychological stress (Romeo, 2010; Romeo et al., 2013). Specifically, after the termination of the stressor, prepubertal animals take double time to return to

baseline corticosterone levels compared to adults (Romeo, 2010). Another study showed that a long-term social stress procedure (7 weeks) from adolescence into adulthood found a sustained increase in basal corticosterone as much as a year after the stress exposure (Schmidt et al., 2007, Sterlemann et al., 2008). Similarly, blunted cortisol responses are found in the subsequent acute stress test among 9-12 years children who have exposed to ELS in the past month (Trickett et al., 2014). Therefore, ELS exposure during adolescence could cause higher reactivity cortisol levels and hyporesponsive HPA axis, resulting in blunted cortisol responses to later stress exposure (Vaillancourt et al., 2008; Trickett et al., 2014). On the other hand, the maturation of many brain regions involved in the modulation of HPA reactivity is likely to influence the HPA function and stress responsiveness during puberty (Romeo et al., 2006). For instance, the hippocampus and medial prefrontal cortex play important roles in corticosteroid-dependent negative feedback (Herman et al., 2003), because GR is distributed through the CNS, with a high concentration in the medial prefrontal cortex and in the hippocampus (Funder, 1994). A persistent decrease in expression of GR in the hippocampal formation has been found in long-term social stress procedure from adolescence into adulthood (Schmidt et al., 2007, Sterlemann et al., 2008, Uys et al., 2006), which suggests that the HPA negative feedback loop has a long-lasting impairment. Isgor and colleges reported that male rats experienced chronic ELS during adolescent maturation showed higher and prolonged corticosterone response to acute stress in adulthood compared to animals that were not exposed to chronic ELS during adolescence (Isgor et al., 2004). This study also reported that adolescent chronic ELS exposure resulted in lower levels of hippocampal GR accompanied by a delayed shutdown of the HPA response to acute stress in adulthood, in comparison to controls, suggesting reduced GC-dependent negative feedback (Isgor et al., 2004). Other findings also support the enduring effect of ELS on behavioral changes: adult rats exposed to adolescent chronic stress exhibit poor learning, decreased memory abilities and increased emotional reactivity (McCormick and Mathews, 2010, McCormick et al., 2010; Tsoory et al., 2006).

In general, the developmental stage of puberty/adolescence is a second sensitive and vulnerable period with a new major change in HPA axis activity (Somerville et al., 2010). The HPA axis shifts from hyporesponsivity into hyperresponsivity with higher basal and reactive cortisol levels from childhood to adolescence (Gunnar et al., 2009). In contrast to the nurturing caregiving of the HPA axis in earlier life, nurturing caregiving no longer buffers cortisol reactivity to stress during the adolescent period (Hostinar et al., 2015). The evidence for long-lasting effects of stressors in adolescence on adult HPA function is mixed (Fuhrmann et al., 2015). As autonomy and sexual maturation increase over the adolescent period, interaction with environmental cues may reprogram the HPA axis in a new confounder manner (Kuhlman et al., 2015). Gonadal hormones in adolescence may cause dynamic changes in the stress response system, which lead to enhanced early programming of the HPA axis in ELS (Heim et al., 2001). Maturation of brain regions that modulate HPA reactivity also influences the stress response system, which interacts with environmental factors to lead to enduring effects on HPA functional alternations.

The long-lasting effects of ELS on gene expression

In addition to timing effects of ELS, individual differences in response to later stress exposure and alterations in adult behavior may be mediated by enduring effects of ELS on gene expression. It is worth noting that not all individuals who are exposed to ELS develop further stress-related disorders or exhibit patterns of HPA-axis dysregulation (Cicchetti & Rogosch, 2001; Tarullo & Gunnar, 2006). There are emerging evidences that support the theory that genotypic variations interacting with ELS may contribute

to variability in clinical outcomes. A number of primates and murine studies suggest several genes: CRHR1, 5HTTLPR, FKBP5 that regulate the activity of HPA axis and CRH are important in mediating the effects of ELS on risk for stress-related disorders.

Corticotropin-releasing hormone receptor 1 gene (CRHR1) polymorphism

Recent studies have examined variation in the gene coding for the CRH type I receptor, which mediates the hormonal and behavioral effects of CRH in response to stress (Mueller et al., 2003). The interaction of ELS with CRHR1 variations has been linked to HPA-axis dysregulation in adults and the risk for depression (Tyrka et al., 2008; Bradley et al., 2008; Polanczyk et al., 2009). Bradley et al. reported the interaction of ELS and polymorphisms of CRHR1 were involved in regulating the stress response and psychiatric illness in adulthood (Bradley et al., 2008). They used a population of inner-city African-American, who were reported high levels of ELS exposure, such as childhood physical, sexual abuse, and emotional abuse. Significant interactions of genetic variations and ELS is observed in a haplotype of the CRHR1 that modify adult risk for depression (Bradley et al., 2008). They found a specific TAT haplotype of CRHR1 polymorphism, involving the single nucleotide polymorphisms (SNPs) rs7209436, rs110402, and rs242924 has protective effects against depression for individuals who were exposed to severe ELS (Bradley et al., 2008). These protective genotypes were also found to protect against depression development in two independent ethnic samples with ELS (Bradley et al., 2008; Polanczyk et al., 2009). Binder et al. hypothesized that the CRHR1 polymorphisms (rs7209436, rs110402 and rs242924) also can moderate the risk for other psychological disorders, such as PTSD (Binder et al., 2009). However, they did not find the interaction effects of this three SNPs and ELS on PTSD symptom development, suggesting that the interaction effects with these polymorphisms may be specifically related to the development of depression (Bradley et al., 2008, Binder et al., 2004). Licinio et al. found another CRHR1 haplotype, consisting of rs1876828, rs242939 and rs242941, was associated with greater antidepressant treatment response in depressed Mexican-Americans (Licinio et al., 2004). The study of Tyrka et al. showed that a CRHR1 genotype could moderate the effect of childhood maltreatment on cortisol responses in adulthood. Specifically, those psychiatrically healthy individuals that experienced severe ELS who carried the protective CRHR1 haplotype, rs242924 and rs110402, did not show enhanced cortisol response to acute stress than those carrying other CRHR1 genotypes (Tyrka et al., 2009). It indicated that even they did not develop to psychological disorders, those individuals without protective CRHR1 haplotype still have a relatively high risk for pathogenesis. They also found that for those healthy individuals with no history of moderate to maltreatment did not show the genetic variations, which suggested that cortisol level consequences are mediated by gene and early life environment interaction (Tyrka et al., 2008). The study of Cicchetti et al. revealed that the TAT haplotype of CRHR1 (involving rs110402, rs242924, and rs7209436) has protective effects against cortisol dysregulation with better HPA axis regulation in children with ELS. Maltreated children who possessed two copies of the TAT haplotype of CRHR evinced a flattened diurnal cortisol change, which is a sign of allostatic load (Cicchetti et al., 2011). While nonmaltreated children did not show any variation in their pattern of diurnal cortisol change. Interestingly, a same cortisol slope change is observed in maltreated children carrying zero or one copy of the TAT haplotype and nonmaltreated children, suggesting that the CRHR1 TAT haplotype has protective effects against cortisol dysregulation. Regardless of their number of TAT haplotype copies of CRHR1, there was no difference in the pattern of diurnal cortisol changes in nonmaltreated children (Cicchetti et al., 2011). These findings suggest that the interaction of two copies of CRHR1 TAT haplotype and ELS has detrimental effects with

flattened diurnal cortisol slope (Cicchetti et al., 2011). However, DeYoung et al. indicated that the protective or detrimental effect of two copies CRHR1 haplotype depends on the maltreatment type (DeYoung et al., 2011). They found that maltreated children (physically abused, emotionally abused, and neglected children) who had two copies of the TAT haplotype of CRHR1 had significantly higher levels of Neuroticism, which has a tendency to develop depression, than those nonmaltreated children who also possessed two copies of the TAT haplotype (DeYoung et al., 2011), consistent with previous findings. While, in contrast, they also found that sexually abused children who had two copies of the TAT haplotype appeared to be protected from increased Neuroticism, as they had lower levels of Neuroticism than other types of maltreated children (physically abused, emotionally abused, and neglected children)(DeYoung et al., 2011). Generally, the interaction of ELS and CRHR1 TAT haplotype play a critical role in regulating the pathogenesis and psychological diseases. The protective or detrimental effects of CRHR1 haplotype depend on multiple factors, such as maltreatment types and the types of psychological disease. It could be speculated that the CRHR1 TAT haplotype may at least partly moderate the association between ELS and HPA axis functioning.

Serotonin transporter (5-HTTLPR) gene polymorphism

A large number of studies had investigated the association of the polymorphism in the serotonin transporter gene with depression (Caspi et al., 2010; Sharpley et al., 2014), as serotonin transporter is one of the main targets of most antidepressants (Tamminga et al., 2002). Caspi et al. found a polymorphic of 5-HTTLPR, with the short (s-) allele associated with lower expression and decreased activity of the serotonin transporter (Caspi et al., 2003, Lesch et al., 1996). They found that individuals carrying the s-allele have a higher risk to develop depression and suicide attempt compared to l-allele carries, with ELS exposure (childhood maltreatment). The enhanced cortisol reactivity to acute stress was observed in l-allele carrying young adults who have a self-reported higher degree of stressful life events during the 0-5 ages (Mueller et al., 2011). Specifically, the number of adverse life events was negatively associated with cortisol reactivity among young adults with l/l genotype, which means they are protected even they have experienced more severe ELS (Mueller et al., 2011). On the contrary, among those who carry at least one s-allele, the number of adverse life events was positively related to cortisol reactivity, which means they have relatively high cortisol reactivity level even they have experienced mild or moderate ELS (Mueller et al., 2011). Consistently, a meta-analysis of 11 studies showed that individuals with s/s genotype had increased cortisol reactivity levels to acute stressors compared to individuals with s/l or l/l genotype (Miller et al., 2013). Chen et al. studied the association between the 5-HTTLPR and diurnal cortisol indicators. A higher morning cortisol level and a flattened diurnal cortisol change are observed in adolescent girls with s/s genotype, as compared those with at least one l-allele (Chen et al., 2009). The l-allele of 5-HTTLPR seems to cause flattened cortisol reactivity level, in the long run, which resulting in insensitive HPA axis response to stress exposure. Above studies suggested that the serotonergic system is involved in the development of the HPA axis. On the other hand, the interaction of 5-HTTLPR genotype and ELS has been found to impact on other stress-related disorders and behavioral patterns, such as PTSD, post-trauma suicide attempt and alcohol abuse (Caspi et al., 2010). 5-HTTLPR genotype is associated with individual differences in the functioning of brain regions involved in emotion processing and regulation, such as amygdala reactivity (Hariri et al., 2005). In particular, the amygdala is one of the main target of gluco- and mineralcorticoids and can indirectly regulate HPA axis activity. For example, 5-HTTLPR s-carriers showed an enhanced amygdala neuronal activity in response to fearful stimuli than those carrying the l-allele (Hariri et al., 2002;

Heinz et al., 2005). Xie et al. found that those individuals who had ELS (childhood adversity) and 5-HTTLPR s-allele genotype have a higher risk to develop lifetime PTSD compared with those who had ELS and carrying l-allele following adult traumatic exposure, which results were observed in European American and African American (Xie et al., 2009). These findings are consistent with the results of imaging study: a negative correlation was observed between ELS and amygdala activation in l/l genotype carriers and a positive correlation in s-allele carriers (Canli et al., 2006). Increased amygdala reactivity to negative emotional stimuli was observed in s-allele carries with ELS, while, l-allele showed protective effects on negative emotional stimuli response (Canli et al., 2006). A meta-analysis also supports that those s/s genotype carriers represent a risk factor for PTSD in high trauma exposure (Gressier et al., 2013). Additionally, the altered gene transcription and decreased transporter activity of the serotonin transporter in the s-carriers have been found in in vitro and in vivo imaging studies (Heils et al., 1997; Stoltenberg et al., 2002). This altered serotonin transporter function seems to lead to altering emotional brain activation pattern and might further increase the risk for psychiatric disorders. It could be speculated from above studies that the interaction of ELS and 5-HTTLPR s-allele genotype cause increased the cortisol reactivity level and flattened cortisol feedback slope, which can directly impair the HPA axis over time. This interaction also enhances amygdala activity and might lead to GR insensitivity over time, which can indirectly disrupt the HPA axis feedback loop. Therefore, 5-HTTLPR variations lead to early differences in emotional processing and altering the cortisol reactivity level during later stress exposure, thereby increasing the susceptibility to many psychiatric disorders. It is fairly to speculate that if individuals are exposed to stress during sensitive periods of HPA axis functioning, such as early childhood or adolescence, then 5-HTTLPR s-allele genotype may be particularly relevant to the development of pathogenesis and psychological diseases.

FKBP5 gene polymorphism

FKBP5 polymorphism is another genetic variant that has been reported to interact with adverse early life environment to affect HPA axis activation. FK506 binding protein 5, which is encoded by FKBP5 gene, is a co-chaperone of the GR, that plays a key role in regulating the GR sensitivity (Schiene-Fischer et al., 2001; Vermeer et al., 2003). Activation of GR transcription is initiated by the binding of GC to the receptors causing GR dimerization and FKBP4 that displace FKBP5. Increased expression of FKBP5 acts as negative feedback on the GR system (Gillespie et al., 2009). Therefore, FKBP5 availability and activity is an important moderator for GR sensitivity, which is a critical element of HPA axis modulation. Binder et al. identified three SNPs of the FKBP5 gene (rs3800373, rs1360780, and rs9470080) and childhood adversity have interaction effects on the risk for PTSD (Binder, 2009). They found that those individuals carrying rs3800373, rs1360780 and rs9470080 are associated with a higher risk for current PTSD symptoms following severe ELS (child abuse) (Binder, 2009). These rs3800373 and rs1360780 FKBP5 genotypes are associated with increased peritraumatic dissociation in children after medical trauma (Koenen et al., 2005) and higher levels of peritraumatic dissociation have been shown to be predictors of PTSD in adults (Ozer et al., 2003). The increased FKBP5 protein levels have been found in rs3800373 and rs1360780 carriers, which over-expressed FKBP5 have been shown to disrupt an intracellular feedback loop between the GR and FKBP5, leading to GR resistance and decreased negative feedback of the HPA-axis (Binder, 2008). Xie et al. also found a significant interaction between the FKBP5 polymorphisms (rs3800373 and rs1360780) and child abuse to predict PTSD symptoms in African American population (Xie et al., 2010); while the same associations were not significant in European Americans. The difference in early trauma types could be a

possible explanation (Xie et al., 2010). Specifically, European Americans have a higher level of sexual abuse, while African Americans have a higher level of crimes witnessed or experienced. Another study reported that the individuals carrying FKBP5 genotype rs9470080 with early childhood trauma have a higher risk to develop lifetime PTSD compared to other genotype carriers (Boscarino et al., 2012). The interaction of the early adversity and FKBP5 genotypes: rs1360780, rs3800373, and rs9470080 are not just associated with PTSD, but also have been found to related to the risk for developing major depression (Wang et al., 2018; Appel et al., 2011). Wang et al. analyzed a large number of depressed individuals and found a significant association with rs1360780, rs3800373 and rs9470080 genotype and an increased risk of depression under childhood adversity (Wang et al., 2018). A study in the German population showed a significant interaction between the rs1360780 genotype and childhood abuse on the development of depression (Appel et al., 2011). The interaction of rs1360780 genotype and childhood trauma events in predicting the onset of major depression also has been found in adolescent and young adults (Zimmermann et al., 2011; Dackis et al., 2012; Kohrt et al., 2015). A decreased feedback of the HPA response via the GR signaling has been found in patients with major depression, and more significant in those with history of early-life trauma (Heim and Nemeroff, 2001; Heim et al., 2000). Therefore, it is fair to speculate that these SNPs might be related to GR resistance and disrupt the HPA axis feedback loop, which could potentially increase the risk for the development of major depression symptoms. On the other hand, some studies reported the sex difference could be a factor that influences the FKBP5 polymorphism effect: the interaction of FKBP5 polymorphism (rs1360780 genotype) and childhood adversity is related to a higher risk for depression development in men than women (Lavebratt et al., 2010). Another study reported that FKBP5 rs1360780 moderated the association between current adversity and depressive symptoms for victimized girls with rs1360780, but it did not moderate the association between early-life adversity and depressive symptoms in boys (VanZomeren-Dohm et al., 2015). These data suggest gender difference may be related to FKBP5 polymorphisms and risk for development of depression. Generally, all findings indicated that the FKBP5 polymorphisms interact with ELS to contribute to FKBP5 over-expression and leads to maladaptive changes in GR sensitivity over time. These changes resulted in long-term alterations of HPA axis functioning and maladaptation to later stress exposure in adulthood.

Discussion

Usually, the CNS is set to cope with various stress efficiently by modulating the internal physiological activities (McEwen, 2007). Failure of stress adaptation could cause long-lasting alterations in HPA axis and lead to behavioral changes and psychological diseases (McEwen and Gianaros, 2011). However, it is important to note that not all individuals with stress exposure develop disorders. At first, the occurring timing of adverse events is essential. Early childhood is one of the most sensitive periods in HPA axis functioning, which shift from hyperresponsive to hyporesponsive to stress (Daskalakis et al., 2003). In this period, nurturing caregiving is the key buffering factor on optimal HPA axis development to protect against HPA axis impairment (Kuhlman et al., 2017; Bernard et al., 2010). ELS exposure during this period may interfere normal development of the hyporesponsive HPA axis, resulting in higher basal cortisol and enhanced cortisol response to stress exposure (Brand et al., 2010; Hibel et al., 2009). Many studies showed that those infants who are exposed to ELS, including maternal emotional withdrawal, inter-parental violence witness and maltreatment showed higher cortisol levels at baseline and flattened diurnal cortisol slope (Bugental et al., 2003; Hibel et al., 2009; Bernard et al., 2010). These altered cortisol levels could lead to GR insensitivity and alter the physiological of HPA axis development over time (Kuhlman et al., 2017; Cohen et al., 2012). Further, disrupted HPA axis feedback loop regulation contribute to delayed recovery from later stress exposure in adult life (Kuhlman et al., 2017).

The development stage of puberty/adolescence is another sensitive period with a new major change in HPA axis activity, with a shift from hyporesponsivity to hyperresponsivity (Somerville et al., 2010; Gunnar et al., 2009). Puberty is characterized by dramatically increased cortisol reactivity level following acute stress exposure (Sapolsky et al., 2000), which could be caused by significant and sustained secretion of gonadal steroids and adrenals that are the primary source of cortisol (Ernst and Mueller, 2008). The prolonged cortisol response to acute stress is observed in adolescents compared to adults. If adolescents are exposed to recurrent and persistent stress, this elevated and prolonged cortisol reactivity could lead to impaired HPA axis functioning over time. The maturation of many brain regions, such as the hippocampus and medial prefrontal cortex, during puberty could be another explanation of HPA axis sensitivity. Because the GR concentration is high in these brain regions and GR are main mediators of GC-dependent negative feedback, which modulates HPA reactivity (Romeo et al., 2006; Herman et al., 2003; Funder, 1994). A persistent decreased GR expression in the hippocampus has observed in adolescents following chronic social stress (Schmidt et al., 2007). In addition, a lower GR hippocampal level and prolonged increased cortisol reactivity level were found in adults with adolescent ELS exposure, which lead to a delayed shutdown of the HPA response to acute stress (Isgor et al., 2004). Therefore, the interaction between ELS, gonadal hormones, and maturation of brain regions decrease GR expression and contribute to the enduring alternation in HPA functioning.

In addition to timing effects of ELS, individual differences in response to later stress exposure and alterations in adult behavior may be mediated by enduring effects of ELS on gene expression. Firstly, CRHR1 TAT haplotype, consisting of rs7209436, rs110402, and rs24924, is found to protect against depression development in the presence of childhood trauma exposure (Bradley et al., 2008). Specifically, those individuals who experienced ELS did not have protective CRHR1 haplotype showed an increased cortisol response to acute stress in adulthood comparing those with protective CRHR1 haplotype. Moreover, these genetic variation effects were not observed in those healthy individuals without ELS

exposure, suggesting that cortisol response difference depends on the genetic variation as well as early life events. Additionally, two copies of CRHR1 TAT haplotype has been found to have detrimental effects, evincing a flattened diurnal cortisol change, in children who have physically abused, emotionally abused and neglected maltreatment (Cicchetti et al., 2011). While opposite findings were observed in sexually abused children, two copies of CRHR1 TAT haplotype have protective effects against Neuroticism development (DeYoung et al., 2011). It could be concluded from above studies that CRHR1 haplotype plays a critical role in regulating cortisol level, while its protective or detrimental effects are depending on multiple factors, such as experienced maltreatment types in childhood and the types of psychological disease.

Secondly, 5-HTTLPR is another genetic variant that has been found to interact with ELS to affect HPA axis activation. Individuals who carry the s-allele have a higher risk to develop depression, PTSD and suicidality compared to l-allele carries, with ELS exposure (childhood maltreatment)(Caspi et al., 2003; Lesch et al., 1996; Caspi et al., 2010). In addition, the flattened diurnal cortisol change and enhanced cortisol reactivity to acute stress were observed in l/l carrying young adults with ELS compared to individuals with s/s or s/l genotypes (Mueller et al., 2011; Chen et al., 2009). 5-HTTLPR s-carriers also showed an enhanced amygdala neuronal activity in response to fearful stimuli than those carrying the l-allele (Hariri et al., 2002; Heinz et al., 2005). Increased amygdala reactivity to negative emotional stimuli was observed in s-allele carries with ELS, while, l-allele showed protective effects on negative emotional stimuli response (Canli et al., 2006). Enhanced amygdala activity might lead to GR insensitivity over time, which can indirectly disrupt the HPA axis feedback loop. Therefore, 5-HTTLPR variations lead to early differences in emotional processing and altering the cortisol reactivity level during later stress exposure, thereby increasing the susceptibility to many psychiatric disorders.

Finally, FKBP5 polymorphism is another genetic variant that has been reported to interact with adverse early life environment to affect HPA axis activation. Three FKBP5 genotypes; rs3800373, rs1360780 and rs9470080 are associated with a higher risk for current PTSD and depression development following severe ELS (child abuse) (Binder, 2008; Wang et al., 2018). Over-expressed FKBP5 protein has been observed in this FKBP5 genotype carriers, which leads to GR resistance and decreased negative feedback of the HPA-axis (Binder, 2008). On the other hand, the sex difference could be a factor that influences the FKBP5 polymorphism effect: FKBP5 rs1360780 moderated the association between current adversity and depressive symptoms in victimized girls, but did not moderate the symptoms in boys (VanZomeren-Dohm et al., 2015); the interaction of FKBP5 polymorphism and ELS is related to a higher risk for depression development in men than women (Lavebratt et al., 2010). All findings indicated that the FKBP5 polymorphisms interact with ELS to contribute to FKBP5 over-expression and leads to maladaptive changes in GR sensitivity over time. These changes resulted in long-term alterations of HPA axis functioning and maladaptation to later stress exposure in adulthood. Therefore, the variations of the genes that are involved in the HPA axis could explain the individual differences in the susceptibility to neurobiological stress response system and adaptation ability to stress in the adult life.

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