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Mini Review

Early Postnatal Stress Impacts Brain Development

Li-Tung Huang[1,2]*

[1]Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

[2]Department of Traditional Chinese Medicine, Chang Gung University, Taiwan

***Corresponding author:** Huang LT, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Taiwan. #123 Ta-Pei Rd, Niausung, Kaohsiung 833, Taiwan, Tel: +886-975056169; Fax: +886-7-7338009; Email: huang_li@pie.com.tw, litung.huang@gmail.com

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Abstract

Early postnatal stress can affect the development of the Hypothalamic-Pituitary-Adrenal (HPA) axis, and cause psychopathology later in life. This mini-review briefly mentions the concept of developmental origins of health and disease. HPA axis alteration, psychopathology, and epigenetic modifications following early postnatal stress are also discussed. Finally, the clinical importance of coexistence of early postnatal seizure and stress are emphasized.

Keywords: Postnatal stress; Epigenetic; Psychopathology; Hypothalamic-pituitary-adrenal axis; Seizure

Introduction

The concept of developmental origins of health and disease (DOHaD)

Early-life adverse environment has been demonstrated as one of the most important factors affecting life-long health [1,2]. Gluckman et al [3]. proposed the concept of DOHaD by observing the enduring effects of the early, both prenatal and postnatal, environment on physical health and disease in adulthood [3]. The DOHaD approach has become fascinating that an international society is formed. Epigenetic modifications regulate gene expression without altering the DNA sequence. Current evidence shows that the notion of epigenetic modifications is applied to the DOHaD approach [4,5].

Early postnatal stress

In higher mammals, early-life stressors include prenatal, early postnatal, and adolescence stress [6]. In rodents, early postnatal stress generally refers to the first 2 weeks after birth [7]. Early-life adversity (childhood abuse and neglect, loss of parents, or extreme poverty) occurs worldwide and are all too common in the lives of children [8,9] In the Dunedin Study birth cohort of 1037 children, followed prospectively for 32 years, maltreatment includes maternal rejection, harsh discipline, sexual abuse, physical abuse, and disruptive caregiver changes [10]. For each child, the cumulative index counts the number of maltreatment indicators experienced during the first decade of life; 63.7% of children experienced no maltreatment, 26.7% experienced one form of maltreatment, and 9.6% experienced two or more forms of maltreatment [10].

Stress hyporesponsive period (SHRP)

The rodent fetal and postnatal HPA axis is substantially different from that of the adult, both in structure and function. Previous studies in rodents demonstrated that during the first 2 weeks of life, normal maternal behavior ensures a quiescent stress response in the pup, the so-called SHRP [7], when neonatal rats have low basal levels of corticosterone and the corticosterone response to stressors is blunted. SHRP is found in both rats and mice [11] during which the central component of the HPA axis is still responsive [12].

A comparable hyporesponsiveness may occur during infancy in humans and may extend throughout childhood. At birth, glucocorticoid levels increase sharply in response to stressors, such as a heel lance. However, the HPA axis becomes insensitive to stressors in the first year of life [13].

HPA axis alteration and psychopathology following early postnatal stress

Corticotropin Releasing Hormone (CRH) is expressed and released in several types of neuronal populations that are involved in cognition and emotion. Early postnatal life is a critical period that CRH plays a major role in neuroplastic changes. Hippocampal CRH neuron is involved in postnatal stress-induced synaptic plasticity [14].

Stress imposes varying effects on glucocorticoid circulation levels in children depending on the stressor. Exposure to maternal separation, such as attending day care centers, can lead to increased glucocorticoid secretion [15], whereas exposure to severe abuse is associated with decreased glucocorticoid levels [13]. Also, there are mixed findings from studies investigating HPA axis activity in children and adolescents with a history of maltreatment. De Bellis and colleagues reported A Blunted Adrenocorticotropic Hormone (ACTH) response to CRH challenges, but no differences in cortisol responses in girls aged 7-15 years who had been sexually abused [16]. HPA axis response to CRH also was investigated by Kaufman and colleagues. They reported ACTH hyperresponsiveness among a subsample of individuals that experienced ongoing adversity; however, there were no differences in cortisol measures when compared to depressed nonabused and normal control [17]. By contrast, Hart et al. [18], reported a pattern of cortisol suppression during stressful situations in preschoolers with history of maltreatment [18].

Karemaker et al. [19] demonstrated that HPA axis activity in school-age children was decreased in prematurely born children treated with dexamethasone during the neonatal period. However, no changes in HPA were observed when children had been treated neonatally with hydrocortisone [19]. In the same cohort of children, dexamethasone-treated girls displayed more behavioral problems, such as attention and social problems, which were associated with changes in the HPA axis.

Childhood maltreatment is linked with adult-onset major

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depression disorder MDD and Post-Traumatic Stress Disorder (PTSD). MDD subsequent to childhood maltreatment is associated with increased cortisol and inadequate inhibitory feedback regulation of the HPA axis [20]. In contrast, research studies in PTSD have shown reduced cortisol levels [21]. These findings indicate a possible dissociation of HPA axis activity: HPA axis hypoactivity in those with maltreatment-related PTSD [21], but hyperactivity in maltreated individuals presenting with MDD [20].

Early-life adversity is one of the most prominent environmental factors associated with an increased risk of developing mood and anxiety disorders [22]. People who were exposed to early-life adversity are also more likely to develop PTSD [23]. More than 30% of mental disorders are directly related to postnatal stress [24,25]. Similarly, patients suffering from MDD had a fourfold increased risk for depression following multiple adverse exposures [26].

Epigenetic modifications in brain in the context of early postnatal stress

Epigenetic changes involve DNA methylation at cytosine-guanine sequences-CpG sites, histone posttranslational modifications (histone methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, and propionylation), and microRNAs [27]. It is now clear that stress during development has a significant epigenetic impact on the brain, and the relationship between the stress response and epigenetics in the brain is bidirectional [28]. In mammals [29,30], maternal behavior plays an important role in the behavioral development of the offspring. In addition, epigenetic modification of gene expression may help explain the link between a set of maternal behaviors and an offspring's HPA response to stress [31].

McGowan et al. [32] showed that suicide victims who experienced childhood abuse had higher overall methylation in their rRNA genes and expressed less rRNA. This difference in methylation was specific to the hippocampus [32] McGowan et al. examined epigenetic differences in the *NR3C1* promoter postmortem in hippocampal tissue collected from 36 men [33]. Retrospective interviews identified 12 suicide victims with a history of childhood abuse, 12 suicide victims without abuse, and 12 controls. The suicide and abuse victims had increased cytosine methylation of the *NR3C1* promoter and decreased levels of glucocorticoid receptor mRNA as compared to the other groups. Patch-methylated *NR3C1* promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decreased Nerve Growth Factor-Inducible protein A (NGFI-A) transcription factor binding and NGFI-A-inducible gene transcription. These findings translate from rats to humans, and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression [33]. In peripheral tissue, Tyrka et al. [34] found that childhood adversity was associated with increased DNA methylation of several sites within the glucocorticoid receptor 1F promoter region in lymphocytes in adulthood [34].

Coexistence of early postnatal stress and seizure

Seizure is one of the most common pediatric emergencies, with the highest incidence in the first year of life. Animal studies have demonstrated early-life seizures differ from adult seizures by the seizure behaviors, the electroencephalogram features, and their consequences. Notwithstanding the higher susceptibility to seizures, the immature brain is less vulnerable to seizure-induced injuries than the mature brain [35]. However, under some circumstances seizure in the immature brain can cause permanent brain damage [36,37].

For humans, most early-life seizures occur in premature and sick neonates [38] who are hospitalized and separated from their mothers, and thus, under stress [39]. Reciprocally, early postnatal stress may prime the occurrence of seizures and act via glucocorticoids, thereby potentiating the excitotoxic effects of concurrent neurological insults [40], such as seizure [36].

Currently, more attention is being paid to the effect of early-life stress on adult-onset seizure; however, little work has focused on the effect of early postnatal stress on the early-life seizure [5]. Indeed, to study the coexistence of early postnatal stress and seizures is of both experimental and clinical importance.

Conclusion

Early postnatal stress can program the HPA axis development and causes psychopathology later in life. Epigenetic modification plays an important role in the development of psychopathology. In addition, coexistence of early postnatal stress and seizure is harmful for brain development. Future works depend on research based on the molecular mechanisms underlying the relationship between early postnatal stress and seizure and psychopathology, as well as the development of targeted and effective intervention programs.

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