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Invited review

Long-term effects of early life stress exposure: Role of epigenetic mechanisms

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ABSTRACT

Stress is an adaptive response to demands of the environment and thus essential for survival. Exposure to stress during the first years of life has been shown to have profound effects on the growth and development of an adult individual. There are evidences demonstrating that stressful experiences during gestation or in early life can lead to enhanced susceptibility to mental disorders. Early-life stress triggers hypothalamic-pituitary-adrenocortical (HPA) axis activation and the associated neurochemical reactions following glucocorticoid release are accompanied by a rapid physiological response. An excessive response may affect the developing brain resulting in neurobehavioral and neurochemical changes later in life. This article reviews the data from experimental studies aimed to investigate hormonal, functional, molecular and epigenetic mechanisms involved in the stress response during early-life programming. We think these studies might prove useful for the identification of novel pharmacological targets for more effective treatments of mental disorders.

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Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type-2; CNS, central nervous system; CRH, corticotropin-releasing hormone; DHA, docosahexaenoic acid; FC, frontal cortex; GABA, gamma-aminobutyric acid; GC, glucocorticoid hormone; GR, glucocorticoid receptor; 5-HT, serotonine; HDACi, HDAC inhibitors; Hic, hippocampus; HPA, hypothalamic–pituitary–adrenal; MR, mineralocorticoid receptor; MS, maternal separation; NA, noradrenaline; NMDA, N-methyl-D-Aspartate; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotrophin-3; NT4, neurotrophin-4; OXT, oxytocin; PCMS, prenatal chronic mild stress; PD, postnatal day; PFC, prefrontal cortex; PS, prenatal stress; PVN, paraventricular nucleus.

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1. Introduction

Until recent years, it was falsely believed that brain and body were shaped by experiences only when the child became able to respond rationally to the social environment without taking into account early life events. However, it is now accepted that both the embryo and the fetus are highly responsive to the gestational environment and in deed, several animal studies have described that pre and postnatal exposure to adverse events like stress can influence the offspring's neurodevelopment. Moreover, the neuroendocrine and the immune systems have also been described to be altered by stress inducing behavioral changes and thus affecting neuroplasticity [1–5]. Additionally, several reports indicate that stress plays a fundamental role in the etiology and evolution of many diseases including neuropsychiatric disorders like depression, autism and bipolar disorder [6,7].

Interpretation of retrospective studies from the 1960's suggests that exposure to prolonged stress during pregnancy cause developmental and behavioral disorders of the descendants. The brain is particularly susceptible to early-life programming by deregulation of the HPA axis and this can be manifested as stress hyper-reactivity and increased susceptibility to affective disorders like anxiety, depression and schizophrenia in childhood or adulthood [8–12]. Alteration of the circadian rhythm, imbalance of neurotransmitters in the brain and impaired immune function has also been described as consequences of perinatal stress exposure [10,13,14].

The term neuroplasticity refers to the potential of the brain to reorganize by creating new neural pathways to adapt, as it needs. This phenomenon requires the stable modulation of gene expression, which is mediated at least in part, by epigenetic processes such as DNA methylation and histone modifications. The sensitivity of the mature phenotype to environmental factors and the subsequent risk of disease are determined by the interactive influence of both genome and epigenome [15]. Although the link between prenatal exposure to stress and altered postnatal behavior is not fully understood, emerging evidences indicate that epigenetic regulation prior to birth, can exert profound effects on the development and functioning of the brain and over many neurodevelopmental syndromes [16].

The aim of this article is to overview the current state of knowledge in the field describing different animal models of pre and postnatal stress and discussing the epigenetic mechanisms involved in the modulation of the physiological response.

2. HPA axis response to stress

The physiological response to a stressful event involves the activation of the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system and the immune system whose physiological mediators are glucocorticoids (GCs), catecholamines and cytokines respectively [17]. The neuroendocrine stress response plays a key role in the adaptation to the environment, however, excessive or chronic stress exposure may lead to persistent maladaptation of neuronal circuits and may promote the development of psychiatric pathologies, such as mood or anxiety disorders [18] that often arise in adolescence [19,20].

The HPA axis is an adaptive and plastic system and is characterized by inter- and intra- individual variability. A stressful experience triggers the activation of the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These hormones bind to their specific receptors (CRHR1 and V1b) in the anterior pituitary stimulating the release of adrenocorticotropic hormone (ACTH). ACTH stimulates glucocorticoid synthesis (cortisol in human, corticosterone in rodents), which regulate different processes [21,22]. The biological effects of GCs are usually adaptive; however, inadequate or excessive activation of the HPA axis may contribute to the development of pathologies [23,24].

Glucocorticoids bind to two types of receptors: mineralocorticoid (MR) and glucocorticoid receptors (GR). Upon binding to GRs, glucocorticoids modulate the transcription of HPA components creating a regulatory negative feedback loop [25–27]. Given the distinctive pharmacology of GRs and MRs, it has been suggested that while MRs regulate basal HPA tone, GRs mediate the glucocorticoid negative feedback following stress [28].

Interestingly, the effects of long-term changes in the function of the HPA axis observed as a consequence of developmental adversities (e.g., pre or postnatal stress exposure) exhibit similarities with psychiatric disorders characterized by abnormalities in the HPA axis function and in the stress response [29].

3. Early life stress

The pre and postnatal periods are critical for the development of the nervous system. Exposure to adverse events early in life may profoundly affect brain development leading to long-lasting effects on neuronal structure and behavior playing a key role in the etiology of mood and anxiety disorders [30]. The interactions between the genome and the environment during the perinatal interval generate windows of vulnerability in which interference by a stressor could lead to abnormalities at birth (low weight), to growth retardation, or structural and functional changes that remain in adulthood [31].

Animal models are useful tools that help us understand how genetic vulnerability factors can modulate responses to early environmental experiences. By controlling environmental exposure to different stressors and following animals prospectively from or before birth, these models provide insights about behavioral and physiological mechanisms involved in the pathways through which early stress might produce long-term effects. In this review we will focus on models of pre and postnatal stress.

3.1. Prenatal stress (PS)

During the gestational period animals are susceptible to factors that can disrupt the homeostasis and therefore development is affected. In humans, psychosocial work stress during pregnancy has been related to postnatal consequences such us reduction in birth weight and time of gestation [32]. Numerous animal models of prenatal stress (PS) are conceived to mimic suboptimal womb environments. Different paradigms have been used in order to study the effects of stress exposure over development and predisposition to lifelong health problems including immobilization [33], exposure