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Review

Long-term effects of early environment on the brain: Lesson from rodent models

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ABSTRACT

The postnatal period is characterized by extensive neuronal plasticity, synaptic organization, and remodeling. High neuroplasticity renders the brain sensitive to the remodeling effects induced by environmental factors, such as exposure to adversity, which can imprint neurochemical, neuroendocrine, morphological, and behavioral changes.

Early experiences that influence developmental trajectories during maturation of the brain can have a wide range of long-lasting effects, modulating stress-coping strategies in adult life and inducing vulnerability or resilience to psychopathologies, depending on the gene × later experience interplay.

Future studies will clarify how manipulation of the early environment induces these effects acting on genetic and epigenetic factors.

Contents

1. Introduction

In most species, the fetal, perinatal and postnatal periods are the most sensitive periods of life, because they are characterized by extensive neuronal plasticity, synaptic organization, and remodeling activity. Brain development is determined by genetic factors and environmental and epigenetic events [1–3]. High neural plasticity during these sensitive stages allows the maturing circuits to respond and adapt to external and internal factors [4]. However, because increased neuroplasticity also entails high sensitivity to remodeling by environmental factors, exposure to adversity in early postnatal development can imprint persistent neurochemical, neuroendocrine, and behavioral changes [5].

Among environmental factors, stress shapes future responses to subsequent adversities and influences one's susceptibility to neuropsychiatric disorders in adult life. Stress is a natural condition; however, exposure to challenging experiences (i.e., demanding conditions that affect deviation from homeostasis [6]) during critical developmental windows can contribute to disease vulnerability.

Early adversity can affect the susceptibility to psychiatric disorders in later life depending on many different external features,

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such as nature of stressors, time of exposure during development, severity of exposure as well as biological factors as gender, age and predisposing genetic polymorphisms in genes associated with mood regulation, stress response and inflammatory processes [2]. In addition to environmental and genetic factors, epigenetic alterations that are induced by early life experiences are also a key mechanism of the long-lasting effects of these events on neurobiological susceptibility to disease [2,37].

Preclinical studies in animal models have provided critical information on how manipulation of the early environment can induce chronic neurobiological and behavioral effects, attempting to establish a causal link between early experiences and later processes in life [8,9]. During early postnatal life, particularly in the initial PostNatal Days (PNDs 1–15), mouse pups possess a limited behavioral repertoire due to their immaturity. Further, for a newborn individual, its mother is nearly exclusively the principal environmental element with which it interacts and thus has a critical function in its development. The maternal contribution through pup-oriented care behavior regulates the reciprocal interaction between mother and pup, and the attachment bond is necessary for the pup's brain to develop appropriately.

Based on human studies that have suggested that alterations in the attachment bond induce long-term changes in the brain, thus compromising the development of systems that are involved in emotionality and motivation [10–12], preclinical research in rodents and nonhuman primates have focused on experimental manipulations to effect quantitative and qualitative changes in mother-pup interactions [13–26].

Various strategies have been proposed in rodents to modulate the mother-pup interaction during development [3,27–30], and several studies have reported the outcomes of such critical experiences on the susceptibility to stress exposure [21,32–34], increasing the susceptibility to psychopathological phenotypes, such as depression-like behavior [35,36] and enhanced sensitivity to drugs of abuse [37–41] later in life.

This review briefly summarizes the main results of studies that have modeled early postnatal experiences in animals.

We will begin by describing the conceptual frameworks that have driven (and were inspired by) the modeling of early life critical experiences through experimental manipulation in animals. We will discuss the most frequently used approaches for postnatal manipulation and the behavioral phenotypes that result. Then, we will introduce the principal effects of these manipulations on brain development, focusing on the hypothalamic-pituitary-adrenal (HPA) axis and some brain networks that are involved in the psychopathological outcomes, demonstrating how these circuits modify their responses to several experiences in adult life. Some results concerning molecular mechanisms underlying the effects of early manipulations will be also provided through manuscript, even if a detailed investigation of these mechanisms is beyond the goal of this review. Finally, we will argue how examining gene (and epigenetic) x environment interplay is a *sine qua non* condition for understanding how the same events determine susceptibility to or resilience from mental illness.

2. Conceptual frameworks

The process of experimentally modeling critical features of human conditions in laboratory animals is obviously based on theoretical models.

Various theoretical frameworks have been proposed to examine how challenging early-life experiences—in particular, those that involve the attachment figure—lead to pervasive and long-lasting effects later in life.

Because early postnatal life is characterized by the close relationship between pup and mother (the most important aspect of the environment during the first several weeks after birth), the mother-offspring bond has been the focus of all conceptual models.

The "*maternal mediation hypothesis*" [42,43] posits that of all early environmental cues, maternal care is critical in directing infant development. In fact, the mother produces clues of the forthcoming environment and, consequently, pups will begin to regulate their behavioral strategies consistently with these signals [44–47]. This conceptual framework indirectly suggests a linear relationship between the future outcome of an individual and its early environment.

Recently, the exclusivity of the role of pup-oriented maternal behaviors was cast into doubt, wherein the input that originates from the pups has also been suggested to be crucial [48]. Thus, a more complete theoretical model, assimilating notions that are derived from the "diathesis-stress" framework [49,50], should consider the individual as a developing organism that can modify its phenotype in response to changes in environmental conditions (phenotypic plasticity)[51].

In this perspective, by introducing a critical function for individual appraisal, clues for the future environment that are derived from maternal stimulation are actively evaluated by developing pups [52]. The "*match/mismatch*" hypothesis that is derived therein states that neonatal challenges inform the growing individual of an adult environment that is similar to the one that is provided by the mother and that early life experience shapes a subject's behavior to cope with similar conditions later in life [52–54]. If an inconsistency occurs between the early "programming" environment and the environmental conditions in adulthood (*phenotypic mismatch*), individuals will be more likely to experience a detrimental outcome [55–57]. The "match/mismatch" model implicitly introduces the innovative concept that adverse events during early life constitute a source of adaptation for certain individuals (the effect of "stress inoculation") [42,58]. In this context, exposure to a challenging but moderately stressful environment could also induce a more adaptive response to stressful experiences later in life [59].

This suggests that specific genetic predispositions influence the adaptive changes to early experiences. Therefore, shifting from an "optimal" to an "adaptive" perspective [60], early life experiences can have an adverse or beneficial impact on brain and behavioral development [61–67], depending on the interaction between genetic and environmental factors [68].

The "*differential susceptibility*" model, proposed by Belsky [53,69–72], suggests that certain individuals, likely for genetic reasons, are more susceptible than others to "positive" and "negative" rearing environments. According to these authors, gene-environment interactions should not be restricted to negative environmental influences, but they must be interpreted in terms of the differential susceptibility of individuals to environmental conditions "for better or for worse" [69,70,72]; thus, "vulnerability genes" might be better operatively defined as "plasticity genes" [53,60,73]. This assumption suggests that the programming effects of early environmental challenging conditions differentially affect individuals, depending on their genetic predisposition, and that the same environmental experiences can lead to disparate, even opposite, outcomes later in life [74].

Daskalakis [59] attempted to reconcile these various models by proposing the "*three-hit*" model, a new concept of vulnerability and resilience to long-lasting effects of postnatal experiences on the response to subsequent challenging environmental conditions. This theoretical framework, taking into account environmental factors (and their proactive effects) and the differential susceptibility to them, suggests that the interaction between genetic components (hit 1) and early-life environmental conditions (hit 2) establishes gene expression patterns that promote a specific a phenotype dur-

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