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The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome

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Summary Stressful experiences during early-life can modulate the genetic programming of specific brain circuits underlying emotional and cognitive aspects of behavioral adaptation to stressful experiences later in life. Although this programming effect exerted by experience-related factors is an important determinant of mental health, its outcome depends on cognitive inputs and hence the valence an individual assigns to a given environmental context. From this perspective we will highlight, with studies in rodents, non-human primates and humans, the three-hit concept of vulnerability and resilience to stress-related mental disorders, which is based on gene—environment interactions during critical phases of perinatal and juvenile brain development. The three-hit (i.e., hit-1: genetic predisposition, hit-2: early-life environment, and hit-3: later-life environment) concept accommodates the cumulative stress hypothesis

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Genetic predisposition;
Early life environment;
Later life environment

stating that in a given context vulnerability is enhanced when failure to cope with adversity accumulates. Alternatively, the concept also points to the individual's predictive adaptive capacity, which underlies the stress inoculation and match/mismatch hypotheses. The latter hypotheses propose that the experience of relatively mild early-life adversity prepares for the future and promotes resilience to similar challenges in later-life; when a mismatch occurs between early and later-life experience, coping is compromised and vulnerability is enhanced. The three-hit concept is fundamental for understanding how individuals can either be prepared for coping with life to come and remain resilient or are unable to do so and succumb to a stress-related mental disorder, under seemingly identical circumstances.

1. Introduction

It is well-documented that during critical periods of brain development stressful experiences can modulate the functioning of specific circuits that underlie adult emotional and cognitive functioning, and behavior (Taylor, 2010). These effects exerted by stress are mediated by the autonomic nervous system and the hypothalamus–pituitary–adrenal (HPA)-axis. Hence, decades of research have been devoted to understand how the mediators of these systems such as adrenaline and other biogenic amines, neuropeptides and hormones can modulate brain function and behavior for life (Maras and Baram, 2012). These programming effects induced by the stress mediators suggest enduring changes in the transcriptome underlying DNA methylation and chromatin modifications. In fact, recent research has revealed that the mediators and their receptors of the HPA-axis themselves are prime targets of epigenetic modification. This includes corticotrophin releasing hormones (CRH), vasopressin and their receptors, and also the receptors for circulating adrenal corticoids in the limbic-cortical circuitry (Murgatroyd and Spengler, 2012). Although rapid progress has been made in unraveling this epigenetic mechanism induced by early experience, it is still unresolved how this modulation of programming by the environment precisely occurs (Franklin et al., 2012).

Here we focus on the HPA-axis and its glucocorticoid endproducts, i.e., cortisol and corticosterone in human and non-human primates and only corticosterone in rodents, collectively called CORT. These hormones coordinate and synchronize daytime and sleep-related events, regulate the organism's response to stress and facilitate adaptation (de Kloet et al., 2005). We ask the question how CORT action during stress can change from a protective into a harmful signal by focusing on the environmental programming effects powered by the hormone.

To address this question this review reflects the content of the Presidential Symposium held under the title "Resilience and vulnerability: adaptations to early-life adversity outcome" at the 42nd ISPNE Conference in the New York Academy of Sciences. Thus we first briefly discuss, for rodents, monkeys and humans, the development of the pup's/infant's HPA-axis at perinatal life when they are particularly susceptible to environmental influences. We briefly review rodent (Daskalakis et al., 2011a) and non-human primate (Parker et al., 2006) animal models, that are appropriate to exploit gene–environment interactions at these critical periods in the perspective of later-life outcome. We focus on a mechanism involving excitatory neurotransmission and stress mediators (Champagne et al., 2008; Bagot et al., 2012a). Next this analysis is projected to the human situation. We conclude with the presentation of the three-hit concept of vulnerability and resilience. This concept unifies the currently dominant viewpoints that have precipitated as the cumulative stress hypothesis, and the stress inoculation and match/mismatch hypotheses.

2. Early-life stress in animal models

Mother-pup interactions during the first postnatal period have been studied the last 60 years in rodents and in non-human primates to evaluate the significance of early-life experiences for individual differences in adult neuroendocrine activity, emotional responses, cognitive performance and behavior. Some researchers studied the impact of experimental early-life manipulations such as neonatal handling and maternal separation (Levine, 2005), and others examined the outcome of naturally occurring variations of maternal care (Meaney, 2001). Also significant progress has been made with studies using monkeys exposed to moderate postnatal stressors (Parker et al., 2006).

2.1. Stress hypo-responsive period (SHRP) and the short-term effects of maternal absence

The SHRP is a developmental period, from postnatal days (*pnd*) 1–10 in mice and *pnd* 3–14 in rats, in which the elevation of CORT is attenuated after exposure to mild stressors, that otherwise trigger a profound response in the adult animals (Schapiro et al., 1962; Sapolsky and Meaney, 1986; Levine, 2001; Schmidt et al., 2003a). The human HPA-axis development is in concordance with that of rats (even though rats are prematurely born) since the axis is not yet fully developed at birth and CORT secretion manifests a comparable SHRP during postnatal months 6–12. During this period human babies are dependent on their caregivers for normal development, and adverse experiences in this period can have a long-lasting impact (Gunnar and Quevedo, 2007).

There are phylogenic differences, however, in HPA-axis development between rodents and primates. Detailed studies with the New World monkeys, the marmosets, have shown basal hyperactivity of the HPA-axis in neonates, but without an apparent circadian rhythmicity. From infancy to adulthood the pattern of stress responsiveness remains similar. Hence in view of its neonatal hypercorticism the marmoset is an interesting animal model to study the outcome of

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