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How age, sex and genotype shape the stress response

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ABSTRACT

Exposure to chronic stress is a leading pre-disposing factor for several neuropsychiatric disorders as it often leads to maladaptive responses. The response to stressful events is heterogeneous, underpinning a wide spectrum of distinct changes amongst stress-exposed individuals'. Several factors can underlie a different perception to stressors and the setting of distinct coping strategies that will lead to individual differences on the susceptibility/resistance to stress. Beyond the factors related to the stressor itself, such as intensity, duration or predictability, there are factors intrinsic to the individuals that are relevant to shape the stress response, such as age, sex and genetics. In this review, we examine the contribution of such intrinsic factors to the modulation of the stress response based on experimental rodent models of response to stress and discuss to what extent that knowledge can be potentially translated to humans.

Contents

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1. Introduction

A stressor is by definition a stimulus that triggers a stress response. This stress response is generated when our brain perceives something as a potential threat. Perception to stress is dependent on a combination of factors intrinsic to the stressful stimulus (e.g. duration and intensity) and intrinsic to the individual. This perception varies across individuals, being the same stimulus relatively innocuous for some and a potential threat for others. Such individuals' variation is based on objective factors (e.g. age, sex, genetics) but also on subjective factors like stored memories that influence sensory inputs and respective processing; in this review, we discuss the relevance of these objective factors.

After processing a certain stimulus as a potential threat, the sympathetic nervous system is activated leading to the production of cathecolamines, adrenalin and noradrenaline, that trigger several physical outcomes to prepare the body to respond to that threat - the “fight or flight” response, as coined by Walter Cannon (Cannon, 1915). Increased heart rate, vasoconstriction and increased expenditure of energy reserves are some of the examples of this sympathetic stress-response (Jansen et al., 1995). Stress is however, also embodied by the hypothalamic-pituitary-adrenal (HPA) axis response, that by primarily activating the hypothalamus and the pituitary, triggers the adrenal production of glucocorticoids (McEwen, 2005). Glucocorticoids (cortisol in humans and corticosterone in rodents), in turn, impact several systems in an attempt to cope with the stressor and reinstate homeostasis, the so-called resistance phase of Selye's general adaptation theory (Selye, 1950).

Similarly to what happens with stressor perception, the ability to cope with a stressor is also dependent on individual factors such as genetics (de Kloet et al., 2005), age and sex (Bale and Epperson, 2015), but also on the aspects of the stressor itself, such as intensity, unpredictability and duration. The response to an acute stressful stimulus is for the most part beneficial and is primarily an evolutionary mechanism; in fact, it is a set of events, orchestrated by the brain, in order to adapt to that environmental challenge. If a stressor persists in time, or if it is too intense, the ability to cope with it can deteriorate and eventually become exhausted. Exhaustion can take form either through neuropsychiatric manifestations or other somatic complaints, the so-called maladaptive response to stress (Sousa and Almeida, 2012), that is the focus of this review.

In this review, we first center on how the stress response varies across the individual's lifespan, and the animal models that have been used to elucidate this subject. Then, we discuss how factors related to sex can influence stress response, by analyzing studies that report sex differences on the outcome of stress exposure, and also the influence of hormonal variability in shaping that response. Finally, we also compare the stress effects on different rodent strains, highlighting the impact of the genetic component on the stress response shaping. Emphasis is given on how the insights from experimental models can potentially be translated into humans.

2. The effect of age in the stress response

2.1. Stress exposure during the prenatal period

The origin of many health problems and susceptibility to disease can be traced back to the uterine life. Fetal development is a period highly sensitive to environmental factors as cells are proliferating and differentiating rapidly, in a delicate and precisely orchestrated process, to give rise to complex systems. Therefore, disturbances by stress can lead to erroneous developing steps that can either manifest immediately in the postnatal period (activational effects) or later in life (programming effects), increasing the susceptibility to certain disorders during adulthood (Seckl and Meaney, 2004). These alterations can disclose either directly or through interaction with other triggers in life.

During the prenatal period, the focus of the research on the impact of stress has been largely on the fetal exposure to glucocorticoids via the placenta, either by maternal exposure to stressors or by the administration of glucocorticoids.

2.1.1. Glucocorticoid metabolism across the placenta

Glucocorticoids are important to fetal development and are associated with organ maturation that is critical for extra-uterine life. The association of glucocorticoids with rapid tissue maturation has been particularly important for infants at risk of preterm birth. The administration of glucocorticoids is a widely used approach to induce rapid surfactant production in the lung and thereby improve neonatal viability. Excessive glucocorticoids, however, negatively interfere with fetal growth and maturation pattern, and imprint alterations that can persist throughout life. A protective barrier of the placenta to excessive fetal exposure to either maternal or exogenous glucocorticoids operates through the action of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD) that metabolizes glucocorticoids to inactive 11-keto forms. The protective role of placental 11β-hydroxysteroid activity has been revealed, amongst others, by a study showing that the offspring from pregnant rats with reduced 11β-HSD activity display changes associated with increased exposure to glucocorticoids, like low birth weight and hypertension (Edwards et al., 1993). However, when glucocorticoids exceed a certain limit, such as in prolonged stress exposure during maternity or glucocorticoid therapy, the available 11β-HSD saturates and loses its efficiency. In addition, some synthetic glucocorticoids, such as dexamethasone, have low affinity for 11β-HSD, and therefore readily cross the placenta (Seckl and Holmes, 2007).