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Perspectives on stress resilience and adolescent neurobehavioral function

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ABSTRACT

Interest in adolescence as a crucial stage of neurobehavioral maturation is growing, as is the concern of how stress may perturb this critical period of development. Though it is well recognized that stress-related vulnerabilities increase during adolescence, not all adolescent individuals are uniformly affected by stress nor do stressful experiences inevitability lead to negative outcomes. Indeed, many adolescents show resilience to stress-induced dysfunctions. However, relatively little is known regarding the mechanisms that may mediate resilience to stress in adolescence. The goal of this brief review is to bring together a few separate, yet related lines of research that highlight specific variables that may influence stress resilience during adolescence, including early life programming of the hypothalamic-pituitary-adrenal (HPA) axis, stress inoculation, and genetic predisposition. Though we are far from a clear understanding of the factors that mediate resistance to stress-induced dysfunctions, it is imperative that we identify and delineate these aspects of resilience to help adolescents reach their full potential, even in the face of adversity.

1. Introduction

It is well established that prolonged or chronic exposure to stress can lead to a variety of adverse physiological and psychological consequences, including obesity, drug abuse, and mood disorders (McEwen, 2005, 2007; de Kloet et al., 1998). Furthermore, a growing body of evidence indicates that periods marked by significant brain maturation and plasticity, such as perinatal and adolescent development, may be especially vulnerable to these disruptive effects of stress (Romeo et al., 2009; Eiland and Romeo, 2013). Less appreciated, however, is the fact that not all individuals exposed to extended or repeated stressors necessarily go on to develop neurobehavioral dysfunctions. The factors that mediate this resilience to stress-induced vulnerabilities are unclear, but likely involve an interaction between genetic and environmental variables (Rutter, 2013; Southwick and Charney, 2012). The purpose of this review is to discuss possible mechanisms that may contribute to stress resilience, particularly during the adolescent stage of development. Given the scarcity of data that directly addresses stress resilience during adolescence, this review will also suggest potential future lines of research to help fill this gap in our understanding.

2. Adolescence and stress-related vulnerabilities

An emergent body of research has begun to show the short- and long-term effects of exposure to stress during adolescence on a diverse set of negative physiological and neurobehavioral outcomes (Eiland and Romeo, 2013; McCormick and Green, 2013; McCormick, 2010; Hollis et al., 2013; McCormick and Mathews, 2010; McCormick et al., 2010). It has been proposed that adolescents may show a heightened sensitivity to stressors based on at least three converging factors (Romeo, 2013). First, animal studies have indicated that peripubertal individuals display greater hormonal stress responses compared to adults following a variety of physical and psychological stressors (Romeo, 2010a, 2010b; McCormick and Mathews, 2007). Second, neuroanatomical studies have reported that the brain areas known to be highly sensitive to stressors in adulthood, namely the amygdala, hippocampus, and prefrontal cortex, all continue to mature during adolescence (Giedd and Rapoport, 2010). Third, the adolescent brain may be more responsive to the stress-related hormones than the more mature brain, as a previous study in rats showed that exposure to similar levels of corticosterone increased gene expression for glutamate receptor subunits to a greater degree in the adolescent compared to adult hippocampus (Lee et al., 2003). Taken together, these data argue that changes in hormonal stress reactivity coupled with the continued maturation of

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stress-sensitive neural circuits contribute to the marked increase in stress-related vulnerabilities often observed during adolescence (Fig. 1).

3. Adolescence and stress resilience

Despite the convergence and interaction of these hormonal and neurobiological variables that may render the adolescent particularly vulnerable to stressors, not all adolescents are adversely affected by stress and experiencing stressors during adolescence does not inevitability result in negative outcomes. However, it is unclear what may account for the different reactions that adolescents show in response to stress exposure.

Some differences in the neurobehavioral responses to adolescent stress across studies are undoubtedly mediated by subtle or significant differences in the specific experimental paradigms and/or assays used. For instance, studies that exposed adolescent rats to social defeat stress found either increased or decreased anxiety-like behaviors in adulthood (Watt et al., 2009; Weathington et al., 2012), but these diametrically opposed results can likely be explained by experimental differences, such as the length and frequency of the social defeat and the animal housing conditions (i.e., single vs. group) used in these two studies. More intriguing, however, is the difference in how individual animals respond to a stressor *within* an experiment. A greater understanding and appreciation of this variation may potentially shed light on what makes some animals more or less resistant to stressful experiences.

To illustrate this stress-induced variability, I present a specific example from a pilot study we recently conducted. Briefly, in this study we exposed adolescent male rats to 1 h of restraint stress every other day from postnatal day (PND) 28–49. This age span was used as this 3 week period in rodents is associated with the most significant changes in physiological, neurobiological, and behavioral parameters as animals transition into adulthood (Spear, 2000). We then tested these animals in the forced swim test in young adulthood to measure depressive-like behaviors (Porsolt et al., 1977). We found that the rats exposed to restraint stress during adolescence showed a shorter latency to immobility than age-matched non-stressed controls (Fig. 2; unpublished observation). Though these results suggest that adolescent stress exposure leads to depressive-like behaviors in adulthood, these data are presented here to provide an example of the relatively high degree of variability in the experimental group. Specifically, the mean and standard deviation of the control group are 176.0 and 33.6, respectively, while the stress group is 72.2 and 79.3, respectively. This high standard deviation in the experimental group indicates a rather large spread around the mean. Though not surprising that individual differences exist in responsiveness to a relatively complex set of stimuli experienced throughout adolescence, data such as these do lead to the simple question: why do some animals appear to be more affected than others? Here, we will highlight three interrelated factors that may impart greater resilience to an adolescent facing a stressful environment: early life programming of the hypothalamic-pituitary-adrenal (HPA) axis, stress inoculation, and genetic predisposition. It is important to note that these factors are neither unique to stress resilience during adolescence, nor the only elements likely at work modulating an individual's resilience to stress. Instead, these factors are discussed to illustrate potential mechanisms through which resilience to adolescent stress may be realized and provide examples of future lines of research that could be investigated.

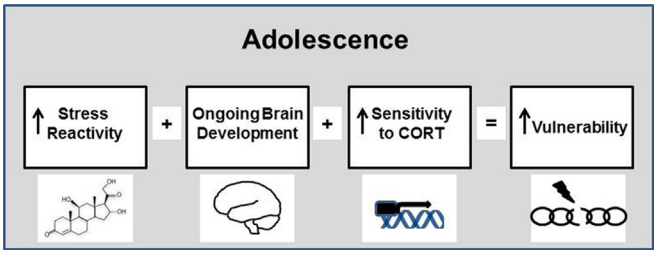

Fig. 1. A schematic representation of factors that may contribute to the increase in stress-related vulnerabilities observed during adolescence. Specifically, adolescent changes in hormonal stress reactivity, brain maturation, and sensitivity to stress-related hormones may lead to the marked increase in stress-related dysfunctions often associated with adolescence, such as obesity, psychological disorders, and drug abuse.

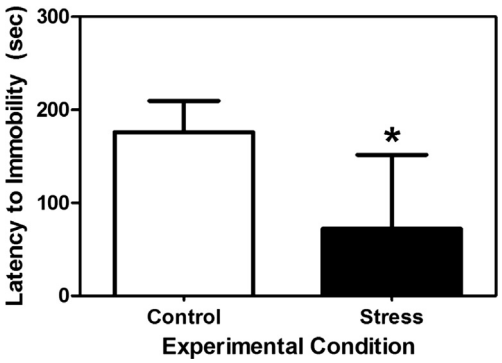

Fig. 2. Mean (±SEM) latency to immobility in the forced swim test exhibited by male rats in young adulthood that had previously been exposed to either 1 h of restraint stress every other day throughout adolescence (postnatal days 28–49; stress) or no restraint stress (control). Asterisk indicates a significant difference between the groups (t (15) = 3.81, p = 0.03). Note the relative large variance around the mean in the stress group (unpublished observation).

4. Early life programming of the HPA axis

The HPA axis is the primary neuroendocrine axis that mediates stress-induced hormonal responses. This response is driven by a cascade of signals beginning with the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH is released into the hypophyseal portal system, which in turn leads to the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary. ACTH then stimulates the secretion of the glucocorticoids (i.e., cortisol in primates and corticosterone in many rodent species) from the adrenal cortex (Herman and Cullinan, 1997; Herman et al., 2003; Ulrich-Lai and Herman, 2009).

In the short-term, release of these hormones mediate many beneficial effects, such as mobilization of energy stores, reduced inflammation, and enhanced immune activity and memory formation (McEwen, 2007; Roozendaal, 2000; Sapolsky et al., 2000; Dhabhar, 2009). However, if individuals experience prolonged or repeated exposure to these stress-related hormones, then negative effects may emerge, including altered metabolism and cognitive deficits (McEwen, 2005; McEwen and Stellar, 1993; McEwen, 2003; Sapolsky, 1999; Herbert et al., 2006; McEwen, 2004; van Praag, 2004). Therefore, factors that modulate the responsiveness of the HPA axis may have significant and widespread consequences for the individual.

Many experiments have addressed how experiences early in life shape HPA axis function and the implications these changes may