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NEUROBIOLOGICAL MECHANISMS SUPPORTING EXPERIENCE-DEPENDENT RESISTANCE TO SOCIAL STRESS

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Abstract—Humans and other animals show a remarkable capacity for resilience following traumatic, stressful events. Resilience is thought to be an active process related to coping with stress, although the cellular and molecular mechanisms that support active coping and stress resistance remain poorly understood. In this review, we focus on the neurobiological mechanisms by which environmental and social experiences promote stress resistance. In male Syrian hamsters, exposure to a brief social defeat stressor leads to increased avoidance of novel opponents, which we call conditioned defeat. Also, hamsters that have achieved dominant social status show reduced conditioned defeat as well as cellular and molecular changes in the neural circuits controlling the conditioned defeat response. We propose that experience-dependent neural plasticity occurs in the prelimbic (PL) cortex, infralimbic (IL) cortex, and ventral medial amygdala (vMeA) during the maintenance of dominance relationships, and that adaptations in these neural circuits support stress resistance in dominant individuals. Overall, behavioral treatments that promote success in competitive interactions may represent valuable interventions for instilling resilience. © 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: amygdala, dominance relationships, infralimbic cortex, medial prefrontal cortex, resilience, social defeat.

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INTRODUCTION

Stressors often generate adaptive behavioral and physiological responses that restore internal homeostasis. However, when stressors are perceived as uncontrollable, prolonged, or especially severe, they can lead to several negative health consequences, including major depression, panic disorder, and post-traumatic stress disorder (PTSD) (Abelson et al., 2007; Meewisse et al., 2007; Heim et al., 2008). Only a portion of individuals exposed to stressful life events develop stress-related psychopathology, suggesting that a great deal of individual variation exists in vulnerability to the negative consequences of stress. More than two-thirds of people in the general population experience a traumatic event at some point in their lifetime, but only 10–20% develop PTSD (Galea et al., 2005; Thomas et al., 2010). Similarly, only 20–25% of individuals exposed to major stressful events develop major depression (Cohen et al., 2007). Understanding the neural circuits and cellular mechanisms that control stress vulnerability is an important step toward identifying novel targets for the prevention and treatment of stress-related psychopathology.

Resilience refers to an individual's capacity to cope with stress and adversity so that they avoid the negative psychological and biological consequences that would otherwise impair physical and psychological well-being (Luthar et al., 2006). Resilience may be demonstrated by resistance to the negative effects of stress or by recovery to a normal state of functioning more quickly than expected following traumatic stress. It is important to distinguish between resistance to and recovery from

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Abbreviations: BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; DRN, dorsal raphe nucleus; HPA, hypothalamic–pituitary–adrenal; 5-HT, serotonin; IL, infralimbic cortex; LAB, low-anxiety-related behavior; LAL, long attack latency; MeA, medial amygdala; NAc, nucleus accumbens; NMDA, N-methyl-*D*-aspartate; PL, prelimbic cortex; PTSD, post-traumatic stress disorder; SAL, short attack latency; vMeA, ventral medial amygdala; vmPFC, ventral medial prefrontal cortex.

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stressful events, as these processes might involve separate brain regions, neurochemicals, and identifying biomarkers (Yehuda et al., 2006). In animal models, the distinction is not always clear, and resilience usually refers to a decrease in stress-induced changes in future behavior. This body of work indicates that resilience is not simply a passive response involving a failure to display the neuroendocrine, cellular, and molecular changes characteristic of susceptible individuals, but is also an active response that involves distinct neural circuits and cellular mechanisms (Russo et al., 2012).

In this review, we focus on neurobiological mechanisms controlling active processes that characterize resilient individuals. Several animal models of stress resilience focus on mechanisms underlying individual differences that are likely related to genetic and epigenetic factors. We briefly review literature on individual differences in stress vulnerability, although several excellent reviews have recently addressed this topic (Coppens et al., 2010; Russo et al., 2012; Wu et al., 2013). Here, we instead emphasize animal models that investigate mechanisms controlling experience-dependent forms of stress resistance with a focus on resistance to social defeat in Syrian hamsters. In cases of experience-dependent stress resilience, individuals exposed to specific environmental or social stimuli show a reduction in the effects of stress. We maintain that understanding the neurobiological mechanisms controlling the development of resilience should provide the foundation for future evidence-based interventions targeting those at risk of stress-related psychopathology.

INDIVIDUAL DIFFERENCES IN RESILIENCE

It is well recognized that only a subset of people develop mental health problems following exposure to traumatic and/or stressful events. Likewise, animals exhibit considerable variability in behavioral and physiological responses to stress, and the mechanisms underlying these individual differences have been explicitly studied to better understand the biological basis of resilience.

Coping styles

Individual differences in stress responses that are consistent over time and across contexts are referred to as coping styles (Koolhaas et al., 1999). Individual variation in aggressive behavior is associated with how rodents responded to a variety of challenging situations, with individuals employing either proactive or reactive coping styles. Proactive rats exhibit high levels of offensive aggression in a resident–intruder paradigm, active burying of a shock-probe in a defensive burying test, and high amounts of swimming during a forced swim test. In contrast, reactive rats exhibit low levels of offensive aggression, avoidance of a shock-probe, and high levels of floating (Koolhaas et al., 2007). Several neuroendocrine and neurochemical markers differentiate proactive and reactive individuals. Proactive rats display greater sympathetic nervous system reactivity but no difference in stress-induced plasma glucocorticoids compared to rats with a reactive coping style (Koolhaas et al., 2010). Also, proactive rats show increased sensitivity of 5-HT1a and 5-HT1b autoreceptors compared to reactive rats, indicating that they have enhanced tonic inhibitory control of the serotonin (5-HT) system (de Boer and Koolhaas, 2005).

Proactive and reactive coping styles have also been investigated in feral house mice bred for a bimodal distribution of attack latencies in a resident–intruder test. Mice bred for a long attack latency (LAL) are more vulnerable to the effects of chronic social defeat compared to mice bred for a short attack latency (SAL). Specifically, LAL mice showed a longer lasting body weight loss, a greater increase in corticosterone, and increased anxiety- and depression-like behavior following chronic social defeat compared to SAL mice (Veenema et al., 2003). The LAL mice also exhibited a lower hippocampal mineralocorticoid to glucocorticoid receptor ratio, which is characteristic of the hypothalamic–pituitary–adrenal (HPA) axis dysregulation often found in human depression (Veenema et al., 2003). The coping styles of LAL and SAL mice are also associated with differences in 5-HT signaling. In response to forced swim stress, SAL mice show decreased 5-HT concentrations in the frontal cortex, striatum, lateral septum, hippocampus, amygdala, and brain stem compared to LAL mice (Veenema et al., 2005). Consistent with proactive rats, SAL mice are characterized by enhanced somatodendritic 5-HT1a autoreceptor activity (de Boer et al., 2009). In another animal model of coping styles, Wistar rats have also been bred for high (HAB) or low (LAB) anxiety-related behavior. LAB rats are characterized by increased inter-male aggression, reduced HPA axis activity to nonsocial stressors, and changes in 5-HT neurotransmission (Veenema and Neumann, 2007). Thus, high aggression phenotypes are often associated with changes in the regulation of stress hormones and the 5-HT system that support a proactive coping style.

A proactive coping style, however, is not always beneficial. Coping styles may differ in behavioral flexibility insofar as animals with a reactive coping style appear more guided by environmental stimuli while animals with a proactive coping style seem more likely to develop routines. For example, in pigs proactive individuals have far more difficulty switching responses in a T-maze reversal learning test compared to reactive individuals (Bolhuis et al., 2004). Similarly, high-aggression hamsters show increased impulsivity compared to low-aggression hamsters as the former repeatedly bar press for immediate, small rewards, whereas the latter will delay responding for large rewards (Cervantes and Delville, 2009). Overall, the neurochemical and neuroendocrine changes that support a proactive coping style may promote stress resilience and appear adaptive in some context but lead to behavioral inflexibility and impulsivity in others. Interestingly, in some cases a flexible coping strategy may be advantageous compared to a consistent active or passive coping strategy. Rats can be categorized as active or passive copers based on whether they exhibit many or few escape attempts during a series of supine restraint tests, respectively. Further, rats that are categorized as active in one trial and passive