Neurobiology of Stress 1 (2015) 66–79

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Peripheral and central mechanisms of stress resilience

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ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form
19 September 2014
Accepted 22 September 2014
Available online 30 September 2014

Keywords:
Resilience
Stress
Depression
Anxiety
Neuroimmune
Plasticity

ABSTRACT

Viable new treatments for depression and anxiety have been slow to emerge, likely owing to the complex and incompletely understood etiology of these disorders. A budding area of research with great therapeutic promise involves the study of resilience, the adaptive maintenance of normal physiology and behavior despite exposure to marked psychological stress. This phenomenon, documented in both humans and animal models, involves coordinated biological mechanisms in numerous bodily systems, both peripheral and central. In this review, we provide an overview of resilience mechanisms throughout the body, discussing current research in animal models investigating the roles of the neuroendocrine, immune, and central nervous systems in behavioral resilience to stress.

1. Introduction

Decades of research on human stress resilience have followed its initial description in at risk children in the 1970s (Masten, 2001). Resilience is defined as the adaptive maintenance of normal physiology, development and behavior in the face of pronounced stress and adversity. Human resilience literature contains countless examples of adults and children who, despite marked psychological stress, display minimal adverse changes in emotional wellbeing or behavioral disturbances (Feder et al., 2009; Yehuda et al., 2006b; Alim et al., 2008; Fredrickson et al., 2003; Bonanno, 2004). Although it is tempting to attribute human resilience to the possession of exceptional abilities and coping mechanisms, both social and biological, most people do not develop anxiety and depression when faced with stress (Masten, 2001; Bonanno, 2004). Resilience is a common outcome that more likely involves the successful application of the body's adaptive stress response to maintaining the status quo. The biological processes underlying resilience are often collectively termed “allostasis” and constitute variation in bodily systems that functions to maintain homeostasis in response to a stressor (McEwen, 2002). In some cases, allostasis is exaggerated or fails to cease along with the stressor, and mechanisms that were once protective can become pathological. This phenomenon—termed “allostatic load”—can potentially result in physiological and psychological damage, including enhanced susceptibility to disorders such as depression and anxiety (McEwen, 2002; Charney, 2004).

Mechanisms of resilience are of great interest due to the serious burdens imposed on patients and society by stress-related disorders including anxiety and depression. One in six Americans will develop Major Depressive Disorder (MDD) during their lifetime, a particularly alarming statistic as only 30% of patients achieve complete remission of symptoms following treatment with current first-line therapies, the monoamine-based antidepressants (Krishnan and Nestler, 2008; Kessler et al., 2005). When not adequately treated, MDD can become a chronic, recurrent condition characterized by escalating disability (Moussavi et al., 2007). Comprehensive knowledge of the etiology of depression is still lacking. Understanding the adaptive, allostatic mechanisms that protect most individuals against psychopathology can potentially inform therapeutic development and treatment strategies for more vulnerable individuals.

Depression and anxiety are increasingly considered to be “whole body” illnesses involving the dysregulation of multiple systems, both peripheral and central. Similarly, resilience likely results from successful allostatic mechanisms in the

Abbreviations: CUS, chronic unpredictable stress; SCUS, subchronic unpredictable stress; CSDS, chronic social defeat stress; LH, learned helplessness; LG, licking and grooming; OVX, ovariectomy; SDR, social disruption stress.

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http://dx.doi.org/10.1016/j.ynstr.2014.09.004

hypothalamo–pituitary–adrenal (HPA) axis, autonomic nervous system, immune system and the brain (McEwen, 2002). In this review, we summarize recent research into the roles of the neuroendocrine, immune and central nervous systems in resilience to stress, focusing primarily on animal models. We describe both active, compensatory mechanisms as well as passive mechanisms in which the absence of a maladaptive stress response promotes resilience. We present resilience as an integrated process by which adaptive mechanisms in multiple systems promote psychological resilience to stress.

2. Animal models for the study of stress vulnerability and resilience

Research on human subjects has yielded important insights into the roles of various neurotransmitters, neuropeptides and hormones as well as genetic factors in the neurobiology of resilience (for comprehensive reviews, see Charney, 2004; Russo et al., 2012). For ethical and practical reasons, animal models are often employed to examine the causative effects of stress on biological processes in the brain and body. Resilience to stress has been documented and characterized in animal models throughout the lifespan. Below, we describe in detail several behavioral paradigms commonly used to elicit and study stress resilient phenotypes in juvenile and adult animals.

2.1. Early life stress

Models of early life stress have informed our understanding of a form of resilience called stress inoculation, whereby early stressful experience attenuates stress response in adulthood. In children, early stress can have a "steeling" effect, promoting subsequent stress resistance and successful psychological functioning (Rutter, 2006). Animal models of early life stress typically involve exposure to stressful stimuli during either the prenatal or postnatal periods. Prenatal stressors include maternal stress such as glucocorticoid administration or food deprivation while early postnatal stressors include brief bouts of maternal separation, altered maternal care behavior, or glucocorticoid administration (Lupien et al., 2009). Prolonged early life stress can cause programmed HPA axis overactivity, altered glucocorticoid response, structural changes in the brain, and deleterious effects on cognition, emotion and behavior (Lupien et al., 2009). These effects can be reconciled with the concept of stress inoculation by imagining adult outcomes of early life stress as a U-shaped curve—animals exposed to moderate stress in early life show better outcomes and more adaptive responses to stress in adulthood than do animals exposed to minimal or severe stress (Macri et al., 2011). Stress inoculation has been demonstrated in both primates and rodents. Infant squirrel monkeys separated from their mothers for brief, intermittent periods demonstrate reduced hormonal stress response in subsequent developmental stages (Lyons et al., 2010; Parker et al., 2005). They also demonstrate cognitive and emotional resilience across measures relevant to anxiety and depression, such as enhanced novelty tolerance, exploratory behavior and behavioral response inhibition (Lyons et al., 2010; Parker et al., 2004, 2005). There is a rich literature on stress inoculation in rodents demonstrating that rats exposed to early life stress, including brief maternal separations and neonatal corticosterone administration, display blunted HPA axis response to stress in adulthood as well as behavioral resilience in the form of reduced anxiety-like behavior and enhanced performance in cognitive tasks (Macri et al., 2009; Plotsky and Meaney, 1993; Macri and Wurbel, 2007; Levine, 1962; Levine et al., 1967). The relationship between early life stress exposure and subsequent resilience in both primates and rodents follows the abovementioned U-shaped curve. Prolonged maternal separation and social isolation in infant rhesus monkeys produce an increased stress response and "despair-like" behavior in subsequent social separation tests (Young et al., 1973). Rats exposed to moderate early life stress show enhanced measures of resilience compared to both severely and minimally stressed rats (Macri and Wurbel, 2007). For example, early postnatal rats exposed to brief daily handling (a moderate stressor) subsequently show attenuated stress response compared to undisturbed pups and pups exposed to prolonged daily maternal separation (a more severe stressor) (Plotsky and Meaney, 1993; Macri et al., 2004).

2.2. Chronic unpredictable stress

Chronic unpredictable stress (CUS) is a useful model for examining stress vulnerability and resilience in rodents (Ricon et al., 2012; LaPlant et al., 2009). In CUS paradigms, animals are exposed to varying mild stressors sequentially for a period of 1–7 weeks (Krishnan and Nestler, 2011; Willner, 1997). Stressors can include mild foot shock, physical restraint, tail suspension, light/dark cycle disruption, food or water restriction, changes to cage mate, etc., and are changed after several hours to minimize habituation (LaPlant et al., 2009; Willner, 1997). CUS produces a range of depression and anxiety-like behaviors in rodents including anhedonia, measured as decreased sucrose preference, despair-like behavior, measured as increased immobility in the forced swim and tail suspension tests, and novelty suppressed feeding, measured as a decrease in approach to a novel food item (Krishnan and Nestler, 2011; Mineur et al., 2006; Feng et al., 2012). Mice exposed to CUS also display decreased grooming, aggression, and sexual behaviors. Certain CUS-induced behavioral changes, such as novelty suppressed feeding, can be reversed only by chronic antidepressant treatment (Willner, 1997), making CUS relevant to human antidepressant responses. Female mice display immobility in the forced swim test after just 6 days of subchronic unpredictable stress (SCUS) whereas males are generally resilient to SCUS and require 20–28 days of CUS exposure to elicit depression- and anxiety-like behavior (Hodes, G.E. et al., *Soc. Neurosci. Abstr. 219.01, 2011*). Interestingly, age is a factor in response to CUS—male rats exposed to 60 days of CUS in the juvenile period exhibit greater memory retention in a two-way shuttle avoidance task compared to rats exposed to the same stressor in adulthood, indicating enhanced cognitive resilience (Ricon et al., 2012). Sex differences and age effects in susceptibility to CUS-induced depression and anxiety-like behavior make this a powerful tool for investigating the hormonal and neural basis for stress vulnerability and resilience across the lifespan.

2.3. Chronic social defeat stress

Chronic social defeat stress (CSDS) is a prolonged social stress paradigm used to delineate stress resilient and susceptible phenotypes in adult rodents. In the CSDS model, a C57BL/6J mouse is repeatedly subordinated by a larger, aggressive CD-1 mouse for 10 consecutive days (Golden et al., 2011). Each physical bout is followed by overnight sensory contact with the aggressor through a plastic partition. Following CSDS, approximately 2/3 of experimental mice, termed "susceptible," develop a constellation of depression-like behaviors including social avoidance and anhedonia (Krishnan et al., 2007; Donahue et al., 2014) as well as metabolic syndrome marked by dysregulated feeding peptides, weight gain and insulin insensitivity (Chuang et al., 2010; Lutter et al., 2008). Conversely, the remaining 1/3 of mice, termed "resilient," develop a much milder phenotype, including elevated corticosterone and increased anxiety-like behavior (Krishnan et al., 2007).