

Commentary

Expanding Our Understanding of Neurobiological Mechanisms of Resilience by Using Animal Models

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The original conceptualization of stress and the stress response has been developed based on the understanding that certain environmental exposures and life events can be both detrimental to individual's health and wellbeing, and also promote physiological responses that can be adaptive. Interestingly, until recently, the majority of translational research focused on neurobiological processes involved in the abnormal or altered stress response, on the vulnerability to stress, or the negative consequences of stress. Only recently the field started focusing on the concept of resilience, exploring the possibility that, similarly to stress vulnerability, there could be unique mechanisms involved in resilience to stress. Defining resilience has not been easy and within clinical research, resilience often refers to the ability of an organism to deal with, or adapt to, the pathological effects of stress. This seemingly subtle shift in research focus actually has immediate and substantial implications to stress research, as it suggests that some individuals are particularly adept at dealing with stressful situations, and if we examine this subgroup of individuals, we are likely to find different or compensatory changes, or changes in biological processes that are diametrically opposed to those found in stress-vulnerable individuals.

It has long been known that significant individual variability in vulnerability to severe stress or trauma exists with respect to the development of psychiatric consequences like post-traumatic stress disorder (PTSD), however, the resilience perspective might suggest that this can be accounted for by individual variability in resilience. Insofar as the mechanisms of vulnerability and resilience do not overlap completely, the study of the neurobiology of resilience is not simply a mirror of the study of stress vulnerability, but it could offer new perspectives on pathophysiology or treatment of stress-induced anxiety disorders such as PTSD and depression. Together with the study of stress vulnerability, understanding the neurobiology of resilience could

provide a more comprehensive picture in the service of understanding pathophysiology, development of new treatments for stress-induced psychiatric disorders, and identifying markers for primary and secondary prevention. More importantly, if individuals who have low levels of resilience can be treated in such a manner so as to increase their levels of resilience, this could greatly reduce the incidence of stress-induced psychiatric disorders.

Understanding the neurobiology of resilience in clinical research can be hindered by ethical constraints, but can be readily explored by employing animal models of stress and trauma. One promising approach for studying the neurobiology of resilience is the use of the cut-off behavioral criteria (CBC), as proposed by Cohen *et al.* This method, here applied to predator-odor-exposed animals that are later tested for startle and anxiety behavior, allows for identification of not only vulnerable groups (extreme behavioral response) but also resilient subgroups (minimal behavioral response). By examining experimental procedures that increase the incidence of minimal responders after predator odor exposure, neurobiological mechanisms of resilience can be explored.

In a recent study by Cohen *et al.* (2011), the authors used predator odor exposure with CBC to demonstrate that neuropeptide Y (NPY) expression in hippocampus, periaqueductal gray, and amygdala are associated with resilience to predator odor effects. The authors also report that NPY infusion into the hippocampus, 1 h following predator odor exposure, leads to a larger ratio of resilient animals whereas blockade of the NPY-1 receptor in the hippocampus decreases the incidence of resilient behavior. These findings suggest that NPY-1 receptor activation in the hippocampus is involved in, or even critical for, the development of resilience after stress exposure. These results are in agreement with previous reports of association of NPY plasma levels and resilience to traumatic stress in human subjects (Yehuda *et al.*, 2006) and polymorphisms in the NPY gene and resilience in non-human primates (Lindell *et al.*, 2010). Where the study by Cohen *et al.* (2011) adds to the literature about NPY and resilience is the specific mechanism and the neuroanatomical region (ie, enhanced activation of the NPY1 receptor in the

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hippocampus) for NPY effects. The hippocampus is critical for contextual processing, and we had argued that contextual processing is central in PTSD (Liberzon and Sripada, 2008). There is also a well-documented role for the hippocampus in stress responsivity, and although significant controversy regarding hippocampal volume abnormalities in PTSD existed in the literature, accumulating evidence confirms hippocampal abnormalities in PTSD. Various studies of animal models of PTSD have consistently implicated hippocampal abnormalities in PTSD, and the changes in brain-derived neurotrophic factor (BDNF) and its receptor (TrkB) signaling in the hippocampus have been reported both in SPS (Takei *et al.*, 2011) and predator-exposure models (Roth *et al.*, 2011). Cohen *et al.* (2011) further extended these findings by reporting increases in BDNF and a decrease in glucocorticoid receptor expression in the hippocampus with increased NPY expression. The link between NPY and glucocorticoid signaling has been reported in SPS animal model of PTSD (Cui *et al.*, 2008), however, additional research is needed to establish the link between NPY-1 receptor activation in the hippocampus and changes in BDNF and glucocorticoid receptor expression.

The animal models of PTSD studies have been helpful in identifying target mechanisms involved in PTSD pathophysiology and possible vulnerability. The role of glucocorticoid, serotonergic, glutamatergic, and catecholaminergic systems have been consistently implicated in vulnerability and resilience to stress, and is continuously studied. Application of CBC by Cohen *et al.* brings a new dimension to this effort by creating an opportunity to focus on highly resilient groups, and highlighting novel neurobiological

targets like NPY in the hippocampus for the study of neurobiology of resilience.

DISCLOSURE

The author declares no conflict interest.

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