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Animal models in translational studies of PTSD

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Summary Understanding the neurobiological mechanisms of post-traumatic stress disorder (PTSD) is of vital importance for developing biomarkers and more effective pharmacotherapy for this disorder. The design of bidirectional translational studies addressing all facets of PTSD is needed. Animal models of PTSD are needed not only to capture the complexity of PTSD behavioral characteristics, but also to address experimentally the influence of variety of factors which might determine an individual's vulnerability or resilience to trauma, e.g., genetic predisposition, early-life experience and social support. The current review covers recent translational approaches to bridge the gap between human and animal PTSD research and to create a framework for discovery of biomarkers and novel therapeutics.
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1. Introduction

Activation of stress-responsive neuroendocrine systems is an essential component of an individual's capacity to respond to a threat. Elevated levels of epinephrine and glucocorticoids (GCs; i.e., corticosterone in rodents or cortisol and corticosterone in human and non-human primate) mobilize energy reserves to meet the metabolic demands involved in responding to the threat. Although this process is fundamentally adaptive and restorative, repeated or intense activation of stress-responsive systems may produce detrimental effects on brain and/or behavior (de Kloet et al., 2005). Posttraumatic stress disorder (PTSD) is a condition that occurs following exposure to an extremely traumatic experience that reflects an intense and prolonged response to stress (Yehuda, 2002; Owens et al., 2005; Reeves et al., 2005). People diagnosed with PTSD exhibit a broad range of symptoms including

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hyperarousal, avoidance, intrusive memories and abnormalities in fear responses, which can impair social, occupational and interpersonal functioning (APA, 2000). The phenomenology is striking given that, in most cases, the stressor that produced the initial fear response is no longer present as an active threat. Rather, it is the memory of the experience that appears to perpetuate symptoms.

We have yet to achieve a satisfactory understanding of the etiology and neurobiological basis of PTSD (Zoladz and Diamond, 2013). This lack of a thorough understanding of the basis of PTSD is particularly salient considering that PTSD is the 4th most common psychiatric disorder, with a 6.8% lifetime prevalence in the US (Kessler et al., 1995). In addition, PTSD is associated with increased rates of psychiatric and neurologic disorders (e.g., substance abuse, depression, anxiety, suicide, psychosis, traumatic brain injury, pain) and physical diseases (e.g., cardiovascular, musculoskeletal, respiratory) (Nemeroff et al., 2006). Many patients are resistant to improvement of their symptoms with treatment, and never achieve complete remission. Therefore, animal models of PTSD are of great value for understanding pathophysiology of PTSD and possibly in the development of novel, and potentially more effective, treatment or prevention strategies in PTSD (Miller and McEwen, 2006; Yehuda and LeDoux, 2007; Andero and Ressler, 2012).

Bidirectional translational studies (from bedside to bench and from bench to bedside) can enhance our understanding of the mechanisms underlying the susceptibility of subsets of individuals to develop PTSD, as well as abnormal, delayed or prolonged responses to trauma. In this review we will provide an overview of translational aspects of stress research, with an emphasis on features of PTSD, which are amenable to study in animals. The goal is to provide an update on recent findings on animal models of PTSD with a focus on the neurobiology of stress and trauma, and to address strategies for developing novel pharmacotherapies for PTSD.

2. Preclinical and clinical research on risk factors for PTSD

Whereas initial concepts in stress research focused on a uniform, if not monolithic, response to challenge, PTSD is emblematic of a new paradigm in stress research in demonstrating, first and foremost, that there is enormous individual variability in chronic responses to trauma. It is well-established that only a subset of individuals exposed to trauma develops PTSD, suggesting that individual differences, i.e., risks and resilience factors, are critical factors that must be addressed in any research program on PTSD (Yehuda et al., 2011). How a person responds to a traumatic experience is influenced by multiple factors that are associated with characteristics other than the actual stress exposure such as the age and gender of the individual, personality variables, genetics, social support (Yehuda, 1999; Davidson et al., 2004; Keane et al., 2006) and, their own experiences prior to the traumatic event, most notably, a history of childhood abuse or neglect (Bremner, 2003; Penza et al., 2003; Anda et al., 2006). Clinical and animal studies indicate that early-life stress can result in enduring changes in neuroendocrine regulation (Yehuda et al., 2010b; Belay et al., 2011; Claessens et al., 2011), as well as neurobiological reorganization of forebrain structures, including the hippocampus and prefrontal cortex (McEwen, 2007; Gatt et al., 2009; Davidson and McEwen, 2012). These can increase the risk of developing subsequent depression and anxiety disorders, because they may alter the way individuals experience ongoing life events and challenges. The biological changes associated with such responses, sometimes referred to as sensitization, negatively impact the effectiveness of pharmacotherapy for PTSD (Marshall et al., 1998).

Animal studies have provided insight into how early developmental stress produces lifelong effects on behavior and stress reactivity in animals (Champagne and Meaney, 2006; Claessens et al., 2011). Early postnatal stress in the form of low maternal care or maternal separation lead to numerous changes in brain and behavior, for example, in enhanced conditioned fear together with elevated hippocampal plasticity in adulthood (Champagne et al., 2008; Oomen et al., 2010). In related work, a series of experiments demonstrated that juvenile stress has profound, but complex and sex-specific, effects in responses to stress in adulthood (Bazak et al., 2009; Tsoory et al., 2010; Horovitz et al., 2012; Ricon et al., 2012), including an increase in the prevalence of extreme behavioral responses following exposure to predator scent stress (PSS) (Cohen et al., 2007). Furthermore, maltreatment of rat pups results in a life-long, and even a transgenerational, effect on behavior and DNA methylation (Roth et al., 2009; Franklin et al., 2010).

In addition to early-life experience, a major contributor to individual differences in responses to stress appears to be gender/sex. Epidemiologic survey studies have shown that PTSD is twice as common in women as in men. In addition, there are gender differences in the type of trauma exposure, presentation of illness, and comorbidities (Kessler et al., 1995, 2005a, 2005b; Nemeroff et al., 2006). An example of the pronounced gender difference in PTSD susceptibility was provided by Norris et al., who reported that most (94%) of a large sample of studies that had reported a significant gender effect had identified a greater incidence of PTSD in women compared to men (Norris et al., 2002).

The epidemiological assessments of gender and PTSD susceptibility have led some investigators to emphasize the importance of studying the susceptibility of females, regardless of species, to develop trauma-induced psychopathology (Cahill, 2006; Cohen and Yehuda, 2011). For example, in a rat population exposed to PSS, females were more vulnerable to exhibit a PTSD-like phenotype in terms of magnitude of response, but not in terms of prevalence of extreme behavioral response (Mazor et al., 2009). It should be noted, however, that stress studies in rodents have produced complex, often opposing, gender differences in stress and memory processing (Wood and Shors, 1998; Wolf et al., 2001; Shors, 2002; Conrad et al., 2004; Kuhlmann et al., 2005; Stark et al., 2006; Bangasser and Shors, 2007; Shors et al., 2007; Park et al., 2008; Waddell et al., 2008; Andreano and Cahill, 2009; Schoofs and Wolf, 2009; Maeng et al., 2010; Merz et al., 2010). Ironically, the tendency for females to exhibit greater veracity in their memory retrieval in response to emotion-provoking cues has intrinsic value under moderate stress conditions, but may contribute to women generating more intense and intrusive memories in response to trauma compared to men (Ferree and Cahill, 2009; Ferree et al., 2011; Felmingham and Bryant, 2012). In interpreting