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Review Article

Predator-based psychosocial stress animal model of PTSD: Preclinical assessment of traumatic stress at cognitive, hormonal, pharmacological, cardiovascular and epigenetic levels of analysis

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ABSTRACT

Research on post-traumatic stress disorder (PTSD) is faced with the challenge of understanding how a traumatic experience produces long-lasting detrimental effects on behavior and brain functioning, and more globally, how stress exacerbates somatic disorders, including cardiovascular disease. Moreover, the design of translational research needs to link animal models of PTSD to clinically relevant risk factors which address why only a subset of traumatized individuals develop persistent psychopathology. In this review, we have summarized our psychosocial stress rodent model of PTSD which is based on well-described PTSD-inducing risk factors, including a life-threatening experience, a sense of horror and uncontrollability, and insufficient social support. Specifically, our animal model of PTSD integrates acute episodes of inescapable exposure of immobilized rats to a predator with chronic daily social instability. This stress regimen produces PTSD-like effects in rats at behavioral, cognitive, physiological, pharmacological and epigenetic levels of analysis. We have discussed a recent extension of our animal model of PTSD in which stress exacerbated coronary pathology following an ischemic event, assessed *in vitro*. In addition, we have reviewed our research investigating pharmacological and non-pharmacological therapeutic strategies which may have value in clinical approaches toward the treatment of traumatized people. Overall, our translational approach bridges the gap between human and animal PTSD research to create a framework with which to enhance our understanding of the biological basis of trauma-induced pathology and to assess therapeutic approaches in the treatment of psychopathology.

Contents

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1. General characteristics of post-traumatic stress disorder

Individuals who are exposed to life-threatening trauma, such as wartime combat, motor vehicle accidents, terrorist attacks or rape, are at risk for developing post-traumatic stress disorder (PTSD). People with PTSD endure chronic psychological distress by repeatedly reliving their trauma through intrusive, flashback memories (Reynolds and Brewin, 1999; Speckens et al., 2007). These individuals also exhibit several other physiological and behavioral symptoms, such as persistent anxiety, hyperarousal, cognitive impairments and autonomic and immune system dysfunction (Schmidt et al., 2013; Vanelzakker et al., 2013; Zoladz and Diamond, 2013). Only a subset of traumatized individuals develops PTSD, depending on a multitude of interacting risk factors, including the nature of the trauma, sex, genetics, social support and early life experiences (Koenen et al., 2009; Voisey et al., 2014; Zoladz and Diamond, 2013). Therefore, understanding susceptibility factors that promote persistent and intrusive traumatic memory expression, as well as more global somatic PTSD symptoms, is of great scientific and practical value.

2. The utility of animal models of PTSD

Whereas clinical research is vital for improving our understanding of the basic phenomenology of PTSD and the implementation of novel therapeutics, animal models of PTSD provide a crucial complementary component to this process. In addition to their key role in establishing the safety and initial efficacy of novel therapeutic compounds, animal models are valuable in three key areas of treatment development. First, animal models facilitate the rapid cost effective development of proof of concept studies to identify the most promising pharmacological candidates which can block trauma-induced behavioral and physiological abnormalities. This approach, with direct molecular assays of neural tissue, can improve our understanding of the mechanisms of action of these compounds. Second, animal research provides for assessment of the effects of interventions initiated prior to, or soon after, trauma occurs. This approach provides for the opportunity to develop preventive strategies which would be high risk, expensive and potentially unethical to undertake in people. Finally, animal studies provide for the study of direct tests for different PTSD comorbidities and risk factors that might influence treatment responses in people, such as early life abuse, sex, social support and traumatic brain injury.

Preclinical research on traumatic stress has spawned a vast amount of research on the effects of exposing animals, primarily rodents, to strong stressful experiences followed by physiological and behavioral testing, which, in theory, provides insight into PTSD in traumatized people (Stam, 2007). Such studies have employed several different types of stressors, such as electric shock (Garrick et al., 2001; Li et al., 2006; Milde et al., 2003; Pynoos et al., 1996; Rau et al., 2005; Sawamura et al., 2004; Servatius et al., 1995; Shimizu et al., 2004, 2006; Siegmund and Wotjak, 2007a, b; Wakizono et al., 2007), underwater trauma (Cohen et al., 2005; Richter-Levin, 1998), stress–restress and single prolonged stress paradigms (Harvey et al., 2003; Khan and Liberzon, 2004; Kohda et al., 2007; Liberzon et al., 1997; Takahashi et al., 2006) and exposure to predators (Adamec, 1997; Adamec et al., 1997, 1999a, b, 2006a, c, 2007; Adamec and Shallow, 1993; Blundell and Adamec, 2007) or predator-related cues (Cohen et al., 2000b, 2005, 2006a,b; Daskalakis et al., 2013b; Goswami et al., 2013; Matar et al., 2006). Studies utilizing these stressors have shown that they result in physiological and behavioral changes in rodents that are comparable to those observed in people with PTSD, such as heightened anxiety, an exaggerated startle response, cognitive impairments, enhanced fear conditioning, resistance to fear extinction and reduced social interaction.

All of these paradigms have contributed toward our understanding of how traumatic stress changes aspects of physiology and behavior. However, there remain conceptual limitations to linking the study of stress in animals to generating a syndrome which resembles the clinical features of PTSD. For example, a routine observation of people who experience a horrific event or rats that are exposed to a strong aversive stimulus, such as a shock, is a powerful and persistent memory of the event. However, having a memory of the traumatic event, alone, is not the determinant of whether PTSD develops since only a subset of the individuals with disturbing memories of a horrific experience actually develop PTSD. Moreover, although traumatic memories are a hallmark feature of PTSD, the intrusive memory of the experience is only one component of the entire PTSD syndrome. Our view is that the cluster of symptoms in PTSD represents the inability to cope with the memory of the trauma. The challenge for an animal model of PTSD, therefore, is not only to generate a conditioned fear memory for a traumatic experience, but also to produce physiological and behavioral abnormalities which resemble the susceptibility and great complexity of the entire PTSD syndrome.

3. The usefulness of predator-based animal models of PTSD

Pioneering research by Caroline and Robert Blanchard described how rats exhibit a strong, innate fear of a predator, such as a cat (Blanchard et al., 1975, 1990). Their work also contributed to the development of studies examining predator scent, provided, for example, by cat or fox urine, as a stress-provoking stimulus which can substitute for the live animal (Apfelbach et al., 2005; Rosen, 2004). Further evidence of the effectiveness of predator exposure as a means with which to generate a fear response are findings in which predator exposure activates the hypothalamus–pituitary–adrenal (HPA) axis (Masini et al., 2006; Park et al., 2008; Woodson et al., 2003). At a functional level, extensive research demonstrates that predator exposure exerts a selective activation of brain circuitry (Silva et al., 2013) which may contribute to the profound capacity for predator exposure to impair spatial memory and synaptic plasticity in the hippocampus, and to enhance synaptic plasticity in the amygdala (Diamond et al., 1999, 2006; Mesches et al., 1999; Park et al., 2006, 2008; Vanelzakker et al., 2011; Vouimba et al., 2006; Woodson et al., 2003; Zoladz et al., 2012b). Therefore, the ethological relevance and potency of predator exposure provide a highly relevant approach toward producing an intense, purely psychological, fear response in rodent models of PTSD.

The laboratories of Robert Adamec, Jacqueline Blundell and Hagit Cohen have provided important basic research findings by employing live predator exposure or predator scent to induce PTSD-like symptoms in rodents. The Adamec and Blundell laboratories have shown that exposing rodents to physical contact with a live cat, typically for a period of 5 min, produces PTSD-like changes in physiology and behavior assessed 3 weeks later. Behaviorally, the 5-min cat exposure resulted in heightened anxiety on the elevated plus maze and in the light/dark box, reduced locomotor activity and exploratory behavior in the hole board test and an exaggerated startle response (Adamec et al., 1997, 2006b, 2008a, b, 2009; Adamec and Shallow, 1993; Mitra et al., 2009). These investigators have also examined the neural mechanisms underlying the behavioral effects of unprotected predator stress. They have shown that cat exposure induced molecular and electrophysiological evidence of synaptic plasticity in brain regions important for fear and defensive behavior, such as the amygdala and periaqueductal gray, and that the effects of predator stress can be prevented by NMDA receptor antagonists and the beta-adrenergic receptor antagonist, propranolol (Adamec, 1997, 1998, 2001; Adamec et al., 2001, 2005a, b, 2006c, 2007, 2011, 2012a, b; Blundell et al., 2005; Blundell and Adamec, 2006, 2007; Mitra et al., 2009). More recent work by Blundell and her co-workers has focused on mechanistic and behavioral approaches toward improving our understanding of the formation and persistence of a "traumatic" memory, enhancing its extinction in cat-exposed rodents and preventing the development of PTSD-like behavioral changes (Clay et al., 2011; Fifield et al., 2013, 2015; Mac Callum et al., 2014).

Hagit Cohen's group is well-known for their use of predator scent stress to produce PTSD-like sequelae in rats. These investigators