



## Animal Models of PTSD: What Stress Paradigms Induce Pathological Behavior?

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### Editorial

We are entering a new age when many findings from translational study about anxiety disorders are becoming available [1]. Exposure to traumatic stress can provoke fear-related disorders, including posttraumatic stress disorder (PTSD) [2,3]. DSM-IV lists three main clusters of PTSD symptoms, which are re-experiencing, avoidance, and hyperarousal. Underlying these core symptoms is dysregulation of the fear response, including the overgeneralization of fear, hypersensitivity to fear cues, inability to extinguish fear memories, and impairment of fear extinction [4,5]. A number of factors contribute to variability in an individual's risk of developing PTSD [6]. These include genetic factors (e.g., FKBP5; regulator of the hypothalamic-pituitary-adrenal (HPA) axis during stress), environmental factors (early life experiences such as child abuse), and interactions between genetic and environmental factors, resulting in differences of susceptibility to PTSD [7-9]. The genetic, molecular, and behavioral literature on fear extinction processes is huge and complex [4,10]. Various methods have been employed to generate traumatic stress in animal models of PTSD [11] and there is much literature addressing these models [12]. The animal models have involved single/repeated/chronic stress, escapable/ inescapable stress, Pavlovian fear conditioning/extinction with/without immobilization stress, predictable/unpredictable stress, and other paradigms with configuration for construct validity [12,13]. Behavioral changes occurring in response to such traumatic stress include fear, anxiety-like behavior (hypervigilance), and anhedonia (hyposensitivity) with configuration for face validity [13]. Next, I would like to discuss how stress induces pathological behavior based on findings in two animal models of PTSD, which are inescapable stress in a shuttle box and Pavlovian fear conditioning with immobilization.

We have been using inescapable stress in a shuttle box [14-16]; rats receive inescapable electrical shocks to the feet in a shuttle box with the gate closed and 2 weeks later perform an avoidance/escape task in the shuttle box with the gate open using signal lights as nonspecific anxiogenic stimulation. Rats subjected to inescapable stress showed decreased locomotor activity before the task session like the numbing symptoms (hyposensitivity) of PTSD and an increase of avoidance behavior during the session like the hypervigilance of PTSD. Administration of paroxetine (a selective serotonin reuptake inhibitor) suppressed the hypervigilant behavior of stressed rats during the task session [15]. We have also examined behavioral differences and the effects of exposure to chronic stress prior to inescapable stress in three rat strains [16]. Moreover a time-dependent increase of hypervigilance was observed to be negatively correlated with the number of bromodeoxyuridine-positive cells in the subgranular zone of the hippocampus [17], resembling the hippocampal dysfunction in PTSD patients [18]. Taken together, these findings suggest that the inescapable stress shuttle box paradigm is a useful animal model of PTSD.

Another useful animal model of PTSD is subjecting mice to immobilization stress on a wooden board followed one week later by Pavlovian fear conditioning [19]. Mice subjected to immobilization stress followed by tone-shock mediated fear conditioning showed impairment of fear extinction [19], as well as long-term impairment of spatial memory and enhanced anxiety [20]. These mice were unable to distinguish between danger and safety signals [20], and showed elevation of HPA axis activity with impaired fear extinction and impaired retention of extinction [19]. These findings are consistent with translational evidence that previous trauma is a risk factor for PTSD related to HPA axis activation [21]. The FKBP5 gene encodes FK506 binding protein 5 (FKBP5), which regulates glucocorticoid receptor sensitivity [7] and critically regulates HPA axis activity during the response to stress. Epigenetic modifications of FKBP5 potentially mediate the phenotype of trauma- and stress-related disorders, including the response to dexamethasone treatment [7-9,22]. It has also been demonstrated that dexamethasone administration leads to transient suppression of HPA function which may normalize exaggerated fear in PTSD patients [23,24].

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Received Date: 21 Jul 2016

Accepted Date: 01 Aug 2016

Published Date: 05 Aug 2016

#### Citation:

Sawamura T. Animal Models of PTSD: What Stress Paradigms Induce Pathological Behavior?. *Ann Clin Case Rep.* 2016; 1: 1073.

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In mice subjected to immobilization stress, we found that dexamethasone caused dose-dependent enhancement of both fear extinction and retention of extinction, along with reduced Fkbp5 mRNA expression in the amygdala. Moreover, DNA methylation of the Fkbp5 gene in the amygdala occurred in a dose-dependent and time-dependent manner together with dynamic changes of epigenetic regulation, including the Dnmt and Tet gene pathways [25]. These approaches have provided translational evidence that dexamethasone may be effective for PTSD via mechanisms related to the HPA axis [23,24] and that differential regulation of FKBP5 is a risk factor for PTSD [7-9].

Further investigations in PTSD animal models, including the inescapable stress and Pavlovian fear conditioning with immobilization paradigms, should contribute to answering the remaining questions about this disorder.

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