Review

Biological Psychiatry

# Current Status of Animal Models of Posttraumatic Stress Disorder: Behavioral and Biological Phenotypes, and Future Challenges in Improving Translation

Jessica Deslauriers, Mate Toth, Andre Der-Avakian, and Victoria B. Risbrough

**ABSTRACT**

Increasing predictability of animal models of posttraumatic stress disorder (PTSD) has required active collaboration between clinical and preclinical scientists. Modeling PTSD is challenging, as it is a heterogeneous disorder with ≥20 symptoms. Clinical research increasingly utilizes objective biological measures (e.g., imaging, peripheral biomarkers) or nonverbal behaviors and/or physiological responses to complement verbally reported symptoms. This shift toward more-objectively measurable phenotypes enables refinement of current animal models of PTSD, and it supports the incorporation of homologous measures across species. We reviewed >600 articles to examine the ability of current rodent models to probe biological phenotypes of PTSD (e.g., sleep disturbances, hippocampal and fear-circuit dysfunction, inflammation, glucocorticoid receptor hypersensitivity) in addition to behavioral phenotypes. Most models reliably produced enduring generalized anxiety–like or depression-like behaviors, as well as hyperactive fear circuits, glucocorticoid receptor hypersensitivity, and response to long-term selective serotonin reuptake inhibitors. Although a few paradigms probed fear conditioning/extinction or utilized peripheral immune, sleep, and noninvasive imaging measures, we argue that these should be incorporated more to enhance translation. Data on female subjects, on subjects at different ages across the life span, or on temporal trajectories of phenotypes after stress that can inform model validity and treatment study design are needed. Overall, preclinical (and clinical) PTSD researchers are increasingly incorporating homologous biological measures to assess markers of risk, response, and treatment outcome. This shift is exciting, as we and many others hope it not only will support translation of drug efficacy from animal models to clinical trials but also will potentially improve predictability of stage II for stage III clinical trials.

***Keywords:*** Animal model, Immobilization, Predator stress, PTSD, Shock, Single prolonged stress, Social defeat, Unpredictable variable stress

https://doi.org/10.1016/j.biopsych.2017.11.019

Globally, the prevalence rate for posttraumatic stress disorder (PTSD) is 4% to 6%, with the disorder being described by Koenen *et al.* (1) as a "life sentence due to its association with increased risk of chronic disease, accelerated aging, and premature mortality." Efficacious prophylactic and therapeutic agents are urgently needed (2), and animal models are critical to establish causality of putative mechanisms and verify potential treatment efficacy. Unfortunately, PTSD continues to be diagnosed via a menu of ≥20 separate self-reported symptoms, with little input from neuroscience-based research. Animal models of PTSD rely primarily on face validity for complex human symptoms or predictive validity for current treatments (selective serotonin reuptake inhibitors [SSRIs]), validity types that offer relatively poor translation or bias toward detection of "me too" drugs.

Recently, neuroscience- and molecular-based clinical research has identified PTSD-related phenotypes operationalized not by symptoms but by biological markers (e.g., circuit changes, peripheral biomarkers) or nonverbal dimensional behaviors and/or physiological responses (e.g., sleep, fear-response physiology). This shift enables refinement of current animal models of PTSD to probe novel and hopefully more translatable mechanisms of PTSD. Given these recent advances, it is a good time to examine current rodent models of PTSD and their efficacy in recapitulating these potentially more translatable phenotypes. This review aims to guide readers in identifying paradigms that probe particular PTSD-relevant behavioral and biological constructs of interest for their drug and/or molecular target (e.g., treat extinction deficits, sleep disturbances, circuit abnormalities). We will highlight biological measures incorporated by these models that can support cross-species translation.

PTSD is triggered by multiple trauma types (physical vs. emotional), and given the heterogeneity in biological and environmental factors that likely mediate PTSD in humans, expecting a "one size fits all" PTSD model in rodents is a fool's

errand. Instead, rodent tests should be interpreted within the PTSD-related phenotypes they do and do not produce. This approach will allow for drug targeting of specific mechanisms and constructs and will hopefully result in enhanced translation to the clinic. Within this context, our guidelines in choosing which paradigms to evaluate were that the paradigm must 1) focus on outcome variables that endure long after the trauma and/or stress has ended (e.g., >1 week after the stressor is terminated), 2) measure more than one behavioral outcome variable for reliability and/or robustness, 3) have replicable effects across more than one laboratory, and 4) present an unpredictable, inescapable severe stressor (e.g., vary stressor intensity, duration) to avoid habituation and mimic life-threatening aspects of trauma associated with PTSD (3). We also did not review animal models of fear conditioning and extinction per se, as although this construct is highly relevant to PTSD, excellent reviews of how these models pertain to PTSD can be found elsewhere (within 24–48 hours) (4,5). Overall, paradigms that fit these criteria included those that used foot shocks, predator stress, single prolonged stress, immobilization stress, unpredictable variable stress, or social defeat.

We reviewed these paradigms for efficacy in evoking PTSD-like constructs (learned fear and extinction, avoidance, reduced motivation and/or reward, arousal and cognitive deficits) in addition to biological and physiological phenotypes associated with PTSD (Table 1). One of the most consistent is increased glucocorticoid receptor (GR) sensitivity and enhanced negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis (6). Other established biological phenotypes include increased activity and/or function of the amygdala and reduced function and structural abnormalities in the prefrontal cortex (PFC) and hippocampus (6–9). PTSD is consistently associated with increased inflammation both as a risk factor and in relation to symptom state (10). Finally, sleep disturbances, including reduced sleep duration or fragmented rapid eye movement (REM) sleep, are commonly described in PTSD (6). These phenotypes can be assessed across species as outcome measures of risk or enduring stress response. When conducting our review, we were most interested in which PTSD-related behavioral and biological phenotypes were and were not reliably produced in each paradigm (e.g., consistent over cohorts and laboratories) (Table 1). We also examined approaches to categorize resilient versus susceptible animals and to identify biological/behavioral risk factors (e.g., immune response, early-life stress) that predict individual variance in susceptibility. This is meant not to be an extensive review of each model but instead to highlight robust and replicable findings for models across phenotypes.

## STRESS MODELS

### Inescapable Shocks

Foot or tail shock is one of the most common aversive stressors used in rodent fear models, typically to examine acute stress responses, fear learning, or depression-like effects under chronic exposure (e.g., learned helplessness model) (11). Although it is not considered ethologically valid, shock is highly feasible and does not cause injury (Figure 1). A single exposure to foot shocks induce enduring (≤56 days) PTSD-like phenotypes: hyperarousal, generalized avoidance, sleep disturbances, hippocampal-dependent memory deficits, and thermal hyperalgesia (see Supplemental Table S1 for details and references). The generalized avoidance and depression-like effects are sensitive to long-term administration of SSRIs (11–15). Parameters, however, vary substantially (e.g., 1–20 shocks, 0.3–1.5 mA, 0.5–10 seconds) across laboratories, species, and strains. Susceptible and resilient animals have been defined by success or failure to escape subsequent shock exposures (16). Interestingly, REM immediately (24 hours) before foot shock exposure predicts long-term emergence of hyperarousal after the foot shock protocol (17), suggesting that this paradigm may be useful in examining treatments. This paradigm also induces enhanced neuronal activity in the PFC and amygdala and decreased volume in the hippocampus (13,18–23) (Table 2). Some of these behavioral and circuit effects manifest weeks after the trauma (Table 2 and Supplemental Table S1), a finding that can be exploited to examine different preventive versus treatment strategies for early versus late effects of trauma.

Overall, the major strengths of shock-exposure models are 1) in some cases, enduring (≤8 weeks) avoidance, hyperarousal, spatial-memory deficits and fear response to trauma cues (e.g., shock context) in both rats and mice; 2) sensitivity to sleep disturbances and induction of fear-circuit pathology; and 3) the tight control over the stimulus parameters. Limitations include 1) little data in female subjects (Supplemental Tables S2 and S3); 2) the relatively nonethological stressor; and 3) varied shock protocols across laboratories.

### Predator-Stress Model

Predator-stress paradigms consist of a single-stress exposure—either unprotected exposure to a predator, exposure with a physical barrier, or exposure to a predator scent—that is inescapable, unpredictable, and ethological (Figure 1) (24). These manipulations evoke enduring behavioral and physiological abnormalities ≤3 months after exposure, including general avoidance, exaggerated fear response, hyperarousal, and hyperalgesia (see Supplemental Table S1 for details and references). In a direct predator-exposure paradigm, avoidance of trauma-related cues is assessed via subsequent exposure to predator odors in different contexts (25,26) (Supplemental Table S1). Cue avoidance is also sensitive to long-term administration of clinically effective SSRIs, mainly sertraline and amitriptyline (27,28).

Predator exposure recapitulates some biological phenotypes in PTSD. The number of dendritic spines is reduced in the hippocampus, while amygdala activity (c-Fos and dendritic spines number and/or length) is increased (29–31) (Table 2). Predator stress produces enhanced negative feedback of the HPA axis (25,32) and an inverse correlation between post-exposure levels of adrenocorticotropic hormone and corticosterone and avoidance behaviors (33), suggesting that reduced HPA response to stress may predict long-term anxiety-like effects in this model (34). Predator stress can induce long-term inflammation in the brain that is sensitive to anti-inflammatory treatments; however, peripheral inflammation effects are not well described [for review, see Deslauriers *et al.* (10)].