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Animal Models of Post-Traumatic Stress Disorder and Recent Neurobiological Insights

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Abstract

Post-traumatic stress disorder (PTSD) is a complex psychiatric disorder characterized by the intrusive re-experiencing of past trauma, avoidant behavior, enhanced fear, and hyperarousal following a traumatic event in vulnerable populations. Preclinical animal models do not replicate the human condition in its entirety, but seek to mimic symptoms or endophenotypes associated with PTSD. Although many models of traumatic stress exist, few adequately capture the complex nature of the disorder and the observed individual variability in susceptibility of humans to develop PTSD. In addition, various types of stressors may produce different molecular neuroadaptations that likely contribute to the various behavioral disruptions produced by each model, although certain consistent neurobiological themes related to PTSD have emerged. For example, animal models report traumatic stress- and trauma reminder-induced alterations in neuronal activity in the amygdala and prefrontal cortex, in agreement with the human PTSD literature. Models have also provided a conceptual framework for the often observed combination of PTSD and co-morbid conditions such as alcohol use disorder (AUD). Future studies will continue to refine preclinical PTSD models in hopes of capitalizing on their potential to deliver new and more efficacious treatments for PTSD and associated psychiatric disorders.

Keywords

alcohol use disorder; animal model; individual differences; neurobiology; post-traumatic stress disorder

Introduction

Post-traumatic stress disorder (PTSD) is defined by the DSM-V as a debilitating stress-associated neuropsychiatric disorder that develops following exposure to a traumatic event such as rape, war, violence, or natural disaster (DSM-5, 2013). **Fundamentally, stress is a real or perceived perturbation to an organism's physiological or psychological homeostasis** (McEwen, 2007). Importantly, not all individuals that are exposed to a stressful or traumatic event will develop PTSD, indicating the presence of potential resilience or

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protective factors (Figure 1). It is estimated that approximately 8% of the population will develop PTSD (Breslau *et al.*, 1998; Kessler, 2000), although this number is significantly greater in combat veteran populations (Kessler *et al.*, 1995; Kessler, 2000). Individuals with PTSD develop significant psychological distress as well as behavioral disruptions that are used to diagnose the disorder. The primary symptoms of PTSD include intrusive memories, such as flashbacks or nightmares, avoidance of people and places that are reminders of the trauma, negative changes in cognitions and mood (negative trauma-related emotions, inability to experience positive emotions), and alterations in arousal and reactivity (DSM-5, 2013). PTSD is also associated with biological disturbances, in particular disturbances in the hypothalamo-pituitary adrenal (HPA) stress axis. Individuals with PTSD exhibit blunted HPA activity immediately after the traumatic event (Yehuda, 2005; Daskalakis, 2013) and enhanced negative feedback as evidenced by greater glucocorticoid suppression following dexamethasone administration (Belda, 2008; Ströhle, 2008), suggesting that the HPA axis is hypoactive in individuals with PTSD.

While animal models of PTSD are critical for understanding the neurobiological mechanisms and behavioral manifestations associated with the disorder, **it is important to evaluate the data vigilantly, as many of the symptoms associated with PTSD also manifest in other psychiatric disorders such as depression**. To date, there is no single accepted model of PTSD, although several stress paradigms mimic the behavioral symptoms and neuroendocrine alterations characteristic of PTSD. Yehuda and Antelman (1993) identified five central criteria that should be fulfilled by animal models of stress in order for them to be useful for understanding the transition to PTSD (see Table 2). The stressor must 1) be capable of inducing biological and behavioral responses of PTSD, 2) produce these responses in an intensity-dependent manner, 3) produce alterations that persist over time, 4) induce behavioral alterations that have bidirectional expression (enhanced or reduced responsivity) and 5) produce inter-individual variability (Yehuda and Antelman, 1993; Yehuda and LeDoux, 2007; Daskalakis *et al.*, 2013b). PTSD develops in response to various types of different types of stressors only in a portion of individuals. It is challenging to model the human condition in its entirety, but investigators have developed various stress paradigms that mimic one or several of the behavioral and biological characteristics of the PTSD phenotype, including avoidant behavior, anxiety-like behavior, hyperarousal, enhanced fear responses, and alterations in brain or HPA stress responses (Liberzon *et al.*, 1999; Cohen *et al.*, 2006b, 2009, 2011; Kozlovsky *et al.*, 2009; Neumann *et al.*, 2011; Corley *et al.*, 2012; Knox *et al.*, 2012; Zoladz *et al.*, 2012). Importantly, PTSD often co-exists with other mental health disorders such as substance abuse disorders (Blanco, 2013). Approximately 20-40% of individuals with PTSD meet the criteria for alcohol use disorder (AUD), making it the most commonly co-occurring mental health disorder in humans affected by PTSD (Kessler *et al.*, 1995; Blanco *et al.*, 2013). **The objective of this review is to provide an overview of some of the current animal models of PTSD as they address the five criteria identified by**Yehuda and Antelman (1993)**and according to their contribution to the understanding of the neurobiological changes associated with PTSD and predominating co-morbid conditions such as AUD**.

While the physical and psychological effects of stress cannot always be readily distinguished, current animal models of PTSD may still be classified into one of three categories based on the primary type of stressor utilized to induce PTSD-like symptoms. These include physical stressors, social stressors, and psychological stressors, factors that are capable of eliciting both shared and unique patterns of neuroadaptation (e.g., Warren *et al.*, 2013).

Physical Stressors

Animal models of PTSD that use physical stressors include footshock, stress-enhanced fear learning (SEFL), restraint stress, and single prolonged stress. Physical stress paradigms are used alone or in combination to mimic varying degrees of stress and to examine behavioral responses to subsequent stressors. While widely accepted and useful models of PTSD, one disadvantage is the difficulty in examining individual variability in the development of PTSD. Also, it is difficult to tease out the effects of stress versus the physical aspects of pain associated with the various physical stressors.

Footshock

Electrical shock is a commonly used physical stressor and can be administered to an animal's but is most commonly administered via a metal rod floor (Van Dijken *et al.*, 1992; Servatius *et al.*, 1995; Pynoos *et al.*, 1996). Brief shock periods (10-15 min) include either several footshocks that are short in duration (1-6 s) or fewer, longer-duration footshocks, with intensities ranging from 0.1 mA to 0.25 mA (Van Dijken *et al.*, 1992; Pijlman *et al.*, 2003a,b; Louvart *et al.*, 2005; Daviu *et al.*, 2010). Tailshock paradigms often consist of long (2 h; 0.2 mA) sessions of greater than 40 tailshocks (Servatius *et al.*, 1995). Animals that are exposed to electrical shock exhibit reduced locomotion in new environments following the shocks and robust conditioned fear responses when exposed to cues associated with the shocks (Pijlman *et al.*, 2003a; Armario *et al.*, 2004; Rudy *et al.*, 2004; Johansen *et al.*, 2011). Repeated footshock produces heightened anxiety-like behavior as measured by the elevated plus maze test (Belda *et al.*, 2008). Furthermore, footshock with situational reminders, in which the animal is returned to the shock context for one minute once per week, results in elevation of acoustic startle responsiveness reflective of hyperarousal (Pynoos *et al.*, 1996). HPA dysfunction, including decreased basal levels of cortisol and enhanced negative feedback, are hallmark characteristics of PTSD (Daskalakis *et al.*, 2013a). Inescapable footshock models have largely failed to reproduce the distinctive physiological perturbations associated with PTSD, including HPA and autonomic dysfunction. While studies have shown that both males and females show decreased corticotropin-releasing factor mRNA levels in the paraventricular nucleus, only female animals exhibit enhanced negative feedback (Louvart *et al.*, 2006). Additionally, studies have begun examining individual differences in extinction of footshock-conditioned tone fear (for review, see Holmes and Singewald, 2013).

Stress-enhanced fear learning (SEFL)

Fanselow and colleagues developed the SEFL model of PTSD, which utilizes footshock to stimulate a traumatic event (Rau *et al.*, 2005; Rau and Fanselow, 2009). In contrast to

Pavlovian fear conditioning models, where rodents are trained to associate shock delivery with a cue, in the SEFL model, animals are exposed to either no shock or 15 unpredictable footshocks (1 mA, 1 s) in one context (Context A) then 24 h later are exposed to either no shock or a single footshock in a novel environment (Context B) differing in light, sound, and odor (Rau *et al.*, 2005). On day 3, animals are re-exposed to Context B without exposure to footshock to assess fear memory. Freezing behavior, a measure of learned fear in rodents, is measured prior to the single shock in Context B on the second day and during context re-exposure on the third day (Rau *et al.*, 2005). Utilizing this model, the authors demonstrated that exposure to several footshocks enhances subsequent fear responses and that these effects persist for up to three months (Rau *et al.*, 2005; Rau and Fanselow, 2009). The SEFL model of PTSD simulates non-associative sensitization of fear that occurs prior to the actual test event. Consequently, this is a useful model for examining how prior exposure to traumatic events mediates learned fear in rodents. Further studies are needed to assess how this stressor affects other characteristics of PTSD such as heightened anxiety, hyperarousal, and neuroendocrine dysfunction, and also whether the first trauma produces sensitization to a second stressor that is distinct from the first (rather than to the same stressor).

Underwater trauma

The forced swim test, when used alone, is a widely accepted model of depression and will not be discussed here (for review, see Krishnan and Nestler, 2011). Underwater trauma, however, has been utilized as a model of traumatic stress. It involves placing an animal in a container of fluid and allowing it to swim for 30 s before gently submerging it and allowing the animal to struggle completely under the surface for 30 s before removing it from the container (Richter-Levin, 1998; Moore *et al.*, 2012). This model produces significant increases in anxiety-like behavior in adult and adolescent rats (Richter-Levin, 1998; Moore *et al.*, 2012).

Restraint stress

Immobilization stress or restraint stress consists of restraining the animal utilizing plastic restraint tubes or immobilizing the animal by attaching the four limbs and head to wooden boards in a prone position (Kvetnansky and Mikulaj, 1970; Gameiro *et al.*, 2006; Vallès *et al.*, 2006). Animals are subjected to either single sessions lasting from 15 min to 2 h, sub-chronic sessions (3 d; 1 h per day), or chronic restraint stress (40 d; 1 h per day) (Liberzon *et al.*, 1997; Gameiro *et al.*, 2006). Both acute and chronic restraint stress paradigms produce significant increases in anxiety-like behaviors as well as enhanced nociception (Gameiro *et al.*, 2006). Restraint stress is often used in conjunction with the forced swim test, a common model of immobility induction (Liberzon *et al.*, 1997). In the stress/re-stress or time-dependent sensitization model of PTSD, an initial stressor (restraint stress) causes sensitization to subsequent stressors (forced swim test) (Yehuda and Antelman, 1993). Utilizing this model, studies have demonstrated an enhanced HPA negative feedback similar to what is seen in PTSD (Liberzon *et al.*, 1997); however, there are limited studies exploring behavioral symptoms and the model has not been used to examine individual differences in stress reactivity.

Single prolonged stress (SPS)

Another widely used animal model of PTSD that utilizes physical stressors is the SPS model described by Liberzon and colleagues (Wang *et al.*, 2008; Yamamoto *et al.*, 2009; Knox *et al.*, 2012). In this model, rats are subjected to a variety of different stressors. In the standard SPS protocol, the animal is restrained for 2 h followed by a 20-min forced swim test and then exposure to diethyl ether until loss of consciousness (Iwamoto *et al.*, 2007). Critical to this model is a 7-day period following the stressor where the animals are left undisturbed. This incubation period is thought to be essential for the development of PTSD-like symptoms (Liberzon *et al.*, 1999). Utilizing the SPS model of PTSD, Liberzon and colleagues discovered an enhanced HPA negative feedback as indicated by suppressed adrenocorticotropin hormone (ACTH) levels following administration of cortisol. The enhanced HPA negative feedback in the SPS model of PTSD was attributed to up-regulation of glucocorticoid receptors in the hippocampus (Liberzon *et al.*, 1999), which is a principal site of HPA negative feedback regulation (Herman *et al.*, 2012). Interestingly, this effect was evident at 7 days post-stress, but not at the 1-day time point (Liberzon *et al.*, 1999). In addition to enhanced HPA negative feedback, the SPS paradigm also produces other symptoms associated with PTSD including hyperarousal and enhanced freezing (Khan and Liberzon, 2004; Imanaka *et al.*, 2006). Furthermore, SPS increases anxiety-like behaviors as measured in the elevated plus maze (Imanaka *et al.*, 2006). Collectively, these findings suggest that the SPS model of PTSD is capable of producing several symptoms characteristic of PTSD including exaggerated HPA negative feedback, heightened anxiety, hyperarousal, and enhanced fear.

Co-morbidity with AUD

Since a significant number of individuals with PTSD meet the criteria for AUD, co-morbidity of these two disorders presents a huge financial and health burden to society and an important research area. Studies examining physical stressors as animal models of traumatic stress have found mixed results when examining alcohol consumption post-stress. In mice selectively bred for high-alcohol preference (HAP1 lines), footshock stress increases alcohol drinking during adolescence but not adulthood (Chester *et al.*, 2008). Logrip and Zorrilla (2012) have shown that low-drinking animals with a history of stress exposure (light-cued footshock) significantly increased alcohol self-administration following a period of time, suggesting that prior stress exposure sensitizes low drinkers to self-administer alcohol during a subsequent relapse session. Restraint stress (1hr/day; 10 days) increases alcohol consumption in a two-bottle choice limited access paradigm in male Sprague-Dawley rats (Gomez *et al.*, 2012); however, studies in mice show strain-dependent effects on stress-induced alcohol consumption, with significant increases in alcohol consumption in 129SVEV mice, but not C57BL/6J mice (Yang *et al.*, 2008). Finally, the SEFL model, a well-characterized model of PTSD, increases acquisition of voluntary alcohol consumption in previously alcohol-naïve rats before and after a 40-day period of forced abstinence, demonstrating that a single traumatic event is capable of producing long lasting fear-associated changes in alcohol consumption (Meyer *et al.*, 2013). Interestingly, rats that received the stress after prior exposure to alcohol did not consume more alcohol after

reinstatement to drinking, suggesting that this type of stress does not alter previously acquired drinking habits (Meyer *et al.*, 2013).

Social Stressors

Social stressors include housing instability, social isolation/maternal separation and social defeat. Animal models of PTSD utilizing social stressors often use them in conjunction with other psychological models of PTSD such as predator odor exposure (described in the next section).

Housing instability

Housing instability consists of randomly pairing animals from different cages with each cage change (Zoladz *et al.*, 2008). This model is often preceded by a cat exposure ranging in duration from one exposure per week for two weeks to daily exposures 5 days per week over 5 weeks (Park *et al.*, 2001; Zoladz *et al.*, 2008, 2012; Zoladz and Diamond, 2013). Animals that underwent 2 cat exposures separated by 1 week followed by chronic social instability exhibited several PTSD-like symptoms, including HPA dysfunction as indicated by decreased basal corticosterone levels and enhanced corticosterone suppression during the dexamethasone suppression test (indicative of enhanced negative feedback, Zoladz *et al.*, 2012). Additionally, animals exhibited heightened anxiety, as measured by the elevated plus maze, and enhanced freezing behavior in response to contextual reminders of the initial stressor (Zoladz *et al.*, 2012). Predator (cat) exposure 5 days/week for 5 weeks in parallel with chronic housing instability produced heightened anxiety-like behavior and impaired acclimation to novel environments (Saavedra-Rodríguez and Feig, 2013).

In addition to housing instability, social isolation occurring during adulthood for a period of 1 day to 8 weeks or maternal isolation can also produce symptoms of PTSD (Imanaka *et al.*, 2006; Pibiri *et al.*, 2008). Social isolation in adult mice increases contextual freezing time measured during a fear conditioning paradigm in which an electric footshock is paired with a tone as well as impairs fear extinction (Pibiri *et al.*, 2008). Additionally, social isolation during adolescence produces heightened anxiety and HPA alterations, including higher baseline corticosterone concentrations and failure to suppress corticosterone following dexamethasone administration (Butler *et al.*, 2014). **Interestingly, social housing, as opposed to social isolation, has been reported to reverse the long-term impairment of reward function** (Von Frijtag, 2000).

Early life stress

Early life stress been identified as a contributing factor to the development of PTSD in adulthood (Cloitre *et al.*, 2009). It has been reported that exposure to trauma as a child can increase PTSD-like symptoms following the event, but can also influence the development and complexity of PTSD-like symptoms as an adult (Cloitre *et al.*, 2009). Maternal separation is a commonly utilized animal model of social isolation that mimics childhood trauma by separating pups from their mother for 1-3 h per day on postnatal days 2–9. Studies using this model have reported numerous sex-dependent changes in anxiety-like behavior, acoustic startle responses, and HPA responses (de Jongh *et al.*, 2005). Both males

and females exhibit heightened anxiety-like behaviors as adults (Kalinichev *et al.*, 2002); however, hyperarousal studies report conflicting results, which may be attributable to the use of different arousal tests (Kalinichev *et al.*, 2002; de Jongh *et al.*, 2005). Adult males exhibit 35% higher startle amplitudes following maternal separation when compared to controls (Kalinichev *et al.*, 2002). In comparison, female rats show significantly greater startle potentiation in both light-enhanced startle responses and in fear-potentiated startle, in which rats are presented with light/shock pairings prior to startle stimuli (de Jongh *et al.*, 2005). These results parallel clinical studies demonstrating that women suffer from a higher prevalence of anxiety disorders than men (Pigott, 1999, 2003). When combined with subsequent stressors such as the SPS model as an adult, maternal separation exacerbates SPS-induced increases in anxiety-like behavior and contextual freezing behaviors (Imanaka *et al.*, 2006).

Maternal separation also produces long-lasting changes in the HPA axis. Twenty-four hours after maternal separation, pups show increased corticotropin-releasing factor (CRF) levels in the median eminence (Pihoker *et al.*, 1993). The preponderance of the literature reports an accentuated ACTH/corticosterone response to subsequent stressors such as a 15-min swim or mild handling stress (Kalinichev *et al.*, 2002; Aisa *et al.*, 2007); however, after a 15-min restraint stress, ACTH levels are significantly lower than controls, indicating a blunted stress response (Daniels *et al.*, 2004). Together, these data suggest that maternal separation produces long-lasting changes in PTSD-like behaviors and HPA dysfunction, although the results are not always consistent.

Social defeat

The social defeat model is often used to induce the anxiety-like and avoidance symptoms that define PTSD. Mice (C57BL/6) are exposed to a single aggressor mouse (CD1) for either 1 or 5 days (Krishnan *et al.*, 2007; Yang *et al.*, 2013). Importantly, animals can be further classified into susceptible and resilient populations (Krishnan *et al.*, 2007; Russo *et al.*, 2012). Both susceptible and resilient animals subjected to social defeat exhibit increased anxiety-like behaviors measured by the elevated plus maze; however, only susceptible animals show increases in avoidance behaviors at day 11 and day 39 post-stress. Interestingly, no changes were noted in morning corticosterone levels at day 11; however, susceptible animals show blunted corticosterone levels, while resilient animals have increased corticosterone levels at day 39 post stress (Krishnan *et al.*, 2007). Collectively, these data demonstrate that social defeat produces bidirectional behavioral and biological manifestations characteristic of PTSD that persist over time in susceptible populations of animals, identifying a useful model for studying the neurobiological mechanisms of PTSD. Whether these behavioral changes are intensity-dependent is currently unknown and warrants further investigation.

Comorbidity with AUD

Similar to other models of PTSD, exposure to social stressors has produced mixed results in terms of altering alcohol consumption. Maternal separation, in particular, has produced mixed results with studies reporting an increase, decrease, or no change in voluntary alcohol consumption (Jaworski *et al.*, 2005; Daoura *et al.*, 2011; Oreland *et al.*, 2011). Many of the

discrepancies are due to differences in duration of maternal separation, time post-stress to alcohol consumption, and voluntary ethanol consumption paradigms. As seen with maternal separation studies, exposure to stressful situations during early life can produce robust and long-lasting changes in PTSD-like behaviors and co-morbid conditions such as alcohol abuse. Becker and colleagues demonstrated that social isolation during adulthood does not increase voluntary ethanol consumption, but social isolation during early development produces significant increases in alcohol intake compared to group-housed mice (Lopez *et al.*, 2011). This finding is further supported by studies showing a significantly increased alcohol consumption in a two-bottle choice intermittent access model in rodents socially isolated during adolescence (Butler *et al.*, 2014). Social defeat has been shown to increase alcohol preference and consumption (Croft *et al.*, 2005). While studies have shown increased cocaine preference in susceptible animals following social defeat, whether there is individual variability in alcohol consumption remains to be elucidated (Krishnan *et al.*, 2007).

Psychological Stressors

As discussed above, both physical and social stressors are capable of producing several behavioral and neuroendocrine alterations distinctive of PTSD-like symptoms. However, those models generally examined mean group stress effects without consideration of the individual variability in stress reactivity. Thus, an important concern when selecting an animal model of PTSD (particularly when designing studies to identify mechanisms, co-morbidities, biomarkers, and susceptibility for the development of PTSD) is the ability to separate resilient populations from susceptible populations (Figure 1), a criterion that may be best addressed with psychological stressors.

Predator and Predator Odor

Predator and predator odor exposure is a psychological stressor commonly employed as an animal model of PTSD. Animals are exposed to predator odor in a variety of ways, including indirect exposure to a predator (cat), predator urine (bobcat, fox), predator feces or litter, or trimethylthiazoline (TMT), a synthetic compound isolated from fox feces (Cohen *et al.*, 2003; Cohen *et al.*, 2006a; Corley *et al.*, 2012). Predator odor exposure produces lasting increases in freezing behaviors and avoidance behaviors (Takahashi *et al.*, 2005; Edwards *et al.*, 2013).

In addition to the behavioral effects mediated by predator odor exposure, this model also produces dysregulation of the HPA axis and sympathetic nervous system, two notable characteristics of individuals with PTSD (Cohen and Zohar, 2004; Cohen *et al.*, 2006b). As mentioned previously, predator odor is often combined with other models of stress such as social instability (Zoladz *et al.*, 2008). This more complex version aims to model three important factors in the development of PTSD, the initial stressor (predator odor) used to produce behavioral and physiological changes, a second predator odor exposure used to mimic “re-experiencing” symptoms, and daily social instability (Zoladz *et al.*, 2008). The rationale behind this modeling stems from the fact that lack of social support and stability in humans increases PTSD susceptibility (Andrews *et al.*, 2003). This model produces significant physiological and behavioral alterations including reduced growth rate, increased

adrenal gland weight, cognitive impairments, endocrine disruptions, heightened anxiety, and exaggerated startle reactivity (Zoladz *et al.*, 2008). Predator odor stress satisfies many of the diagnostic criteria for PTSD, including enhanced fear, hyperarousal, avoidance, and heightened anxiety. Importantly, mimicking the human condition, these symptoms are persistent, often lasting weeks or months. This model can also be used to examine individual differences in susceptibility to develop PTSD-like behaviors (Cohen *et al.*, 2003, 2006a; Cohen and Zohar, 2004). One such model uses cat exposure and separates rats into "maladapted" and "well-adapted" groups based on anxiety-like behavior and arousal levels (Cohen *et al.*, 2003). Utilizing this model, approximately 25% of animals exposed to predator develop "PTSD-like" behavioral and endocrine dysregulation (Cohen *et al.*, 2003). Because animals can be subdivided on the basis of stress reactivity, this model allows for the examination of individual differences in alcohol consumption post-stress. In our lab, rats are separated based on avoidance of a predator odor-paired context, and high-avoidance rats exhibit robust and lasting increases in alcohol intake following a single predator odor exposure (Edwards *et al.*, 2013). This high avoidance behavior and escalation of alcohol consumption are associated with unique patterns of neuronal activation relative to non-avoiders and unstressed controls (see below). Collectively, these data suggest that predator odor exposure may be a useful model for examining mechanisms associated with vulnerability and resistance to the development of PTSD as well as the development of AUD in PTSD.

Recent Neurobiological Insights Gained from Animal Models of PTSD

We conclude with a discussion of some recent neurobiological findings related to PTSD symptomatology using innovative animal models of traumatic stress conditioning and co-morbidity. At a conceptual level, it is presumed that **individual differences in structural brain plasticity** (Freund, 2013) **and** central neuroadaptations in specific circuits contribute to susceptibility to and/or resilience from PTSD following exposure to a traumatic stressor, although it is important to keep in mind that central stress systems are also responsive to multiple humoral factors, such as adrenal steroids (Rodrigues *et al.*, 2009), cytokines (Crews *et al.*, 2011), and endocannabinoids (Hill *et al.*, 2008, 2013). As PTSD is considered a chronic, relapsing disorder provoked by traumatic stress reminders, many investigators have measured biochemical markers related to the persistence of the phenotype (long-term plasticity) and/or the effects of traumatic re-experiences (short-term activation).

A novel use of underwater trauma (Richter-Levin, 1998) was recently developed into a PTSD model in which animals are conditioned to pair a water-associated zero maze (WAZM) with underwater trauma (Ritov and Richter-Levin, 2014). Traumatic stress (being held underwater) was distinguished from a simple swim stress, as such a distinction between stressful vs. traumatic experiences may be critical for the modeling of PTSD (Koolhaas *et al.*, 2011). One month following this pairing, animals were re-exposed to the WAZM context as a reminder cue, where they spent more time freezing and less time in the open (exposed to the water) quadrants of the maze, indicative of an active avoidance of the traumatic experience. The reminder of the underwater trauma also increased c-Fos immunoreactivity in the basolateral and central nuclei of the amygdala vs. both swim stress and unstressed controls, suggesting that these regions are implicated in the recall of

particularly traumatic memories. Indeed, c-Fos activity likely corresponds to co-activation of a variety of amygdala signaling pathways associated with fear conditioning mechanisms (Mahan and Ressler, 2012), as well as integration with a more extensive affective circuitry (Hermans *et al.*, 2014). In a follow-up study, Ritov and colleagues examined the effects of re-exposure to the WAZM context on neuronal extracellular signal-regulated kinase (ERK) phosphorylation across multiple brain regions (Ritov *et al.*, 2014). The reminder of underwater trauma, but not of swim stress, led to increases in ERK phosphorylation (pERK) in the ventral dentate gyrus and basolateral amygdala, as well as increased correlation of pERK levels in these two regions, suggesting that interaction of these two regions is critical for cue and context reactivity (Maren *et al.*, 2013). Since the re-exposure occurred 24h following the traumatic experience, the authors suggested that these neuroadaptations may correspond to the initial stages of traumatic memory consolidation. Given the ability of ERK/mitogen-activated protein kinase (MAPK) signaling to facilitate gene expression (Sweatt, 2001) and long-term memory maintenance (Davis and Laroche, 2006), interactions with downstream transcriptional mechanisms are likely to mediate the persistent behavioral effects of traumatic stress, and may also dissociate mechanisms of adaptive short-term learning (e.g., fear conditioning) from long-term neuropathology (depression, PTSD, addiction).

In accordance with this conceptualization, re-exposure to a shock-paired context drives ventromedial PFC (vmPFC) activation (as measured by c-Fos expression), and this event is partly predictive of context-induced freezing behavior 28 days (but not 1 day) following the initial stress (Tulogdi *et al.*, 2012). In another study, rats exhibited reduced locomotor activity upon repeated exposure to a predator odor-paired context that was persistent and resistant to extinction (Mackenzie *et al.*, 2010). Rats in that study also exhibited robust mPFC induction of DeltaFosB, a stable transcription factor that mediates long-term neuroadaptive gene expression under a variety of conditions (McClung *et al.*, 2004). DeltaFosB induction also likely represents a more persistent signature of upstream ERK activation (Fasano *et al.*, 2009; Besnard *et al.*, 2011). Indeed, ERK-mediated alterations in gene expression may play a critical role in the development and maintenance of PTSD, and this area warrants further study. The emerging field of epigenetics suggests another dimension of probable mechanisms tying short-term changes in stress reactivity to persistent pathology. For example, a series of investigations from Reul and colleagues has linked psychological stress to the coincident activation of glucocorticoid receptors and the ERK/MAPK pathway, ultimately leading to the phosphorylation and acetylation of histone H3 and chromatin remodeling (Reul, 2014).

Regardless of the investigated biomarker or neuroadaptation, it remains critical to incorporate a stratified experimental design in order to match individual differences in measured stress reactivity with individual molecular or biochemical correlates (Holmes and Singewald, 2013). Such designs will likely provide insight into the specific neurobiology underlying PTSD, and may also reveal valuable protective factors that underlie traumatic stress resilience (Figure 1). Indeed, humans display a considerable amount of resilience in the presence of chronic stress, and this perspective has recently been the focus of intense research (Krishnan *et al.*, 2007; Russo *et al.*, 2012). Stratification of stress reactivity may

also be useful in describing why PTSD associates with multiple co-morbid conditions, such as alcohol abuse (Engdahl *et al.*, 1998). With regard to these two criteria, a recent animal model was developed to better model the effects of traumatic stress reactivity on alcohol drinking behavior (Edwards *et al.*, 2013). This study measured neuronal activation patterns via ERK phosphorylation following exposure to a context previously paired with a bobcat urine traumatic stressor, mimicking symptom provocation studies in PTSD patients. A subgroup of rats that exhibited persistently high avoidance of trauma-related stimuli also displayed escalated and compulsive alcohol drinking. Interestingly, re-exposure to the predator odor-paired context produced a bi-directional regulation of pERK levels in the vmPFC, with high stress-reactive rats exhibiting higher ERK phosphorylation levels, while low stress-reactive rats displayed reductions in ERK phosphorylation. This finding reflects the critical influence of individual responsiveness to traumatic stress challenges on neurobiological signaling. The functional implications of this bidirectional modulation of the vmPFC remain to be determined, although given that high avoidance and excessive drinking persist for several weeks, context-induced changes in vmPFC activity likely integrates with additional neuronal circuitry to mediate PTSD-like symptomatology. For example, the vmPFC projects strongly to the central amygdala (CeA) (Vertes, 2004), and the CeA regulates both central and systemic stress systems (Koob and Le Moal, 2008). Moreover, it should be noted that the vmPFC also coordinates behavioral and physiological responses to stress by activating the HPA axis (Radley *et al.*, 2006; George and Koob, 2010), while circulating glucocorticoids sensitize CeA activity following repeated stress exposure (Shepard *et al.*, 2000; Cook, 2002; Kolber *et al.*, 2008). This may lead to a dual dysregulation of CeA and HPA function that fosters long-term stress-related disorders (Keen-Rhinehart *et al.*, 2009). Importantly, both top-down conceptual frameworks, in which the vmPFC drives stress-associated limbic circuitry (including the amygdala; (Koenigs and Grafman, 2009, Myers-Schulz and Koenigs, 2012), and bottom-up models, whereby amygdala overactivation promotes PTSD (Rauch *et al.*, 2000) have been put forward. Future implementation of optogenetic strategies will be useful in determining the relative contribution of these circuits in animal models of PTSD (Sparta *et al.*, 2013), particularly in terms of parsing out the multimodal functions of regions comprised of various cell types such as the PFC (Ji and Neugebauer, 2012).

Following a traumatic stress reminder, high-drinking, high-traumatic stress-reactive rats also exhibit significantly greater synchronicity between the prefrontal cortex (PFC) and basolateral amygdala (BLA) (as indexed by individual within-subject and between-region correlations in ERK phosphorylation) compared to their low-traumatic stress-reactive counterparts (Edwards *et al.*, 2013). Along with the data of Ritov and colleagues described above, this finding highlights the necessity of examining inter-regional activity in the context of traumatic stress re-exposure, as PTSD likely manifests from a functional dysregulation of highly integrated limbic circuitry. For example, upon symptom provocation, PTSD subjects display strong signal synchronization between the amygdala and the mPFC/anterior cingulate cortex (Rauch *et al.*, 1996; Liberzon *et al.*, 1999; Gilboa *et al.*, 2004). In rodents, stimulation of beta-adrenoceptors in the BLA enhances avoidance memory and also increases plasticity-related protein expression in the mPFC, whereas BLA inactivation reduces mPFC levels of the same signaling proteins (Holloway-Erickson *et al.*,

2012), further suggesting a strengthening of this circuit in PTSD. In the Edwards (2013) study, traumatic context-induced changes in ERK phosphorylation between the BLA and CeA were positively and highly correlated in all trauma-exposed rats (regardless of stress reactivity), but not stress-naïve controls, in agreement with the primary role of this circuit in fear and anxiety (Pape and Pare, 2010). It is hypothesized that rats that exhibit high reactivity to a traumatic stress also exhibit changes in neurotransmission in the CeA, the major output region of the amygdala, that "gates" the activity of downstream effector regions (e.g., hypothalamus and periaqueductal gray) responsible for mediating physiological and behavioral stress responses, including increases in avoidance, anxiety-like behavior, and nociception (Gilpin and Roberto, 2012). This common BLA-CeA correlation also demonstrates that some stress-driven neuronal activity appears to generalize to the simple perception or recording of traumatic stress, while other circuitry (e.g., BLA-PFC) may code individual differences in stress reactivity and possible protective or resiliency factors.

As signaling mechanisms such as c-Fos and ERK couple to numerous receptor cascades, future work should more precisely determine which neurotransmitter systems are driving the observed traumatic stress- and context-induced changes. Such data would inform the development of new pharmaceutical strategies for targeting PTSD, either in isolation or in combination with co-morbid conditions such as alcohol use disorders. In this regard, the ERK/MAPK signaling cascade is activated by numerous receptors for stress-related neurotransmitters and neuropeptides throughout brain stress and reinforcement circuitry, including the PFC. For example, stress and glucocorticoids interact in the PFC to increase CRF1 receptor expression through a CRF/ERK-dependent pathway (Meng *et al.*, 2011). Interestingly, excessive alcohol drinking and alcohol dependence-related behaviors are blocked by systemic administration of either CRF1 receptor antagonists (Gehlert *et al.*, 2007; Richardson *et al.*, 2008, Gilpin *et al.*, 2008; Edwards *et al.*, 2012) or glucocorticoid receptor antagonists (Dina *et al.*, 2008; Vendruscolo *et al.*, 2012). The CRF/ERK signaling cascade in the CeA has also been implicated in stress and pain sensitization (Ji *et al.*, 2007; Fu *et al.*, 2008; Fu and Neugebauer, 2008; Egli *et al.*, 2012), and these neuroadaptations may facilitate the transition to PTSD with or without co-morbid drug dependence (Egli *et al.*, 2012; Logrip *et al.*, 2012; Moeller-Bertram *et al.*, 2012). Chronic stress is also associated with excessive norepinephrine release in the PFC (Arnsten, 2009). Alpha1-adrenergic receptors activate ERK/MAPK signaling (Garcia-Sainz *et al.*, 1999; Vanhoose *et al.*, 2002), while systemic administration of the alpha1R antagonist prazosin reduces excessive alcohol drinking in dependent animals (Walker *et al.*, 2008). Moreover, the beta-adrenergic receptor agonist BLA clenbuterol mimics restraint stress by reducing BLA ERK phosphorylation (Grissom and Bhatnagar, 2011), and this neuroadaptation is prevented by antagonism of beta-adrenergic receptors with propranolol. Edwards and colleagues (2013) revealed that context-induced reductions in BLA ERK phosphorylation correlated with post-conditioning increases in alcohol self-administration. Thus, beta-adrenoceptor-mediated reductions in BLA ERK activity may in part drive stress-induced escalation of drinking. Additional support for this hypothesis is provided by evidence that propranolol reduces excessive alcohol drinking in alcohol-dependent animals (Gilpin and Koob, 2010), highlighting the central role of brain norepinephrine systems in dependence (Gilpin and

Koob, 2008; Silberman *et al.*, 2012). These data support the further use and development of noradrenergic agents for the treatment of PTSD, and are in strong accordance with the demonstrated efficacy of prazosin in both preclinical models (Olson *et al.*, 2011) and PTSD patient populations (Raskind *et al.*, 2003) (Krystal and Neumeister, 2009). Finally, excessive alcohol exposure and dependence itself may contribute to dysregulated signaling in the PFC (George *et al.*, 2012; Kim *et al.*, 2014), leading to the development or exacerbation of PTSD-associated symptoms in rodents (Holmes *et al.*, 2012), consistent with the human literature (Tipps *et al.*, 2014; Perrin *et al.*, 2014).

Conclusion

Like other psychiatric disorders, PTSD represents a multifaceted disease state with underlying disturbances of complicated neurobiological mechanisms. **While current animal models of PTSD have proven useful for examining symptoms associated with the disorder, it remains difficult to distinguish PTSD-like behaviors that may be associated with other psychiatric conditions, such as depression. Furthermore, animal models lack the ability to examine certain symptoms that manifest in individuals with PTSD, such as intrusive thoughts or nightmares. Nonetheless, animal models are critical for understanding the underlying neurobiological mechanisms contributing to the development of PTSD and co-morbid states such as AUD in subpopulations of individuals following exposure to a traumatic stress**. It is anticipated that the further development and refinement of valid animal models will provide better insight into the individual differences that drive propensity for or resilience to the emergence of PTSD. In addition, the continued utilization and integration of innovative neurobiological techniques to determine the most critical functional neuroadaptations underlying PTSD will assist in the discovery of new targets for clinical therapy. In the end, a better understanding of the basic biobehavioral processes underlying traumatic stress reactivity will greatly facilitate the treatment of PTSD as well as associated disease states driven by stress dysregulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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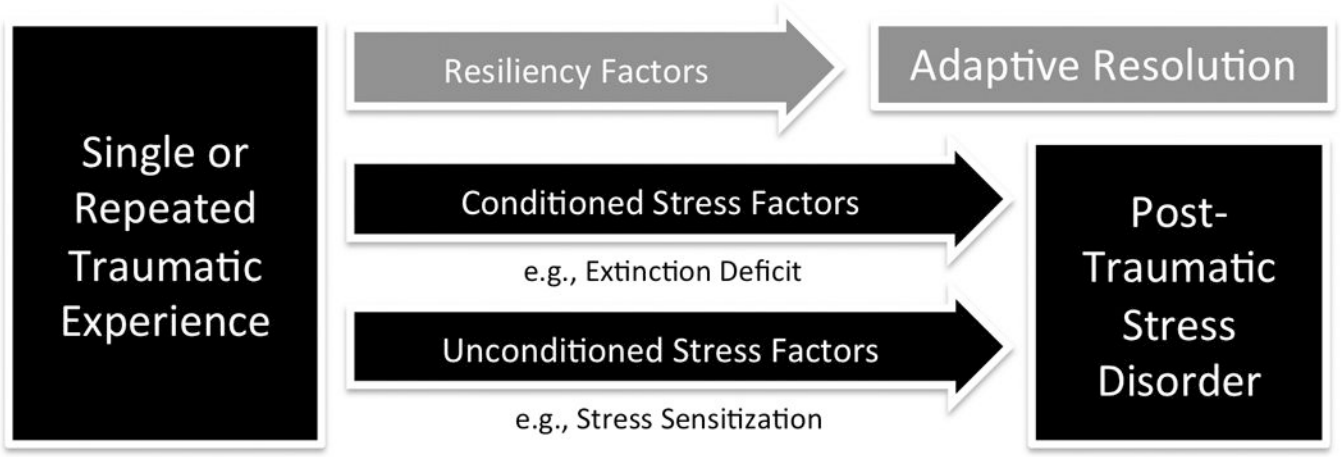

Figure 1.

PTSD can be conceptualized as an enduring, pathological manifestation of both conditioned and unconditioned stress factors following exposure to a particularly traumatic event or series of events. In most situations, an apparently resilient population emerges, in that not everyone manifests PTSD symptoms following a traumatic stress event. As a consequence, PTSD may represent one of the more quintessential psychiatric disorders driven by individual differences in stress reactivity. This characteristic may be critical for preclinical animal modeling, leading to the discovery of both resilience and susceptibility factors at the biomarker/neurobiological level as well as more effective treatments for PTSD and closely related co-morbid conditions such as alcohol use disorder.