In this Chapter

Introduction 165

Current Animal Models of Comorbid AUD and PTSD 167
  A Genetic Mouse Model for Comorbid AUD and PTSD 168

Mechanisms for Comorbid AUD and PTSD 169
  The Common Genetic Factors Hypothesis 170
  The Self-Medication Hypothesis 172
  The HPA Axis Dysregulation Hypothesis 174

Highlights 175

References 176
A Genetic Mouse Model for Comorbid Alcohol Use Disorder and Posttraumatic Stress Disorder

Julia A. Chester
Purdue University, West Lafayette, IN, United States

Introduction

The role of stress in the development of drug use disorders has been the subject of intensive study for many decades. Much progress has been made in understanding the biological and behavioral mechanisms that contribute to individual vulnerability and resilience toward drug-seeking behavior. Stress potently regulates cognitive and emotional brain mechanisms, including those that relate to anxiety, and influences initial propensity to use drugs as well as maintenance of drug-seeking behaviors.

Of all the substance use disorders, alcohol use disorder (AUD) is the most common. Data from the 2012 to 2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) using the new AUD classifications in the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) indicated the 12-month and lifetime prevalence of AUD was 13.9% and 29.1%, respectively (Grant et al., 2015). In the United States alone, AUD has an estimated economic impact of $249 billion dollars each year. Alcohol consumption is the fifth leading cause of premature death, with 88,000 deaths each year and an estimated 2.5 million years of lost life of those who died (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014).

AUD has the highest cooccurrence (termed comorbidity) with mental illnesses in both adolescents and adults (Lipari et al., 2014). Identifying the behavioral
and neurobiological mechanisms that underlie psychiatric comorbidities with AUD is a primary focus of the National Institute on Alcohol Abuse and Alcoholism’s strategic research plan. Of particular interest is addressing the increasingly high incidence of comorbid AUD and posttraumatic stress disorder (PTSD).

PTSD can develop in people after exposure to various types of trauma, such as violence, physical abuse, accidents, natural disasters, and war (Vieweg et al., 2006). Nearly 8% of the US population will develop PTSD at some point in their lifetime; in women, the statistic is approximately 10%–13%, nearly double that in men (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995).

High comorbid rates of AUD and PTSD have been documented for decades (Kessler et al., 1996) and are continuing to rise in military personnel and veterans (Allen, Crawford, & Kudler, 2016). Approximately 30% of people in the general population with PTSD also have a comorbid AUD and most studies report a higher comorbidity prevalence in men than women (Kessler et al., 1995). However, emerging evidence suggests that type of trauma and severity of PTSD in combination with other risk factors for AUD may disproportionally impact lifetime prevalence of comorbid AUD and PTSD in women (Pietrzak, Van Ness, Fried, Galea, & Norris, 2012).

People with comorbid AUD and PTSD represent a special population that suffer greater negative consequences than those with either disorder alone, such as more severe anxiety symptoms, greater alcohol drinking relapse rates, incurrence of higher medical costs, poorer treatment outcomes, and greater losses in work productivity (Blanco et al., 2013). There is currently a critical need to identify appropriate prevention and treatment strategies for comorbid AUD and PTSD. Although there are several promising pharmacological compounds currently being tested in clinical trials, there are no medications approved by the Food and Drug Administration specifically indicated for the treatment of comorbid AUD and PTSD.

Preclinical research in animal models is necessary to understand how genetic and biological mechanisms contribute to the risk for developing comorbid AUD and PTSD in humans and to identify specific and efficacious biological and behavioral treatments for these comorbid disorders. The goals of this chapter are to highlight: (1) epidemiological data on the prevalence of comorbid AUD and PTSD in humans, (2) theories that attempt to explain comorbidity, (3) current animal models of comorbid AUD and PTSD, and (4) findings from our laboratory in a unique genetic mouse model of comorbid AUD and PTSD. We will discuss the translational applicability of this model to speed the identification of novel treatments for humans suffering with comorbid AUD and PTSD.
Current Animal Models of Comorbid AUD and PTSD

Mimicking the characteristics of stressors and how they impact an organism in an ecologically relevant way is critical for developing valid animal models of stress-related disease in humans. Stressor characteristics, including physical, chemical, emotional and cognitive facets, interact with genetic, biological, and environmental factors to produce complex responses that manifest as either adaptive or maladaptive effects on the organism. A primary goal of translational research and the development of valid animal models is to isolate the various heterogeneous factors and explore interactive effects to help understand how these factors promote vulnerability or resilience against stress-related disorders and to develop treatments once the pathological condition has manifested.

Animal models for stress and alcohol interactions have been in existence for almost 100 years, and these models are continually being refined to show robust and reproducible effects that mimic specific aspects of complex human disorders. Models for comorbid psychiatric disorders are just beginning to emerge during a time of exponential growth in knowledge regarding how genetic and environmental factors interact to contribute to brain function and behavior.

Stress effects on alcohol drinking behavior in rodents are not straightforward and appear to depend on many factors such as preexposure to alcohol, timing and duration of stress exposure in relation to drinking, chronicity and type of stressor, and type of alcohol drinking procedure (Becker, Lopez, & Doremus-Fitzwater, 2011; Noori, Helinski, & Spanagel, 2014). Results from several laboratories, including our own, have shown that rodents with a genetic predisposition toward high alcohol drinking are more sensitive to stress-induced drinking behavior than their low alcohol drinking counterparts. For example, footshock exposure reinstated alcohol intake to a greater extent in the Alcohol-Accepting (AA), High-Alcohol-Drinking (HAD), and alcohol-preferring (P) rats (Vengeliene et al., 2003) and in Marchigian Sardinian alcohol-preferring (msp) rats (Hansson et al., 2006) compared to Wistar rats. Restraint stress increased alcohol intake in male P and HAD but not in low-(NP/LAD)-alcohol drinking rat lines (Chester, Blose, Zweifel, & Froehlich, 2004). Repeated, intermittent restraint stress exposure prior to limited-access alcohol sessions produced a sustained increase in alcohol intake over time in male but not female high-alcohol-preferring (HAP2) mice (Chester, de Paula Barrenha, DeMaria, & Finegan, 2006). Although these models indicate stress-induced drinking effects, they are not necessarily models of PTSD and comorbid AUD, specifically.

Developing translational rodent models specifically for PTSD is an emerging research area. PTSD diagnosis in humans requires that the individual was exposed to a specific traumatic stressor. Thus many PTSD models involve exposing animals to physical and psychological traumas and measuring resultant behavioral
responses that mimic clinical signs of PTSD symptomatology, such as fear and anxiety (Flandreau & Toth, 2017). The highly conserved neuroendocrine circuitry in mammals also allows for measurement of hypothalamic-pituitary-adrenal (HPA) axis and other neuroendocrine factors in conjunction with anxiety-related behaviors. PTSD models have included exposure to physical stressors such as footshock, pain, restraint, and cold temperatures; arguably these physical stressors also invoke aspects of psychological trauma. Models of specific psychological trauma include predator stress and social stressors such as housing instability or social defeat. Furthermore, many of these models take advantage of individual differences in responses that may reflect vulnerability or resilience toward developing PTSD, as well as manipulate factors that may increase the likelihood or severity of the PTSD-like behavior, such as repeated or prolonged exposure to the stressors and/or exposure during early life development (Butler, Karkhanis, Jones, & Weiner, 2016).

There are also many learning models of PTSD that rely on fear-conditioning procedures to mimic “maladaptive” learning processes thought to be a primary factor in the development and maintenance of PTSD symptomatology (Lissek & van Meurs, 2015). Associative fear learning involves the pairing of an initially neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US; usually a footshock or predator odor) and then measuring the behavioral response to the CS. Several forms of “maladaptive” learning processes with relevance to the clinical condition have been partially validated in animal models, including impairments in the extinction process, incubation of fear, stimulus generalization, and sensitization to stress.

Demonstrating model validity for comorbid AUD and PTSD has been difficult due largely to an inability to produce escalated and sustained stress-induced alcohol intake—characteristics of human behavior. Previous work has shown increased alcohol intake following traumatic stress using a predator odor model in rats (Edwards et al., 2013; Manjoch et al., 2016), with the “stress-reactive” rats showing persistent increased alcohol intake. In another study, investigators used a stress-enhanced fear learning model to show that repeated exposure to footshock prior to alcohol access enhanced the acquisition of alcohol intake in rats, but stress had no effects on drinking in rats that had already established drinking behavior (Meyer, Long, Fanselow, & Spigelman, 2013). Much work is needed to identify new models and increase the construct and predictive validity of existing animal models of comorbid AUD and PTSD. The field requires many different models to address the heterogeneity of the comorbid disorders and demonstrate construct and predictive validity to appropriately identify individualized treatment strategies in humans.

A Genetic Mouse Model for Comorbid AUD and PTSD

Some of the most exciting tools for studying genetic factors that contribute to the development of AUD are rodent lines that have been selectively bred for
differences in propensity to consume alcohol (Li & McBride, 1995). These lines are extremely valuable for identifying traits that are correlated with the selection phenotypes of high or low alcohol drinking and elucidating the ways in which environmental factors, such as exposure to stress, may interact with a genetic predisposition toward alcohol drinking behavior to influence the development of AUD and comorbid disorders.

In our work, we use replicate mouse lines selectively bred for high (HAP1/HAP2/HAP3) or low alcohol preference (LAP1/LAP2/LAP3). These mouse lines were separately selected from a progenitor population of outbred HS/Ibg mice (Grahame, Li, & Lumeng, 1999), an intercross of eight different inbred mouse strains (A, AKR, BALB/c, C3H/2, C57BL, DBA/2, Is/Bi, and RIII), which contributes a relatively diverse set of possible alleles to “capture” during the selective breeding process. Thus this is a model for genetic heterogeneity in humans and is extremely relevant for translational approaches to identify genetic contributions to behavior.

The use of more than one pair of selectively bred lines to identify genetic correlations between traits is a very strong experimental design because genetic drift can occur between a single pair of selected lines over generations of selective breeding. Replicate lines do not exist for many of the selectively bred rat lines used in the studies reviewed herein, reinforcing the importance of using multiple animal models to obtain converging evidence for genetic relationships between traits. The identification of a correlated trait in more than one pair of replicate lines robustly increases the probability that the relationship between the correlated trait and the selection phenotype reflects a true genetic correlation (Crabbe, Phillips, Kosobud, & Belknap, 1990). To date, several traits have been identified in the HAP/LAP lines that are associated with high alcohol preference or low alcohol preference, such as differences in sensitization to the locomotor-stimulant effects of alcohol (Grahame, Rodd-Henricks, Li, & Lumeng, 2000), conditioned place preference (Grahame, Chester, Rodd-Henricks, Li, & Lumeng, 2001) and conditioned taste aversion to alcohol (Chester, Lumeng, Li, & Grahame, 2003), emotional reactivity (Matson & Grahame, 2015), affect-related behaviors (Can, Grahame, & Gould, 2012), and impulsivity (Oberlin & Grahame, 2009). We have compelling data indicating that mouse lines selectively bred for high or low alcohol preference are a good model for genetic vulnerability factors that may contribute to the development of comorbid AUD and PTSD in humans (discussed below).

**Mechanisms for Comorbid AUD and PTSD**

Genetic factors in combination with environmental and biological factors certainly influence the risk for developing comorbid AUD and PTSD, through
interactive and permissive mechanisms, and the roles of these risk factors are the subject of intense investigation in the field of psychiatric behavioral genetics. Investigators have focused on several primary hypotheses to explain the cooccurrence of AUD and PTSD. From a clinical treatment perspective, it is important to differentiate the role of various factors and identify time of symptom onset in the context of the individual's personal history, such as trauma and alcohol exposure, to improve diagnostic accuracy and treatment outcomes (Shivani, Goldsmith, & Anthenelli, 2002).

The Common Genetic Factors Hypothesis

Recent evidence indicates common genetic factors play an important role in the risk for developing comorbid AUD and PTSD, specifically. Genetic correlation studies in humans report significant overlap in genetic factors contributing to both disorders (Sartor et al., 2011). However, the ultimate challenge in identifying risk factors for comorbid disease is unraveling the complex gene-environment interactions.

Testing the Common Genetic Factors Hypothesis With Acoustic Startle Phenotypes

General Acoustic Startle Response

The acoustic startle reflex is an adaptive, defensive behavior shown by all mammalian species in response to intense acoustic stimuli. Acoustic startle phenotypes have served as useful measures of cognition- and emotion-related brain mechanisms that may be associated with genetic risk for AUD and anxiety disorders in humans (Grillon, Dierker, & Merikangas, 1997).

A genetic relationship between selection for high alcohol preference and greater acoustic startle reactivity has been repeatedly shown in rat lines selectively bred for differences in alcohol consumption (Acewicz et al., 2012; Chester, Blose, & Froehlich, 2003, 2004; Jones et al., 2000). In the HAP and LAP selected mouse lines, we have consistently found higher baseline startle responses in HAP mice than LAP mice from both replicates 1 and 2 (Barrenha & Chester, 2007, 2012; Barrenha, Coon, & Chester, 2011; Breit & Chester, 2016; Chester & Barrenha, 2007; Chester, Kirchhoff, & Barrenha, 2014; Chester & Weera, 2017; Powers & Chester, 2014). These data in selected rodent lines provides strong evidence that genes that regulate acoustic startle reactivity also influence propensity to drink alcohol.

Conditioned Fear-Potentiated Startle

One of the clinical features of PTSD is an exaggerated startle reflex and has been suggested to indicate an overblown response to danger-related cues in the environment that may signal the threat of aversive stimuli (Grillon, 2002).

Fear-potentiated startle (FPS) is a model of fear learning that is commonly used to assess anticipatory fear/anxiety in both humans (Grillon, Ameli, Merikangas, Woods, & Davis, 1993) and rodents (Davis, Falls, Campeau, & Kim, 1993).
In rodents, FPS is produced through classical conditioning procedures that involve repeated pairings of aversive stimuli (usually electric shock) with a neutral stimulus (such as a light) to form an association between the two stimuli. Acoustic startle stimuli are then presented in the presence and absence of the cues that predict aversive stimuli. FPS is evidenced by a potentiated startle response, indicating anticipatory fear or anxiety, in the presence of the cues associated with, or predictive of, aversive stimuli. Several key brain areas modulate the acquisition and expression of FPS, including the lateral, basolateral, and central nucleus of the amygdala. The central nucleus of the amygdala projects to brainstem nuclei critical for the expression of FPS. In addition, cortical areas, such as the perirhinal cortices, project to the lateral and basolateral nuclei of the amygdala and modulate multimodal processing of conditioned stimuli (auditory or visual) and expression of FPS (Davis et al., 1993).

FPS has been suggested to be a particularly relevant translational model for PTSD and an index of associative learning processes that support the development and maintenance of PTSD symptomatology (Grillon, Southwick, & Charney, 1996). Evidence in humans indicates that FPS represents a phenotype predictive of genetic risk for developing anxiety-related disorders (Grillon, Dierker, & Merikangas, 1998).

In rats that differ in genetic propensity toward alcohol drinking, McKinzie et al. (2000) found that P rats selectively bred for high alcohol preference show greater FPS than NP rats selectively bred for low alcohol preference. We have demonstrated strong evidence for a genetic correlation between FPS and alcohol preference in the selectively bred HAP/LAP lines. HAP lines of both replicate lines 1 and 2 show greater FPS than LAP lines (Barrenha & Chester, 2007, 2012; Barrenha et al., 2011; Breit & Chester, 2016; Chester et al., 2014; Chester & Weera, 2017). Male HAP2 mice often show greater FPS than female HAP2 mice (Barrenha et al., 2011; Chester et al., 2014), a finding consistent with data from animal models of PTSD, suggesting that male animals are more susceptible to stress-related anxiety (Cohen & Yehuda, 2011).

This genetic association between greater FPS and high alcohol preference in replicate selected mouse lines that are alcohol-naïve may suggest that the high rate of comorbidity between PTSD and AUD in humans is due, in part, to the influence of common genetic risk factors for both psychiatric disorders. These findings in a genetic mouse model support reports of increased prevalence of comorbid AUD and anxiety disorders in relatives of people with AUD and/or anxiety disorders (Merikangas et al., 1998).

Prepulse Inhibition of the Acoustic Startle Response

One common procedure for assessing cognition-related processing in mammals is prepulse inhibition (PPI). PPI reflects adaptive sensory-motor gating processes that regulate incoming information to the brain (Swerdlow, Braff, & Geyer, 2016) and is a well-established procedure for cross-species modeling of...
brain-behavior functions. Deficits in PPI (defined as a reduction of a startle response to an acoustic stimulus when that stimulus is preceded by a weak prepulse stimulus) have been noted in people with psychiatric disorders such as schizophrenia, obsessive compulsive disorder, and PTSD (Braff, Geyer, & Swerdlow, 2001). Deficits in PPI have also been reported in individuals that are genetically related to subjects clinically diagnosed with AUD but do not themselves have the disorder, suggesting that disrupted PPI might be a phenotypic marker for AUD vulnerability.

Alcohol-naïve rats selectively bred to prefer or avoid alcohol showed comparable levels of PPI (Acewicz et al., 2012 [Warsaw alcohol high-preferring/low-preferring lines]; Jones et al., 2000 [P/NP lines]). We found that baseline PPI was higher in the selectively bred HAP1/2 lines than LAP1/2 lines (Chester & Barrenha, 2007), suggesting there are common genetic mechanisms that regulate PPI and alcohol preference in these mouse lines, but the direction of the effect was reversed from that reported in genetically at-risk humans. We subsequently replicated the greater baseline PPI in HAP2 versus LAP2 mice and showed that alcohol administration increased PPI in HAP2 but not in LAP2 mice (Powers & Chester, 2014). Interestingly, this finding was similar to effects of low-dose alcohol reported in human subjects with higher baseline PPI levels (Hutchison et al., 1997). Hutchison et al. speculated that their results could reflect sensitivity differences in alcohol-induced changes in dopaminergic brain function. This hypothesis fits with the larger literature indicating a prominent role for dopamine and its receptors in modulating PPI (Swerdlow et al., 2016) and alcohol-related behaviors (Koob & Volkow, 2016). Furthermore, many studies show differences in dopaminergic system function between rats selectively bred for high or low alcohol intake (Murphy et al., 2002). In the HAP1/LAP1 selected lines, a single nucleotide polymorphism sequence difference was found near the dopamine D2 receptor (Bice, Lai, Zhang, & Foroud, 2011) and D2 mRNA expression differences have been found in the hippocampus and nucleus accumbens (Bice, Liang, Zhang, Strother, & Carr, 2008).

The Self-Medication Hypothesis

The self-medication hypothesis states that AUD arises because individuals attempt to mitigate symptoms of psychological distress symptoms by consuming alcohol (Cappell & Herman, 1972). In theory, alcohol consumption is then negatively reinforced if alcohol successfully reduces adverse symptoms like anxiety which leads to greater alcohol intake over time. Evidence in the PTSD literature largely supports this process and suggests that the severity of PTSD symptoms predict alcohol craving and intake in a prospective and proximal manner (Langdon et al., 2016).

With respect to genetic contributions to the self-medication hypothesis, several studies suggest that humans with genetic predisposition toward AUD
and/or anxiety disorders are more sensitive to the anxiolytic effects of alcohol
(Sher & Levenson, 1982; Sinha, Robinson, & O’Malley, 1998). However,
Zimmermann, Spring, Wittchen, and Holsboer (2004) did not find a difference
in the effect of alcohol on anxiety between men with and without a family
history of AUD using a fear potentiation procedure.

There have been a few reports of alcohol effects on measures of anxiety in rats
that differ in genetic propensity toward alcohol consumption. Colombo et al.
(1995) reported that the selectively bred Sardinian alcohol-preferring (sP) rats
showed greater innate anxiety in the elevated plus maze than the alcohol-
nonpreferring line (sNP) and that voluntary alcohol consumption in sP rats
reduced anxiety. Stewart, Gatto, Lumeng, Li, and Murphy (1993) found greater
anxiety in P rats than in NP rats (Indiana lines) in three tests of anxiety, and
that alcohol produced anxiolytic effects in P but not NP rats. These findings
suggest that the self-medication hypothesis may be particularly relevant for
exploring mechanisms related to AUD risk in organisms that have increased
genetic propensity for high alcohol consumption and anxiety-related behavior.

The HAP/LAP mouse lines have been useful for testing the self-medication
hypothesis in a unique mouse model for genetic predisposition toward develop-
ing comorbid AUD and PTSD in humans. Using the FPS procedure, we reported
that male and female HAP mice from both replicates show an anxiolytic response
to alcohol, but the LAP lines did not (Barrenha et al., 2011). This finding provides
strong evidence indicating genes that regulate anxiolytic response to alcohol
also regulate propensity toward high alcohol preference, and thus this may be
one of the mechanisms contributing to AUD and PTSD comorbidity in humans.

Results of several studies suggest that mice will drink alcohol in response to
stress-induced anxiety. Footshock stress exposure during adolescence increased
acoustic startle reactivity and alcohol drinking behavior in both male and female
HAP1 mice (Chester, Barrenha, Hughes, & Keuneke, 2008). Breit and Chester
(2016) reported that repeated footshock stress during adolescence increased
the magnitude of FPS in adult HAP2 but not LAP2 mice, indicating genetic prop-
ensity toward high alcohol intake may be linked to vulnerability toward-stress-
induced anxiety in adulthood. Interestingly, adolescent footshock stress did not
alter alcohol-induced conditioned place preference in adult HAP2 or LAP2 mice,
suggesting that the adolescent footshock-induced increase in alcohol drinking
reported in Chester et al. (2008) was due to changes in anxiety-related
mechanisms rather than to direct stress-induced changes in alcohol reward sen-
sitivity. Further, we recently demonstrated construct validity in the HAP/LAP
mouse as a model for comorbid PTSD and AUD. Repeated exposure to fear-
conditioning enhanced limited-access alcohol drinking in HAP2 but not LAP2
mice (Chester & Weera, 2017). Overall, these findings indicate that genetic vul-
nerability toward high alcohol consumption is associated with greater sensitivity
to anxiety-related behavior and stress-induced alcohol drinking behavior.
The HPA Axis Dysregulation Hypothesis

A significant area of focus in the literature concerns exploring the neuroendocrine system as a mechanistic link for comorbid AUD and PTSD. It is beyond the scope of this chapter to discuss the plethora of research findings in support of this mechanistic hypothesis (Anthenelli, 2010). Here, we highlight a few relevant findings as they relate to documented HPA axis correlates in humans with AUD or PTSD and in outbred and genetically selected rodent models.

In humans, cortisol is the primary adrenal glucocorticoid and in rodents it is corticosterone. Glucocorticoids exert negative feedback inhibition on the hypothalamus and pituitary gland to suppress further activation of the HPA axis. Negative feedback inhibition is regulated by neural signals from various brain regions such as the amygdala and hippocampus once the stressor is removed (McEwen, Brinton, Harrelson, & Rostene, 1987). Variations in HPA axis function have been suggested to represent a biological marker for PTSD (de Kloet et al., 2005; Yehuda et al., 2000) and AUD (Stephens & Wand, 2012). A prospective longitudinal study found that people who developed PTSD after motor vehicle accident trauma had lower cortisol levels after the trauma compared to people who did not subsequently develop PTSD (McFarlane, Atchison, & Yehuda, 1997). In people with comorbid PTSD and AUD, Brady et al. (2006) reported blunted HPA axis function that was similar to responses seen in people with a single diagnosis of either AUD or PTSD.

An important, unresolved question is whether HPA axis dysregulation is present before the onset of PTSD or occurs as a consequence of PTSD. There is some evidence that healthy individuals who are at greater genetic risk for developing PTSD (family history positive) have low baseline cortisol levels (e.g., Yehuda et al., 2000). Also, studies in humans with increased genetic risk for AUD have reported blunted HPA axis responsiveness to stressors (e.g., Adinoff, Junghanns, Kiefer, & Krishnan-Sarin, 2005; Wand, Mangold, Ali, & Giggey, 1999).

A lower corticosterone response to anxiogenic stressors in outbred rats has been shown to predict greater susceptibility to develop PTSD-like behaviors (Cohen et al., 2006; King, Abend, & Edwards, 2001; Whitaker, Farooq, Edwards, & Gilpin, 2016; Zoladz, Fleschner, & Diamond, 2012). In the selectively bred P/NP rat lines, P rats showed a smaller corticosterone output profile in response to stress compared to NP rats (Prasad & Prasad, 1995).

Our work in HAP/LAP mice aligns with these findings in rats and humans and suggests that a low level of corticosterone in response to trauma is a biological marker for PTSD-like behavior and is correlated with genetic propensity toward high alcohol preference. We showed that HAP2 mice, when compared to LAP2...
mice, have lower levels of corticosterone 2 hours after fear-conditioning (Chester et al., 2014). In this same study we also reported a similar line difference (LAP2 > HAP2), but in males only, when blood was sampled at the end of the 1-hour FPS test. The corresponding FPS data also indicated the line difference (HAP2 > LAP2) was greater in male than female mice. These data are consistent with findings in other animal models of PTSD indicating that male animals are more susceptible to stress-related anxiety (Cohen & Yehuda, 2011). One possible interpretation of these findings, and a hypothesis we are currently exploring, is that lower corticosterone levels in HAP2 mice may reflect greater negative feedback inhibition on the HPA axis due to enhanced glucocorticoid receptor signaling in the brain and pituitary, rather than reduced corticosterone output from the adrenal glands (Yehuda, 2001). We reported additional support for this hypothesis in Powers and Chester (2014) where a line difference in basal circulating corticosterone (LAP2 > HAP2) was seen after repeated stress exposure. Additional work that assesses a variety of stress-induced biological and behavioral endpoints in these mouse lines will help fill important gaps in the literature.

The idea that low cortisol after trauma is a causal risk factor for PTSD is supported by reported effects where exogenous treatment with cortisol during a trauma reduced the subsequent development (Schelling et al., 2001), and symptoms of, PTSD (Aerni et al., 2004). Rat models of PTSD have shown similar results in which exogenous administration of corticosterone reduced the PTSD-like behaviors (Cohen et al., 2006; Whitaker et al., 2016). However, we did not see any effect of exogenous corticosterone administration on FPS in HAP2 or LAP2 mice when given during fear-conditioning (Chester et al., 2014). These data support the idea that cortisol or related compounds might be a promising preventative treatment for individuals at risk for PTSD, but much more work is needed in this arena.

**Highlights**

- There is a critical need to identify new models and increase the construct and predictive validity of existing animal models of comorbid AUD and PTSD.
- Acoustic startle and HPA axis phenotypes are useful translational measures to explore genetic and biological risk factors that may predict risk for developing comorbid AUD and PTSD.
- Genetic vulnerability toward high alcohol consumption is associated with greater sensitivity to anxiety-related behavior, stress-induced alcohol drinking behavior, and HPA axis dysfunction.
- Mouse lines selectively bred for high or low alcohol preference (HAP/LAP lines) are a relevant animal model for genetic vulnerability factors that may contribute to the development of comorbid AUD and PTSD in humans.
References


Neurobiology of Abnormal Emotion and Motivated Behaviors


