Published in final edited form as:

Pharmacol Biochem Behav. 2014 February ; 117: 61–69. doi:10.1016/j.pbb.2013.12.001.

Connecting the pathology of posttraumatic stress and substance use disorders: monoamines and neuropeptides

Nicole M. Enman^a, Yong Zhang^b, and Ellen M. Unterwald^a

Nicole M. Enman: nicole.enman@temple.edu; Yong Zhang: zhangyo@mail.rockefeller.edu; Ellen M. Unterwald: ellen.unterwald@temple.edu

^aDepartment of Pharmacology and Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, 19140, USA

^bThe Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY, 10065, USA

Abstract

Posttraumatic stress disorder (PTSD) co-occurs highly with substance use disorders (SUD), yet the neurobiological basis for this comorbid relationship remains unclear. PTSD and SUDs result in similar pathological states including impulsive behavior, reward deficiency, and heightened stress sensitivity. Hence, PTSD and SUD may depend on overlapping dysfunctional neurocircuitry. Here we provide a short overview of the relationship between comorbid PTSD and SUD, as well as the potential role of select neurotransmitter systems that may underlie enhanced vulnerability to drug abuse in the context of PTSD.

Keywords

posttraumatic stress disorder; substance use disorders; addiction; monoamines; neuropeptides

1. Introduction

1.1 Epidemiological Data on the Incidence of Co-occurring PTSD and Substance Abuse Disorders, including Drug and Alcohol Dependence Disorders

Psychological trauma is a risk factor for the development of both Posttraumatic Stress Disorder (PTSD) and Substance Use Disorder (SUD). Many persons with PTSD go on to develop secondary psychiatric disorders, and substance use disorders are highly prevalent in the PTSD-afflicted population. In 1995, the National Comorbidity Survey reported that the lifetime prevalence of alcohol use disorder was approximately 52% in men and 28% in women, whereas prevalence of drug use disorder was in 35% men and 27% in women with a history of PTSD [1]. Recently, NESARC (National Epidemiological Survey on Alcohol and Related Conditions) reported similar results, indicating the prevalence of alcohol and drug use disorders in individuals with PTSD to be about 42% and 22%, respectively [2]. NESARC reported the lifetime prevalence of alcohol use disorders at rate of 21-26.7% in

© 2013 Elsevier Inc. All rights reserved.

Corresponding author: Nicole Enman, Center for Substance Abuse Research, Temple University School of Medicine, 3500 N. Broad St. Medical Education and Research Building Room 883A, Philadelphia, PA 19140, Phone: 1-215-707-4426.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

men and 9.9-12.5% in women in the general population [3]. Lifetime prevalence of drug use disorders was 4.4-13.9% and 2.5-6.7% in men and women, respectively [3]. Higher rates of comorbidity are reported in populations at high risk for traumatic stress exposure such as military personnel. For example, a recent study documented that 63-76% of veterans meeting the criteria for substance use disorders had co-occurring PTSD [4]. A positive PTSD diagnosis increased the odds of having an alcohol or drug use disorder or both, 3- to 4-fold [4]. These epidemiological studies suggest that PTSD and SUD are strongly linked.

1.2 Theories on the Causative Relationship between Substance Abuse and PTSD

Concurrent PTSD-SUD is a significant public health concern. Treatment of comorbid PTSD and SUD is costly [5]. Individuals who are dually diagnosed exhibit poorer psychosocial functioning and treatment outcomes than those with PTSD or SUD alone [6, 7].

Understanding the causal nature of comorbid PTSD-SUD may lead to more efficient treatment strategies for dually-diagnosed individuals and better preventative interventions to reduce substance abuse in persons with PTSD.

There are several hypotheses regarding the causal relationship of co-occurring PTSD and SUD. One hypothesis suggests that PTSD temporally precedes the development of a substance use disorder. Under this notion, it is hypothesized that individuals self-medicate their PTSD symptoms with drugs and alcohol or use drugs as an avoidant coping strategy [8]. Alternatively, emotional dysregulation evident in persons with PTSD may lead to impulsive behavior, which may manifest in response to emotional distress and result in drug use as a maladaptive coping mechanism [9]. Drug consumption may result in negative reinforcement of drug-taking behavior, motivating escalating use due to the expectation of symptom relief and culminating in a SUD. A second hypothesis suggests that substance abuse precedes and enhances vulnerability to PTSD. In this scenario, drug abusers may engage in risky behaviors that increase the likelihood of a traumatic experience, subsequently increasing the risk for PTSD [10, 11]. Alternatively, persons with SUD may be at risk for PTSD following a trauma due to pathological arousal and stress states resulting from repeated drug use or withdrawal [12]. A third hypothesis indicates that predispositions shared by PTSD and SUD may influence development of both disorders due to shared risk [13-15]. Regardless of temporal occurrence of PTSD and SUD, it is possible that once comorbidity has been established the two disorders interact and lead to a cyclical relationship. PTSD may maintain, prolong, or exacerbate SUD symptoms through self-medication, while the same relationship could be hypothesized for the maintenance of PTSD symptoms by substance abuse or dependence [12].

Although evidence exists in support of each of the aforementioned hypotheses, this review will focus on potential mechanisms by which PTSD may enhance the vulnerability to SUDs. Many studies demonstrate that PTSD temporally precedes and increases the risk for subsequent development of a SUD [16, 17]. Persons with PTSD perceive their co-occurring PTSD-SUD as functionally related [18], and report self-medicating their untreated symptoms with drugs and alcohol [19]. CNS depressants such as alcohol, benzodiazepines, marijuana, and heroin ease hyperarousal and intrusion symptoms in patients with PTSD, while symptoms of emotional numbing and avoidance are highly prevalent in patients with comorbid cocaine dependence [16, 20]. Studies demonstrate that PTSD symptom severity is positively related to the level of substance use [16, 21, 22], and PTSD severity predicts drug craving in response to trauma- and drug-related cues [23]. Improved PTSD symptomology predicts improvement of SUD symptoms [22, 24, 25]. Taken together, these studies suggest that PTSD enhances the susceptibility to substance abuse. Given the wealth of literature in support of this hypothesis, this review largely focuses on the neurobiological underpinnings that may contribute to this casual relationship. Examples of neurobiological alterations

observed in clinical studies of PTSD and SUD, as well as preclinical rodent models, are presented in Table 1.

2. Common Neuropathological States in PTSD and SUD

PTSD and SUD share common psychopathological states which may provide mechanistic insights regarding the increased incidence of substance abuse in individuals with PTSD. Herein we discuss impulsivity and negative emotional states associated with these disorders including anhedonia and heightened states of anxiety and stress sensitivity, each of which putatively serves as a risk factor for susceptibility to drug abuse in PTSD.

2.1 Impulsivity

Many functional imaging studies demonstrate differences in the activation of the prefrontal cortex in brains of PTSD patients [26]. Hypothetical framework based on these studies suggests that hypoactivity of the ventral medial prefrontal cortex may convey a lack of inhibitory control over networks mediating emotion and arousal in PTSD, while hyperactivity of the dorsal anterior cingulate and insular cortices may contribute to enhanced expression of fear- and anxiety-like states [27]. Altered functional capacities of the prefrontal cortices may also lead to altered executive functioning and cognition in the form of impulsivity or altered decision making behaviors, which could ultimately introduce or perpetuate substance use. Impulsivity measures include impulsive motor action and choice, both of which have putative relationships with drug abuse (reviewed in [28]). Motor impulsivity in humans predicts the severity of psychostimulant abuse [29]. Likewise, rodents with high motor impulsivity escalate their cocaine intake more quickly [30]. Animal studies show that impulsive choice contributes to the severity of substance use. Rats with high impulsive choice in delayed discounting acquire self-administration of psychostimulants at a faster rate and are more likely to reinstate to drug-seeking behavior than low impulsive rats [31, 32]. Additionally, high-alcohol preferring mice are more impulsive than those that prefer alcohol less [33].

Individuals with PTSD demonstrate greater motor impulsivity in the form of more inhibition-related errors in the Go/No-Go task which measures prepotent motor response inhibition [34]. This effect is associated with reduced cortical activation compared to controls [35]. SUD patients with PTSD demonstrate heightened urges to engage in impulsive behavior in response to negative affect, enhanced emotional dysregulation, and difficulty engaging in goal-oriented behavior and controlling impulsive behavior while distressed versus those without PTSD [9]. Together these studies suggest that persons with PTSD may exhibit higher levels of impulsive behavior, particularly in response to emotional stress. Persons with PTSD may act impulsively in favor of immediate emotional relief in response to negative affective states, and such behavior may lead to maladaptive coping strategies including drug use or avoidance behavior. It is important to note that PTSD is not associated with higher levels of sensation seeking. Former prisoners of war with high sensation seeking tendencies demonstrated greater capacity to cope with the stress of captivity and report fewer PTSD symptoms than those with low sensation seeking [36]. Low sensation seeking is consistent with avoidance behavior, a core symptom of PTSD, as persons with PTSD may avoid activities that increase arousal or anxiety [9]. Therefore, it is unlikely that sensation seeking contributes to heightened drug-seeking behavior in PTSD, but impulsivity resulting from loss of cognitive control may increase the likelihood of drug use.

2.2 Reward Dysfunction

Persons with PTSD exhibit symptoms of anhedonia, as well as deficits in hedonic or reward capacity [37-40]. Deficient reward may be mediated by altered function of mesolimbic circuitry including brain regions such as the striatum. For instance, a study of male combat veterans assessed reward function using attractive facial images, a task known to have rewarding value associated with activation of striatal reward circuitry [41]. This study showed that while veterans with and without PTSD rated attractive female images equivalently, veterans without PTSD opted to extend the viewing time of attractive female faces. This effect was attenuated in veterans with PTSD, suggesting that PTSD results in less effort to achieve rewards [39]. In another study using a gambling task to assess reward function, PTSD was associated with lower expectancies of receiving rewards, lower satisfaction with rewards when received, and failure to experience extra satisfaction upon receiving monetary gains under conditions of low expectancy [40]. In conjunction with reduced reward function, imaging studies indicate reduced activation of mesolimbic brain regions in response to monetary gains in a similar gambling task [42], as well as other positively valenced stimuli [43, 44]. Deficient reward function leading to PTSD symptoms of anhedonia and emotional numbing may promote drug use. In addition, anhedonia is recognized as part of the negative affective state experienced upon drug withdrawal, and may reflect a shift in hedonic state due to repeated drug use. The negative emotional state of withdrawal is hypothesized to drive drug use through negative reinforcement mechanisms [45]. Abusers will re-engage in drug use to relieve emotional withdrawal symptoms thereby motivating future drug-taking behavior. Similar behavior may lead to heightened drug abuse in PTSD, as proposed by the self-medication hypothesis. The therapeutic properties of drugs of abuse in PTSD may enhance their reinforcement potential.

2.3 Heightened Arousal States

PTSD and SUD each result in states of heightened arousal including increases in anxiety and responsivity to stress. Hyperarousal symptoms are a core feature of PTSD, as exaggerated physiological and psychological reactivity manifest in response to internal or external trauma-related cues and unrelated stressors. Symptom provocation studies demonstrate heightened levels of anxiety and emotional distress, as well as physiological elevations in heart rate and skin conductance, in response to trauma-related imagery and sounds [46]. Studies examining startle reflexes and autonomic reactivity to non-trauma related stimuli report mixed results; findings of both hyperreactivity and hyporeactivity to non-trauma related acoustic tones in PTSD patients can be found in the literature [47-49]. Additional studies report the direction of responding to aversive imagery and acoustic startle as dependent on the number of trauma exposures or the experimental context, with emphasis on the presence of threat [49-51].

The pharmacological stressor and alpha2 receptor antagonist yohimbine elicits anxiety, panic attacks, and flashbacks in patients with PTSD [52], suggesting that the adrenergic system may be involved in PTSD-associated hyperarousal. Heightened arousal states present in PTSD may be related to symptoms of avoidance. Individuals with PTSD may engage in avoidance of trauma and non-trauma related stress in order to prevent the emergence of hyperarousal and reexperiencing symptoms [53]. Similarly, abstinence from chronic drug use is hypothesized to result in heightened arousal and sensitivity to stress [45]. Increases in arousal and anxiety contribute to the negative affective state characterizing acute drug withdrawal, while increased sensitivity to stress lasts into protracted withdrawal. Importantly, the negative emotional state of withdrawal is hypothesized to motivate continuous substance use via negative reinforcement of drug intake [45]. Stress is a recognized risk factor for relapse to drug seeking behavior in humans and in rodent models

[54-58]. Given that hyperarousal and stress are associated with relapse to drug abuse, the presence of heightened arousal may be a risk factor for increased drug use in PTSD.

PTSD is also associated with increased anxiety sensitivity, a psychological construct that refers to the fear of experiencing anxiety-related sensations, and is theorized to contribute to the maintenance and severity of anxiety symptoms [59]. Anxiety is hypothesized to compromise attentional control over emotion, which may increase vulnerability to trauma-related cues and emotional distress in PTSD [60]. Anxiety sensitivity is positively correlated to severity of PTSD symptoms, and is reduced alongside decreases in PTSD symptom severity [61]. Anxiety sensitivity is associated with substance use, particularly CNS depressants such as alcohol and heroin [62, 63], and is positively associated with anxiety- and depression-related motives for drug use [64]. Therefore, heightened anxiety sensitivity may also underlie the relationship between PTSD and the development of SUD.

3. Animal models

In order to study the neurobiological mechanisms that may contribute to comorbid PTSD-SUD, relevant animal models of each disease must be applied appropriately and in combination. Sufficient rodent models exist to examine drug-seeking behaviors including drug self-administration models and the conditioned place preference paradigm of drug reward. There are an expansive number of stress procedures presently used to induce behavioral phenotypes of fear, anxiety, and depression, however, the validity of procedures used to model “PTSD” is less clear [65]. Ideally, rodent models of PTSD should induce a behavioral phenotype mimicking symptoms in each of the three categories required for diagnosis of the disorder (DSM-IV), as well as accurately recapitulating specific biological observations such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and noradrenergic systems [65, 66]. One rodent model that fulfills these criteria is the single-prolonged stress (SPS) model. SPS is a rat model that induces a behavioral phenotype bearing resemblance to PTSD including heightened anxiety and acoustic startle behavior, enhanced contextual fear conditioning and renewal of fear, as well as impaired extinction of fear and retention of extinction memories [67, 68]. SPS is sensitive to selective serotonin reuptake inhibitors, a first-line pharmacotherapeutic for PTSD [67], and is one of few procedures producing enhanced reactivity of the HPA-axis to exogenous glucocorticoids [67, 69]. This finding may be critical in distinguishing animal models of PTSD from depression or other forms of stress [66, 67]. Many clinical studies demonstrate enhanced suppression of cortisol following an exogenous glucocorticoid challenge (low-dose dexamethasone) in PTSD compared to non-PTSD controls, whereas attenuation of suppression of cortisol has been observed in individuals with depression (see [70] for review).

A comprehensive review of animal models of PTSD has been recently published [71] and so will not be repeated here. Rodent models that are partially validated include physical, psychosocial, or psychogenic stressors. Procedures utilizing foot-shock, swimming, or restraint stress may be useful as the development of PTSD often results from events involving life-threatening bodily harm [71]. Psychosocial stressors include housing instability and social defeat, a model that may be particularly useful in characterizing traumatic interpersonal violence or social stress [71]. Species-specific predator exposure or odor threats are considered ecologically valid psychogenic stressors [71]. Each of these procedures induces a behavioral phenotype resembling PTSD such as long-lasting increases in anxiety, avoidance, and startle responses, as well as altered fear-associated memory and social interactions (reviewed in [71]). The neuroendocrine alterations produced by these methods are varied or undetermined. For instance, combined predator exposure and housing instability as a form of psychosocial stress has been shown to enhance suppression of

corticosterone following a dexamethasone challenge [72]. In contrast, social defeat and isolation leads to heightened corticosterone levels following dexamethasone [73], while defeat alone results in higher ACTH and corticosterone in response to a test combining dexamethasone and corticotropin releasing factor injections [74]. These models may also be useful in characterizing the neurobiology of comorbid PTSD and SUD.

4. Neurobiological Underpinnings of Increased Incidence of Substance Abuse in PTSD: Neurotransmitter Involvement

4.1 Monoamines

4.1.1 Dopamine—As discussed above, individuals with PTSD exhibit deficits in hedonic or reward capacity. Given that reward is largely mediated by the mesolimbic dopamine system, alterations in reward capacity suggest that dopaminergic neurotransmission may be altered in PTSD. In support of this hypothesis, case studies indicate that combat-related PTSD is sensitive to treatment with psychostimulants [75], which enhance dopaminergic neurotransmission. Clinical studies of altered dopaminergic biomarkers in PTSD are limited; however a recent study demonstrated increased density of dopamine transporters in the striatum of violence victims with PTSD compared to traumatized asymptomatic controls [76]. As the dopamine transporter functions to remove dopamine from the synaptic cleft, increased dopamine transporter density may contribute to reduced dopaminergic tone in the striatum, which may in turn lead to symptoms of anhedonia and dampened reward capacity. It has also been hypothesized that reductions in D2 receptors and decreases in dopamine release may contribute to anhedonia and decreased motivation in drug-dependent individuals [45, 77]. D2 receptor density predicts the reinforcing properties of psychostimulants and relapse to drug use in humans, as well as self-administration behavior in primates [78-80]. Striatal D2 receptor levels are decreased in human addicts during abstinence from psychostimulants [81, 82], which has been associated with reduced metabolic activity of the frontal cortex and is hypothesized to contribute to loss of behavioral control and drug-seeking behavior [82]. Consistent with a role for dopamine in impulsive behavior, psychostimulant abusers exhibit impaired inhibitory control [83, 84]. Additionally, striatal D2/D3 receptor availability is involved in risky decision-making and impulsivity in humans [85, 86]. Reduced striatal D2 receptor density is associated with enhanced impulsivity in rodent models [30]. Taken together, these studies suggest that dopaminergic transmission may dictate vulnerability to drug-seeking behavior via altered reward and executive functioning.

In preclinical studies, rodents that demonstrate deficits in reward function, such as during acute drug withdrawal, exhibit enhanced drug-seeking behavior. Specifically, increases in reward thresholds temporally precede and highly correlate with the escalation of cocaine and heroin self-administration in rats [87, 88], suggesting that low levels of reward, potentially driven by hypodopaminergic transmission, are compensated for by increases in drug consumption. Alternatively, a lack of competing natural reinforcement may contribute to an increase in drug-seeking behavior. Based on separate lines of evidence demonstrating reward dysfunction in PTSD and addiction, we hypothesize that dysregulation of reward function occurring in PTSD may be driven by altered dopaminergic transmission, and result in heightened drug consumption due to increases in reward thresholds or deficient reward capacity. In addition, impulsivity mediated by altered dopaminergic function may drive drug use in PTSD. As described above, high impulsive rats acquire and escalate their drug use more quickly and are more likely to reinstate to drug-seeking behavior than low impulsive rats [30-32]. As altered dopamine function is present in both PTSD and SUD, dysregulated dopaminergic transmission may underlie enhanced susceptibility to drug use in PTSD. In

addition, altered dopamine function may be exaggerated in comorbid PTSD-SUD, in which both stress- and drug-induced alterations in dopaminergic function may act synergistically.

4.1.2 Serotonin (5-hydroxytryptamine, 5HT)—Serotonin is important for the regulation of anxiety, mood, stress, and fear responses. A role for serotonin in PTSD has stemmed largely from the ability of selective serotonin reuptake inhibitors (SSRIs) to relieve PTSD symptomology in humans and rodent models, suggesting that hyposerotonergic tone may contribute to PTSD pathology. Serotonin is widely expressed throughout the brain and fourteen receptor subtypes mediate its effects, however only a handful of serotonin receptor subtypes have been implicated in the pathology of PTSD thus far. Rodent models of PTSD demonstrate stress-induced receptor alterations including increased 5HT1A receptor density in the dorsal raphe nucleus and hippocampus, and increased amygdalar 5HT2C receptor expression [89-91]. Altered serotonin receptor characteristics including reduced 5HT1A binding affinity in the hippocampus and enhanced binding affinity of 5HT2A receptors in the prefrontal cortex have been observed in a stress-restress model, which applies re-exposure to a stressor following SPS [89, 90]. Administration of a 5HT1A receptor antagonist partially inhibits SPS-induced increases in glucocorticoid receptors and corticotrophin releasing hormone (CRH) expression, suggesting that this receptor subtype may be required for the development of PTSD pathology (reviewed in [27]). The 5HT2C receptor subtype is implicated in the etiology of anxiety-like behavior. Consistent with this role, amygdalar 5HT2C gene expression is increased following exposure to SPS, and 5HT2C receptor antagonism effectively attenuates SPS-induced increases in freezing behavior following contextual fear conditioning [91]. Interestingly, the 5HT2C and 2B receptors have been shown to be desensitized by SSRIs [92], which may partially underlie the effectiveness of SSRIs in the treatment of PTSD.

Serotonergic neurotransmission is impacted by all major drugs of abuse, and has been implicated in impulsivity, reward, negative affective state of withdrawal, and relapse to drug-seeking behavior—all of which may overlap with PTSD to promote drug abuse. For example, hyposerotonergic tone contributes to increased impulsive behavior in humans and rodents, an effect that may be mediated by the prefrontal cortex. Reduced serotonin function may be a factor in dysphoric mood or anhedonia, as well as heightened anxiety experienced in the negative emotional state of withdrawal. Studies demonstrate that serotonin depletion increases drug-seeking in rodent models of motivation and relapse. Administration of 5HT2A receptor antagonists and 5HT2C receptor agonists attenuate reinstatement of cocaine-seeking behavior, while 5HT2C receptor antagonists increase drug-seeking (see review [28] and references therein). Both 5HT2A and 5HT2C receptors are implicated in the pathology of PTSD and substance abuse, therefore further investigation of these subtypes in the vulnerability to drug use in PTSD is warranted. Reduced serotonin function is associated with PTSD and drug consumption, and contributes to overlapping behavioral states that may increase the incidence of substance abuse in persons with PTSD.

4.1.3 Norepinephrine—The study of altered noradrenergic function has been limited to peripheral biomarkers and behavior in humans with PTSD. Hypotheses largely state that norepinephrine circuitry may be hyperactive in humans with PTSD and that dysregulation of noradrenergic function may underlie PTSD symptoms in the re-experience and hyperarousal clusters. Clinical studies indicate changes including elevated plasma norepinephrine, increased epinephrine and norepinephrine excretion, reductions in platelet α_2 receptors and affinity, and exaggerated sympathetic and behavioral responses to stress in PTSD [27, 93]. Rodents exposed to SPS exhibit decreased basal activity of locus coeruleus neurons, but exaggerated neuronal responses to a noxious stimulus [94]. Consistent with this finding, tyrosine hydroxylase mRNA is decreased in the locus coeruleus following SPS, but is exaggerated following re-exposure to restraint stress [94]. This evidence from rodent studies

suggests that central norepinephrine function may be hyperactive following re-exposure stress in PTSD, which is consistent with human studies examining noradrenergic responses upon stressful challenges. PTSD is associated with increased emotional and physiological reactions to trauma-related cues. For example, audiovisual traumatic imagery increases cerebrospinal levels of norepinephrine and decreases levels of the metabolite homovanillic acid (HVA), which may reflect an increase in conversion of dopamine to norepinephrine in response to re-exposure to stress [95, 96]. The pharmacological stressor yohimbine, which acts to increase norepinephrine levels, exacerbates symptoms of anxiety, panic, and flashbacks in persons with PTSD, thereby also supporting a role for noradrenergic hyperactivity following re-exposure to stress. Yohimbine administration is also associated with decreased metabolic activity of the prefrontal cortex in PTSD, whereas increases in metabolism occur following the same treatment in healthy controls (reviewed in [27]). These effects in the prefrontal cortex support prior results demonstrating that stress alters executive functioning in PTSD, in which heightened urges of impulsiveness are experienced upon emotional distress.

Noradrenergic hyperactivity in PTSD may have motivational significance through increases in impulsivity and negative emotional and arousal states, which may drive persons with PTSD to seek drugs of abuse as a coping mechanism. Similar hypotheses have been proposed in drug addiction, in which noradrenergic hyperactivity has been implicated in the negative affective state of withdrawal and sensitivity to stress during abstinence. Addicts engage in continuous cycles of drug use and withdrawal which may result in negative reinforcement of drug abuse, as consumption in the face of aversive symptoms of withdrawal may lead to subsequent expectations of relief. The norepinephrine system originating in the locus coeruleus is activated upon withdrawal from chronic drug exposure, and noradrenergic perturbations are associated with heightened withdrawal-induced anxiety and sensitivity to stress-induced relapse during drug abstinence (reviewed in [97]).

4.2 Neuropeptides

4.2.1 Corticotropin-releasing factor (CRF)—CRF plays vital roles in stress, emotion, and reward in brain regions where both drug- and stress-induced CRF pathology have been observed. Many pre-clinical studies indicate that CRF is critical in the transition to drug dependence as well as drug-seeking behavior in the context of stress; therefore it is likely that this neuropeptide is involved in susceptibility to SUD in PTSD. It is well recognized that extrahypothalamic CRF systems are hyperactive during acute withdrawal from drugs of abuse, and this contributes to the negative affective state that emerges upon drug abstinence. The negative emotional state of withdrawal includes heightened anxiety, decreased reward function, and enhanced sensitivity to stress, all of which have been associated with aberrant CRF activity [45]. Likewise, persons with PTSD exhibit increased levels of CRF [98-100], which may mediate symptoms of anxiety, hyperarousal, and potential reward dysfunction. In conjunction, hypothalamic levels of CRF are heightened following exposure to SPS [101]. Also in rodents, repeated drug administration and withdrawal symptoms of anxiety and anhedonia are associated with robust elevations in CRF and CRF gene expression, as well as decreases in tissue CRF and CRF binding sites in the limbic forebrain [97]. These effects suggest heightened overall activity of the CRF system [97]. CRF antagonists reverse anxiety generated by withdrawal from all major drugs of abuse, as well as reduce escalated drug intake in unlimited access schedules of self-administration [102]. Blockade of CRF1 receptors prevents the elevation of reward thresholds associated with withdrawal and drug-seeking [103]. Chronic drug taking is associated with increased responsiveness to stress, which serves as a major risk factor for relapse to drug taking behavior in humans and rodents through its ability to induce preoccupation and craving states. Evidence from rodent studies has shown that CRF contributes to stress-induced relapse, as CRF itself is enough to

induce reinstatement of drug-seeking behavior and CRF antagonism attenuates reinstatement induced by stress [104-110].

While only hypothalamic CRF pathology has been suggested in PTSD, it is likely that extrahypothalamic CRF systems are altered in PTSD as well. Many of the described effects associated with drug dependence have been attributed to specific loci including the basolateral and central amygdala, the bed nucleus of the stria terminalis and nucleus accumbens shell as part of the extended amygdala, the ventral tegmental area, and dorsal raphe nucleus in rodents. Hyperactivity of extrahypothalamic CRF systems in PTSD likely contributes to drug-seeking behavior, potentially through its role in stress and interactions with reward systems that mediate negative affective states. Increased CRF activity may lead to anxiety and anhedonia that facilitate the induction of drug-seeking as a form of self-medication. A combination of both stress- and drug-induced CRF pathology may potentiate the transition to drug dependence once drug use has been initiated, as well as enhance the susceptibility to relapse in dually-diagnosed individuals due to heightened sensitivity to stress.

4.2.2 Neuropeptide Y (NPY)—Preclinical studies in rodents demonstrate that NPY promotes coping behavior in response to stress, potentially via its ability to modulate the transmission of stress-related neurotransmitters such as CRF and norepinephrine [111]. Additionally, NPY may play a critical role in behavioral responses to drugs of abuse. For example, mice deficient in NPY exhibit enhanced cocaine self-administration and cocaine conditioned place preference [112]. NPY knock-out mice also show enhanced alcohol consumption whereas mice overexpressing NPY show reduced alcohol preference [113]. NPY receptor antagonism facilitates extinction and reduces reinstatement to drug-seeking behavior in rodent models [114], while NPY administration can alleviate withdrawal from morphine and alcohol and attenuate excessive alcohol drinking associated with the transition to alcohol dependence [115-117]. Alcohol preferring rats have lower levels of NPY in limbic brain regions than non-alcohol preferring rats [118], and show opposing electrophysiological properties in response to NPY [119]. Repeated administration of cocaine leads to reduced levels of NPY protein and mRNA in the nucleus accumbens and prefrontal cortex [120], two brain areas pertinent to the effects of drugs of abuse. The role of NPY in response to drugs of abuse may be mediated in part by its actions on reward-related neurotransmission, as local NPY administration increases extracellular dopamine in the nucleus accumbens shell [121]. In humans with PTSD, reduced levels of cerebrospinal and plasma NPY have been reported [122, 123]. Additionally, a positive correlation between levels of NPY and coping and recovery from PTSD has been shown [124]. Pretreatment with intranasal NPY can attenuate the development of PTSD-like symptoms in the rodent SPS model of PTSD [125]. Given evidence that low levels of NPY may potentiate drug-seeking behavior, NPY pathology may enhance the susceptibility to SUD in individuals with PTSD. NPY may be therapeutically beneficial in the prevention of self-medication of untreated PTSD symptoms with drugs and alcohol due to its ability to convey resilience to stress and negative affect.

5. Conclusions

Clinical studies suggest that PTSD enhances vulnerability to substance use disorders, yet the mechanisms for this comorbid relationship are not well-established. Co-occurring PTSD and SUD likely involves overlapping neuropathology, and further clinical research is necessary to determine the motivating factors or behavioral states associated with substance abuse in individuals with PTSD. Impulsivity, anxiety, and dysfunction of reward and stress systems may contribute to enhanced drug use vulnerability. The development of rodent models recapitulating phenotypes unique to PTSD may aid in this process, and will enhance the

investigation of neurochemical mechanisms underlying behaviors leading to drug use in PTSD. Neurobiological circuitry involved in comorbid PTSD-SUD may include but is not limited to dopamine, serotonin, norepinephrine, CRF, and NPY systems. While not discussed within the scope of this review, known interactions among these monoamines and neuropeptides occur in response to stress and in addiction processes. Further investigation of these neurotransmitters and their interactions in the context of comorbid PTSD-SUD is warranted. The perturbation of each neurocircuit alone, as well as the connections among these systems, may make important contributions to the understanding of the enhanced susceptibility to drug abuse in the presence of PTSD.

References

1. Kessler RC, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*. 1995; 52(12):1048–60. [PubMed: 7492257]
2. Pietrzak RH, et al. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Anxiety Disorders*. 2011; 25(3):456–465. [PubMed: 21168991]
3. Goldstein RB, et al. Sex differences in prevalence and comorbidity of alcohol and drug use disorders: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Studies on Alcohol and Drugs*. 2012; 73(6):938–950. [PubMed: 23036212]
4. Seal KH, et al. Substance use disorders in Iraq and Afghanistan veterans in VA healthcare 2001-2010: Implications for screening, diagnosis and treatment. *Drug and Alcohol Dependence*. 2011; 116(1-3):93–101. [PubMed: 21277712]
5. Brown PJ, Stout RL, Mueller T. Substance use disorder and posttraumatic stress disorder comorbidity: Addiction and psychiatric treatment rates. *Psychology of Addictive Behaviors*. 1999; 13(2):115–122.
6. Drapkin ML, et al. Baseline functioning among individuals with posttraumatic stress disorder and alcohol dependence. *Journal of Substance Abuse Treatment*. 2011; 41(2):186–192. [PubMed: 21546205]
7. Read JP, Brown PJ, Kahler CW. Substance use and posttraumatic stress disorders: Symptom interplay and effects on outcome. *Addictive Behaviors*. 2004; 29(8):1665–1672. [PubMed: 15451135]
8. Khantzian EJ. Addiction as a self-regulation disorder and the role of self-medication. *Addiction*. 2013; 108(4):668–669. [PubMed: 23496062]
9. Weiss NH, et al. The relative and unique contributions of emotion dysregulation and impulsivity to posttraumatic stress disorder among substance dependent inpatients. *Drug and Alcohol Dependence*. 2012; 128(1-2):45–51. [PubMed: 22917752]
10. Kilpatrick DG, et al. A 2-year longitudinal analysis of the relationships between violent assault and substance use in women. *Journal of Consulting and Clinical Psychology*. 1997; 65(5):834–847. [PubMed: 9337502]
11. Kaysen D, et al. Incapacitated rape and alcohol use: A prospective analysis. *Addictive Behaviors*. 2006; 31(10):1820–1832. [PubMed: 16446044]
12. Stewart, SH.; Conrod, PJ. Psychosocial models of functional associations between posttraumatic stress disorder and substance use disorder. In: Ouimette, P.; Brown, PJ., editors. *Trauma and Substance Abuse*. American Psychological Association; Washington D.C.: 2003. p. 29-55.
13. Xian H, et al. Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. *Drug and Alcohol Dependence*. 2000; 61(1):95–102. [PubMed: 11064187]
14. McLeod DS, et al. Genetic and Environmental Influences on the Relationship Among Combat Exposure, Posttraumatic Stress Disorder Symptoms, and Alcohol Use. *Journal of Traumatic Stress*. 2001; 14(2):259. [PubMed: 11469155]

15. Sartor CE, et al. Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychological Medicine*. 2011; 41(07):1497–1505. [PubMed: 21054919]
16. Bremner JD, et al. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *The American Journal of Psychiatry*. 1996; 153(3):369–375. [PubMed: 8610824]
17. Chilcoat, HD.; Menard, C. Epidemiological investigations: comorbidity of posttraumatic stress disorder and substance use disorder. In: Ouimette, P.; Brown, PJ., editors. *Trauma and substance abuse*. American Psychological Association; Washington DC: 2003.
18. Brown PJ, Stout RL, Gannon-Rowley J. Substance Use Disorder-PTSD Comorbidity: Patients' Perceptions of Symptom Interplay and Treatment Issues. *Journal of Substance Abuse Treatment*. 1998; 15(5):445–448. [PubMed: 9751003]
19. Leeies M, et al. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. *Depression and Anxiety*. 2010; 27(8):731–736. [PubMed: 20186981]
20. Najavits LM, et al. Rates and symptoms of PTSD among cocaine-dependent patients. *Journal of Studies on Alcohol*. 2003; 65(4):601–606. [PubMed: 14572180]
21. Back SE, et al. Cocaine dependence and PTSD: A pilot study of symptom interplay and treatment preferences. *Addictive Behaviors*. 2006a; 31(2):351–354. [PubMed: 15951125]
22. Hien DA, et al. Do Treatment Improvements in PTSD Severity Affect Substance Use Outcomes? A Secondary Analysis From a Randomized Clinical Trial in NIDA's Clinical Trials Network. *The American Journal of Psychiatry*. 2010; 167(1):95–101. [PubMed: 19917596]
23. Saladin ME, et al. PTSD symptom severity as a predictor of cue-elicited drug craving in victims of violent crime. *Addictive Behaviors*. 2003; 28(9):1611–1629. [PubMed: 14656549]
24. Back SE, et al. Symptom Improvement in Co-Occurring PTSD and Alcohol Dependence. *Journal of Nervous & Mental Disease*. 2006b; 194(9):690–696. [PubMed: 16971821]
25. Burns MN, et al. Do PTSD symptoms and course predict continued substance use for homeless individuals in contingency management for cocaine dependence? *Behaviour Research and Therapy*. 2010; 48(7):588–598. [PubMed: 20363465]
26. Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. *Expert Review of Neurotherapeutics*. 2011; 11(2):275–285. [PubMed: 21306214]
27. Pitman R, et al. Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*. 2012; 13(11):769–787.
28. Kirby LG, Zeeb FD, Winstanley CA. Contributions of serotonin in addiction vulnerability. *Neuropharmacology*. 2011; 61(3):421–432. [PubMed: 21466815]
29. Moeller FG, et al. The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment*. 2001; 21(4):193–198. [PubMed: 11777668]
30. Dalley JW, et al. Nucleus Accumbens D2/3 Receptors Predict Trait Impulsivity and Cocaine Reinforcement. *Science*. 2007; 315(5816):1267–1270. [PubMed: 17332411]
31. Perry J, et al. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology*. 2005; 178(2-3):193–201. [PubMed: 15338104]
32. Perry JL, Nelson SE, Carroll ME. Impulsive choice as a predictor of acquisition of IV cocaine self-administration and reinstatement of cocaine-seeking behavior in male and female rats. *Experimental and Clinical Psychopharmacology*. 2008; 16(2):165–177. [PubMed: 18489020]
33. Oberlin BG, Grahame NJ. High-Alcohol Preferring Mice Are More Impulsive Than Low-Alcohol Preferring Mice as Measured in the Delay Discounting Task. *Alcoholism: Clinical and Experimental Research*. 2009; 33(7):1294–1303.
34. Swick D, et al. Impaired Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury. *Journal of the International Neuropsychological Society*. 2012; 18(05):917–926. [PubMed: 22595028]
35. Falconer E, et al. The neural networks of inhibitory control in posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience*. 2008; 35(5):413–422. [PubMed: 18787658]
36. Solomon ZKYA. Coping with war captivity: the role of sensation seeking. *European Journal of Personality*. 1995; 9(1):57–70.

37. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th., text revision. Washington DC: Author; 2000.
38. Kashdan TB, Elhai JD, Frueh BC. Anhedonia and emotional numbing in combat veterans with PTSD. *Behaviour Research and Therapy*. 2006; 44(3):457–467. [PubMed: 16446151]
39. Elman I, et al. Probing reward function in post-traumatic stress disorder with beautiful facial images. *Psychiatry Research*. 2005; 135(3):179–83. [PubMed: 15993948]
40. Hopper JW, et al. Probing reward function in posttraumatic stress disorder: expectancy and satisfaction with monetary gains and losses. *Journal of Psychiatric Research*. 2008; 42(10):802–7. [PubMed: 18068725]
41. Aharon I, et al. Beautiful Faces Have Variable Reward Value: fMRI and Behavioral Evidence. *Neuron*. 2001; 32(3):537–551. [PubMed: 11709163]
42. Elman I, et al. Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. *Biological Psychiatry*. 2009; 66(12):1083–90. [PubMed: 19640506]
43. Sailer U, et al. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. *Neuropsychologia*. 2008; 46(11):2836–44. [PubMed: 18597797]
44. Jatzko A, et al. Disturbance in the neural circuitry underlying positive emotional processing in post-traumatic stress disorder (PTSD). *European Archives of Psychiatry and Clinical Neuroscience*. 2006; 256(2):112–114. [PubMed: 16143899]
45. Koob GF, Volkow ND. Neurocircuitry of Addiction. *Neuropsychopharmacology*. 2010; 35(1): 217–238.
46. Lanius RA, et al. A review of neuroimaging studies in PTSD: Heterogeneity of response to symptom provocation. *Journal of Psychiatric Research*. 2006; 40(8):709–729. [PubMed: 16214172]
47. Butler R, et al. Physiological Evidence of Exaggerated Startle Response in a Subgroup of Vietnam Veterans With Combat-Related PTSD. *American Journal of Psychiatry*. 1990; 147(10):1308–1312. [PubMed: 2399998]
48. Shalev A, et al. Auditory startle response in trauma survivors with posttraumatic stress disorder: a prospective study. *American Journal of Psychiatry*. 2000; 157(2):255–261. [PubMed: 10671396]
49. D'Andrea W, et al. Heterogeneity of defensive responses after exposure to trauma: Blunted autonomic reactivity in response to startling sounds. *International Journal of Psychophysiology*. 2013; (0)
50. McTeague LM, et al. Aversive Imagery in Posttraumatic Stress Disorder: Trauma Recurrence, Comorbidity, and Physiological Reactivity. *Biological Psychiatry*. 2010; 67(4):346–356. [PubMed: 19875104]
51. Grillon C, et al. Effects of experimental context and explicit threat cues on acoustic startle in vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry*. 1998; 44(10):1027–1036. [PubMed: 9821567]
52. Bremner JD, et al. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. *Archives of General Psychiatry*. 1997; 54(3):246–254. [PubMed: 9075465]
53. Naifeh JA, Tull MT, Gratz KL. Anxiety Sensitivity, Emotional Avoidance, and PTSD Symptom Severity Among Crack/Cocaine Dependent Patients in Residential Treatment. *Cognitive Therapy and Research*. 2012; 36(3):247–257. [PubMed: 22791927]
54. Sinha R, et al. STress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry*. 2006; 63(3):324–331. [PubMed: 16520439]
55. Brown S, et al. Severity of psychosocial stress and outcome of alcoholism treatment. *Journal of Abnormal Psychology*. 1990; 99(4):344–348. [PubMed: 2266207]
56. Hyman S, et al. Stress and Drug-Cue-Induced Craving in Opioid-Dependent Individuals in Naltrexone Treatment. *Experimental and Clinical Psychopharmacology*. 2007; 15(2):134–143. [PubMed: 17469937]

57. Back SE, et al. Reactivity to laboratory stress provocation predicts relapse to cocaine. *Drug and Alcohol Dependence*. 2010; 106(1):21–27. [PubMed: 19726138]
58. Bossert JM, et al. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. *Psychopharmacology*. 2013; 229(3):453–476. [PubMed: 23685858]
59. Mantar A, Yemez B, Alkin T. Anxiety sensitivity and its importance in psychiatric disorders. *Turkish Journal of Psychiatry*. 2011; 22(3):187–193. [PubMed: 21870308]
60. Sippel LM, Marshall AD. Posttraumatic Stress Disorder and Fear of Emotions: The Role of Attentional Control. *Journal of Traumatic Stress*. 2013; 26(3):397–400. [PubMed: 23606358]
61. Fedoroff IC, et al. Cognitive factors in traumatic stress reactions: predicting PTSD symptoms from anxiety sensitivity and beliefs about harmful events. *Behavioural and Cognitive Psychotherapy*. 2000; 28(01):5–15.
62. DeMartini KS, Carey KB. The role of anxiety sensitivity and drinking motives in predicting alcohol use: A critical review. *Clinical Psychology Review*. 2011; 31(1):169–177. [PubMed: 21074306]
63. Lejuez CW, et al. The association between heroin use and anxiety sensitivity among inner-city individuals in residential drug use treatment. *Behaviour Research and Therapy*. 2006; 44(5):667–677. [PubMed: 16002042]
64. Stewart SH, et al. Anxiety sensitivity and self-reported reasons for drug use. *Journal of Substance Abuse*. 1997; 9(0):223–240. [PubMed: 9494951]
65. Siegmund A, Wotjak CT. Toward an Animal Model of Posttraumatic Stress Disorder. *Annals of the New York Academy of Sciences*. 2006; 1071(1):324–334. [PubMed: 16891581]
66. Yehuda R. Post-Traumatic Stress Disorder. *New England Journal of Medicine*. 2002; 346(2):108–114. [PubMed: 11784878]
67. Yamamoto S, et al. Single prolonged stress: toward an animal model of posttraumatic stress disorder. *Depression and Anxiety*. 2009; 26(12):1110–1117. [PubMed: 19918929]
68. Knox D, et al. Single prolonged stress disrupts retention of extinguished fear in rats. *Learning & Memory*. 2012; 19(2):43–49. [PubMed: 22240323]
69. Liberzon I, Krstov M, Young EA. Stress-restress: Effects on ACTH and fast feedback. *Psychoneuroendocrinology*. 1997; 22(6):443–453. [PubMed: 9364622]
70. Handwerker K. Differential Patterns of HPA Activity and Reactivity in Adult Posttraumatic Stress Disorder and Major Depressive Disorder. *Harvard Review of Psychiatry*. 2009; 17(3):184–205. [PubMed: 19499418]
71. Goswami S, et al. Animal models of post-traumatic stress disorder: face validity. *Frontiers in Neuroscience*. 2013; 7
72. Zoladz PR, Fleshner M, Diamond DM. Psychosocial animal model of PTSD produces a long-lasting traumatic memory, an increase in general anxiety and PTSD-like glucocorticoid abnormalities. *Psychoneuroendocrinology*. 2012; 37(9):1531–1545. [PubMed: 22421563]
73. Carnevali L, et al. Social defeat and isolation induce clear signs of a depression-like state, but modest cardiac alterations in wild-type rats. *Physiology & Behavior*. 2012; 106(2):142–150. [PubMed: 22330326]
74. Buwalda L. Long-Lasting Deficient Dexamethasone Suppression of Hypothalamic-Pituitary-Adrenocortical Activation Following Peripheral CRF Challenge in Socially Defeated Rats. *Journal of Neuroendocrinology*. 1999; 11(7):513–520. [PubMed: 10444308]
75. Houlihan DJ. Psychostimulant treatment of combat-related posttraumatic stress disorder. *Journal of Psychopharmacology*. 2011; 25(11):1568–1572. [PubMed: 20935024]
76. Hoexter MQ, et al. Higher striatal dopamine transporter density in PTSD: an in vivo SPECT study with [99mTc]TRODAT-1. *Psychopharmacology*. 2012; 224(2):337–345. [PubMed: 22700036]
77. Volkow ND, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature*. 1997; 386(6627):830–833. [PubMed: 9126741]
78. Volkow ND, et al. Prediction of Reinforcing Responses to Psychostimulants in Humans by Brain Dopamine D2 Receptor Levels. *The American Journal of Psychiatry*. 1999; 156(9):1440–1443. [PubMed: 10484959]

79. Morgan D, et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. *Nature Neuroscience*. 2002; 5(2):169–174.
80. Wang G, et al. Decreased dopamine activity predicts relapse in methamphetamine abusers. *Molecular Psychiatry*. 2012; 17(9):918–925. [PubMed: 21747399]
81. Volkow N, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry*. 2001; 158(12):2015–2021. [PubMed: 11729018]
82. Volkow ND, et al. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse*. 1993; 14(2):169–177. [PubMed: 8101394]
83. Monterosso JR, et al. Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug and Alcohol Dependence*. 2005; 79(2):273–277. [PubMed: 15967595]
84. Colzato L, van den Wildenberg W, Hommel B. Impaired inhibitory control in recreational cocaine users. *PLoS One*. 2007; 7(2):e1143. [PubMed: 17989775]
85. Ghahremani DG, et al. Striatal Dopamine D2/D3 Receptors Mediate Response Inhibition and Related Activity in Frontostriatal Neural Circuitry in Humans. *The Journal of Neuroscience*. 2012; 32(21):7316–7324. [PubMed: 22623677]
86. Kohn M, et al. Risk-Taking Behavior: Dopamine D2/D3 Receptors, Feedback, and Frontolimbic Activity. *Cerebral Cortex*. 2013
87. Ahmed SH, et al. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. *Nat Neurosci*. 2002; 5(7):625–626. [PubMed: 12055635]
88. Kenny PJ, et al. Conditioned Withdrawal Drives Heroin Consumption and Decreases Reward Sensitivity. *The Journal of Neuroscience*. 2006; 26(22):5894–5900. [PubMed: 16738231]
89. Luo FF, Han F, Shi YX. Changes in 5-HT1A receptor in the dorsal raphe nucleus in a rat model of post-traumatic stress disorder. *Molecular Medicine Reports*. 2011; 4(5):843–847. [PubMed: 21720713]
90. Harvey BH, et al. Endocrine, cognitive and hippocampal/cortical 5HT1A/2A receptor changes evoked by a time-dependent sensitisation (TDS) stress model in rats. *Brain Research*. 2003; 983(1-2):97–107. [PubMed: 12914970]
91. Harada K, Yamaji T, Matsuoka N. Activation of the serotonin 5-HT2C receptor is involved in the enhanced anxiety in rats after single-prolonged stress. *Pharmacology Biochemistry and Behavior*. 2008; 89(1):11–16.
92. Kennett GA, et al. Effect of chronic administration of selective 5-hydroxytryptamine and noradrenaline uptake inhibitors on a putative index of 5-HT2C2B receptor function. *Neuropharmacology*. 1994; 33(12):1581–1588. [PubMed: 7760981]
93. Jacobsen LK, Southwick SM, Kosten TR. Substance Use Disorders in Patients With Posttraumatic Stress Disorder: A Review of the Literature. *American Journal of Psychiatry*. 2001; 158(8):1184–1190. [PubMed: 11481147]
94. George SA, et al. Altered locus coeruleus–norepinephrine function following single prolonged stress. *European Journal of Neuroscience*. 2013; 37(6):901–909. [PubMed: 23279008]
95. Geraciotti TD Jr, et al. Effects of trauma-related audiovisual stimulation on cerebrospinal fluid norepinephrine and corticotropin-releasing hormone concentrations in post-traumatic stress disorder. *Psychoneuroendocrinology*. 2008; 33(4):416–424. [PubMed: 18295412]
96. Geraciotti TD Jr, et al. Effect of traumatic imagery on cerebrospinal fluid dopamine and serotonin metabolites in posttraumatic stress disorder. *Journal of Psychiatric Research*. 2013; 47(7):995–998. [PubMed: 23540599]
97. Craige, C.; Enman, N.; Unterwald, E. The Effects of Drug Abuse on the Human Nervous System. Neuroscience-Net, LLC; 2013. Stress, anxiety, and cocaine abuse.
98. Baker DG, et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. 1999; 156(4):585–588.
99. Bremner J, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *American Journal of Psychiatry*. 1997; 154(5):624–629. [PubMed: 9137116]
100. de Kloet, CS., et al. Progress in Brain Research. Elsevier; 2008. Elevated plasma corticotrophin-releasing hormone levels in veterans with posttraumatic stress disorder; p. 287–291.

101. Wang HT, Han F, Shi YX. Activity of the 5-HT1A receptor is involved in the alteration of glucocorticoid receptor in hippocampus and corticotropin-releasing factor in hypothalamus in SPS rats. *International Journal of Molecular Medicine*. 2009; 24(2):227–231. [PubMed: 19578795]
102. Koob G, Zorrilla E. Neurobiological mechanisms of addiction: focus on corticotropin-releasing factor. *Current Opinion in Investigational Drugs*. 2010; 11(1):63–71. [PubMed: 20047160]
103. Bruijnzeel AW, Prado M, Isaac S. Corticotropin-Releasing Factor-1 Receptor Activation Mediates Nicotine Withdrawal-Induced Deficit in Brain Reward Function and Stress-Induced Relapse. *Biological Psychiatry*. 2009; 66(2):110–117. [PubMed: 19217073]
104. Erb S, Shaham Y, Stewart J. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. *J Neurosci*. 1998; 18:5529–36. [PubMed: 9651233]
105. Erb S, Stewart J. A role for the bed nucleus of the stria terminalis, but not the amygdala, in the effects of corticotropin-releasing factor on stress-induced reinstatement of cocaine seeking. *J Neurosci*. 1999; 19:RC35. [PubMed: 10516337]
106. Lu L, Liu D, Ceng X. Corticotropin-releasing factor receptor type 1 mediates stress-induced relapse to cocaine-conditioned place preference in rats. *Eur J Pharmacol*. 2001; 415:203–8. [PubMed: 11275000]
107. Shaham Y, et al. CP-154,526, a selective, non-peptide antagonist of the corticotropin-releasing factor1 receptor attenuates stress-induced relapse to drug seeking in cocaine- and heroin-trained rats. *Psychopharmacology (Berl)*. 1998; 137:184–90. [PubMed: 9630005]
108. Marinelli PW, et al. The CRF1 receptor antagonist antalarmin attenuates yohimbine-induced increases in operant alcohol self-administration and reinstatement of alcohol seeking in rats. *Psychopharmacology*. 2007; 195(3):345–355. [PubMed: 17705061]
109. Lê AD, et al. Role of corticotropin-releasing factor in the median raphe nucleus in yohimbine-induced reinstatement of alcohol seeking in rats. *Addiction Biology*. 2013; 18(3):448–451. [PubMed: 21967606]
110. Blacktop JM, et al. Augmented Cocaine Seeking in Response to Stress or CRF Delivered into the Ventral Tegmental Area Following Long-Access Self-Administration Is Mediated by CRF Receptor Type 1 But Not CRF Receptor Type 2. *The Journal of Neuroscience*. 2011; 31(31):11396–11403. [PubMed: 21813699]
111. Sah R, Geraciati T. Neuropeptide Y and posttraumatic stress disorder. *Molecular Psychiatry*. 2012; 18(6):646–655. [PubMed: 22801411]
112. Sørensen G, Woldbye DPD. Mice lacking neuropeptide Y show increased sensitivity to cocaine. *Synapse*. 2012; 66(9):840–843. [PubMed: 22544368]
113. Thiele T, et al. Ethanol consumption and resistance are inversely related to neuropeptide Y levels. *Nature*. 1998; 396(6709):366–369. [PubMed: 9845072]
114. Sørensen G, et al. Neuropeptide Y Y5 receptor antagonism causes faster extinction and attenuates reinstatement in cocaine-induced place preference. *Pharmacology Biochemistry and Behavior*. 2013; 105:151–156.
115. Clausen T, Møller M, Woldbye D. Inhibitory effect of neuropeptide Y on morphine withdrawal is accompanied by reduced c-fos expression in specific brain regions. *Journal of Neuroscience Research*. 1998; 64(4):410–417. [PubMed: 11340648]
116. Woldbye DPD, Klemp K, Madsen TM. Neuropeptide Y Attenuates Naloxone-Precipitated Morphine Withdrawal via Y5-like Receptors. *Journal of Pharmacology and Experimental Therapeutics*. 1998; 284(2):633–636. [PubMed: 9454808]
117. Gilpin NW, et al. Neuropeptide Y Opposes Alcohol Effects on Gamma-Aminobutyric Acid Release in Amygdala and Blocks the Transition to Alcohol Dependence. *Biological Psychiatry*. 2011; 69(11):1091–1099. [PubMed: 21459365]
118. Ehlers CL, Somes C, Cloutier D. Are some of the effects of ethanol mediated through NPY? *Psychopharmacology*. 1998; 139(1-2):136–144. [PubMed: 9768551]
119. Ehlers CL, et al. Neuropeptide Y Levels in Ethanol-Naive Alcohol-Preferring and Nonpreferring Rats and in Wistar Rats after Ethanol Exposure. *Alcoholism: Clinical and Experimental Research*. 1998; 22(8):1778–1782.

120. Wahlestedt C, et al. Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. *Proceedings of the National Academy of Sciences*. 1991; 88(6):2078–2082.
121. Sørensen G, et al. Neuropeptide Y infusion into the shell region of the rat nucleus accumbens increases extracellular levels of dopamine. *Neuroreport*. 2009; 20(11):1023–1026. [PubMed: 19579268]
122. Sah R, et al. Low Cerebrospinal Fluid Neuropeptide Y Concentrations in Posttraumatic Stress Disorder. *Biological Psychiatry*. 2009; 66(7):705–707. [PubMed: 19576571]
123. Rasmusson AM, et al. Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biological Psychiatry*. 2000; 47(6):526–539. [PubMed: 10715359]
124. Yehuda R, Brand S, Yang RK. Plasma Neuropeptide Y Concentrations in Combat Exposed Veterans: Relationship to Trauma Exposure, Recovery from PTSD, and Coping. *Biological Psychiatry*. 2006; 59(7):660–663. [PubMed: 16325152]
125. Serova LI, et al. Single intranasal neuropeptide Y infusion attenuates development of PTSD-like symptoms to traumatic stress in rats. *Neuroscience*. 2013; 236(0):298–312. [PubMed: 23376740]
126. Little KY, et al. Cocaine use increases [3HWIN 35428 binding sites in human striatum. *Brain Research*. 1993; 628(1-2):17–25. [PubMed: 8313144]
127. Mash DC, et al. Dopamine transport function is elevated in cocaine users. *Journal of Neurochemistry*. 2002; 81(2):292–300. [PubMed: 12064476]
128. Nikolaus S, et al. Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders--results from in vivo imaging studies. *Reviews in the neurosciences*. 2010; 21(2):119–139. [PubMed: 20614802]
129. Brady KT, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000; 283(14):1837–1844. [PubMed: 10770145]
130. Geraciotti TD, et al. Concentrations of corticotropin-releasing hormone, norepinephrine, MHPG 5-hydroxyindoleacetic acid, and tryptophan in the cerebrospinal fluid of alcoholic patients: serial sampling studies. *Neuroendocrinology*. 1994; 60(6):635–642. [PubMed: 7535389]
131. Greenwald M, Lundahl L, Steinmiller C. Yohimbine increases opioid-seeking behavior in heroin-dependent, buprenorphine-maintained individuals. *Psychopharmacology*. 2013; 225(4):811–824. [PubMed: 23161001]
132. Umhau JC, et al. Pharmacologically induced alcohol craving in treatment seeking alcoholics correlates with alcoholism severity, but is insensitive to acamprosate. *Neuropsychopharmacology*. 2011; 36(6):1178–1186. [PubMed: 21289601]
133. Zhang GF, et al. Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis in Opioid Dependent Subjects: Effects of Acute and Protracted Abstinence. *The American Journal of Drug and Alcohol Abuse*. 2008; 34(6):760–768. [PubMed: 19016181]
134. Shi J, et al. Time-Dependent Neuroendocrine Alterations and Drug Craving during the First Month of Abstinence in Heroin Addicts. *The American Journal of Drug and Alcohol Abuse*. 2009; 35(5):267–272. [PubMed: 19591065]
135. Buffalari DM, et al. Corticotrophin releasing factor (CRF) induced reinstatement of cocaine seeking in male and female rats. *Physiology & Behavior*. 2012; 105(2):209–214. [PubMed: 21889522]

Highlights

- Incidence of comorbid PTSD and SUD
- Causative theories on co-occurring PTSD and SUD
- Pathological similarities in PTSD and SUD
- Neurobiological underpinnings of enhanced incidence of drug abuse in PTSD

Sample of neurobiological observations in PTSD and SUD and relevant rodent models.

Pharmacol Biochem Behav. Author manuscript; available in PMC 2015 February 01.

Human Observations					
Neurotransmitter	Marker or Pharmacological application	Direction/location of change	Behavioral effect	Psychiatric Disorder	Reference
	5HT _{2A} receptor binding affinity	↑prefrontal cortex by re-stress		stress-restress	[90]
	5HT _{2C} receptor	↑amygdala		SPS	[91]
	5HT _{2C} receptor antagonism		↓ anxiety	SPS	[91]
			↓ anxiety	psychostimulant withdrawal	[97]
Norepinephrine	SSRIs		↓ fear, anxiety	SPS	[67]
	Tyrosine hydroxylase	↓ basal, ↑ by re-stress in locus coeruleus		SPS	[94]
		↑ hypothalamus		SPS	[101]
Corticotropin-releasing factor	CRF	↑ amygdala, hypothalamus, frontal cortex		psychostimulant withdrawal	[97]
				psychostimulant withdrawal	[97]
	Tissue CRF	↓ amygdala			
	CRF receptor	↓ amygdala, frontal cortex, nucleus accumbens; ↑ substantia nigra, ventral tegmental area		psychostimulant withdrawal	[97]
	CRF receptor antagonism		↓ anxiety, drug intake, reinstatement of drug-seeking	psychostimulant withdrawal, drug self-administration, conditioned place preference	[102-104, 106, 108, 109]
	CRF administration		↑ reinstatement of drug-seeking	drug self-administration	[105, 110, 135]
	NPY administration		↓ depression, anxiety, startle	SPS	[125]
			↓ withdrawal, alcohol intake	opiate withdrawal, alcohol drinking	[115-117]
Neuropeptide Y	NPY receptor antagonism		↑ extinction, ↓ reinstatement of drug-seeking	conditioned place preference	[114]
	NPY knockout		↑ sensitivity to cocaine reinforcement	drug self-administration, conditioned place preference	[112]

Abbreviations: 5HT, serotonin; DAT, dopamine transporter; DA, dopamine; CRF, corticotropin-releasing factor; CRH, corticotropin-releasing hormone; CSF, cerebral spinal fluid; NE, norepinephrine; NPY, neuropeptide Y; PTSD, Posttraumatic stress disorder; SPS, single-prolonged stress; SSRI, selective serotonin reuptake inhibitor; SUD, substance use disorders