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Substance Use Modulates Stress Reactivity: Behavioral and Physiological Outcomes

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Abstract

Drug addiction is a major public health concern in the United States costing taxpayers billions in health care costs, lost productivity and law enforcement. However, the availability of effective treatment options remains limited. The development of novel therapeutics will not be possible without a better understanding of the addicted brain. Studies in both clinical and preclinical models indicate that chronic drug use leads to alterations in the body and brain's response to stress. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may shed light on the ability of stress to increase vulnerability to relapse. Further, within both the HPA axis and limbic brain regions, corticotropin-releasing factor (CRF) is critically involved in the brain's response to stress. Alterations in both central and peripheral CRF activity seen following chronic drug use provide a mechanism by which substance use can alter stress reactivity, thus mediating addictive phenotypes. While many reviews have focused on how stress alters drug-mediated changes in physiology and behavior, the goal of this review is to focus on how substance use alters responses to stress.

Keywords

Substance Use; Addiction; Stress; CRF; HPA axis

Recreational drug use has existed in nearly every society throughout history. However, this recreational use can spiral into addiction for a subset of vulnerable individuals. One of the factors mitigating this vulnerability is stress. Clinical research demonstrates that chronic stress is a risk factor in the development of addiction [1, 2], and as many as 70% of addicts have experienced trauma within their lifetime [3]. Furthermore, life stress is a critical factor mediating treatment outcomes and relapse rates [4–6]. In light of this, treatments aimed at reducing stress could increase addiction treatment success [7].

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To promote the identification of therapies to reduce stress in addicts, we must first determine the neurobiological mechanisms underlying the interactions between drugs of abuse and stress. Many studies have examined the ability of stress exposure to potentiate addictive phenotypes [8–11]. However, it is just as important to examine how addicts respond to stress and how drugs of abuse can alter stress responsivity. This review will focus on how chronic drug administration in both preclinical and clinical models can lead to alterations in behavioral and physiological responses to stress. Furthermore, we will discuss the neurobiological alterations underlying the ability of chronic drug use to affect responses to stress and the implications of these alterations in designing new treatment options.

Stress-related Psychiatric Disorders and Substance Abuse Comorbidity

Preclinical research has clearly demonstrated that drugs and stressful stimuli exhibit cross-sensitization, whereby experience with drugs leads to an enhanced response to stress and vice versa [12–15]. This cross-sensitization between drugs and stress is likely mediated by the overlap in neural circuitry. Both preclinical and clinical studies have demonstrated that acute stress and drug exposure lead to the activation of similar brain regions [5, 16, 17].

As there is such a clear relationship between the neurobiological circuits underlying stress and addiction, it is not surprising that there is a high comorbidity between substance use disorders (SUD) and post-traumatic stress disorder (PTSD). While overall estimates of SUD prevalence are 3–7% nationally [18], within individuals with PTSD, the lifetime prevalence increases to 19–35% for SUD and 36–52% for alcohol use disorder (AUD) [19–21]. Likewise, PTSD is more common in individuals with SUD, with an estimated lifetime PTSD prevalence of 26–52% (compared to 8% in the total population) [3, 22, 23].

Individuals with both PTSD and SUD have more severe symptomology and exhibit poorer treatment outcomes than those with PTSD or SUD alone [24, 25], suggesting a magnifying effect of substance use on stress responsivity. Poorer treatment outcomes for these disorders, are compounded by additional physical and psychiatric health problems, including higher incidence of depression and anxiety disorders [22, 25–27], as well as cardiovascular and neurological problems [28]. Furthermore, these individuals are more likely to be unemployed and are more prone to violence [24, 29, 30]. Taken together, this suggests that gaining a better understanding of the neurobiological mechanisms underlying this relationship could help reveal unique treatment options for this population.

While much research has focused on patients with PTSD using alcohol and drugs to “self-medicate”, there is evidence that SUD can predate PTSD. Individuals with SUD have a heightened likelihood of trauma exposure, which in turn, leads to a heightened risk of PTSD [31, 32]. Furthermore, SUD, as well as nicotine dependence, can increase PTSD vulnerability after trauma exposure [26, 33, 34]. Regardless of the temporal order of SUD and PTSD, it is clear that SUD can sustain, prolong, or worsen PTSD symptoms [35].

For example, within a population of PTSD patients, those with lifetime substance use, specifically cocaine and marijuana use, exhibited significantly higher PTSD symptomology than those without drug use [36]. Furthermore, PTSD patients that smoke exhibit more

severe withdrawal from nicotine and this withdrawal leads to exacerbated PTSD symptomology [37, 38]. Additionally, PTSD patients that successfully quit smoking exhibit improved negative affect compared to those who are unsuccessful [39]. Moreover, alcohol withdrawal and craving can increase response to trauma cues in alcoholics with comorbid PTSD [40]. Consistent with this, a study of individuals with comorbid SUD and PTSD reported intensified trauma symptoms following relapse [41].

Although the effects of drugs of abuse on stress reactivity may be most prominently seen in individuals with PTSD, they are not the only individuals affected. Drug abuse is often comorbid with other stress-related psychiatric disorders. For example, approximately 20% of individuals with mood disorders and 15% with anxiety disorders report at least one concurrent SUD. Major depression is strongly associated with SUD as individuals with major depression are 7 times more likely to exhibit drug abuse or dependence [42]. When examining lifetime SUD prevalence, 50% of individuals with generalized anxiety disorder (GAD) report problems with substance abuse. The rates of SUD increase individuals with concurrent anxiety disorders, as 46% of individuals with concurrent panic disorder, social phobia, and generalized anxiety disorders report comorbid SUD [43]. As with PTSD, substance use can exacerbate symptoms of anxiety and initiate additional anxiety disorders [44].

Chronic drug use leads to an increased response to stress, even in individuals who do not exhibit comorbid psychiatric conditions. Unfortunately, clinical studies are limited by extreme environmental and genetic variability, which can obscure the data and misinform scientific interpretations. Therefore, this review will focus on the way individuals with SUD respond to stress by further examining how preclinical studies have informed us on potential neurobiological mechanisms underlying the interaction between chronic drug use and stress responsivity.

Corticotropin-Releasing Factor: HPA Axis & Beyond

The high rates of comorbidity between substance abuse and stress-related psychiatric disorders may be mediated by the ability of drugs and stress to activate similar neural circuits. Consistent with this, animal models have demonstrated that both stress and drug exposure lead to an increase in mesolimbic dopamine transmission [45–48]. Though an increase in dopamine transmission may explain how stress can augment the effects of abused substances, it does not explain how drug use affects stress reactivity.

A key system mediating the body’s response to stressful stimuli is the hypothalamic-pituitary-adrenal (HPA) axis (see Fig. 1). In response to stress, there is an increased production of corticotropin releasing factor (CRF) in the hypothalamic paraventricular nucleus (PVN). CRF is a 41 amino acid polypeptide that controls behavioral, hormonal, and sympathetic responses to stress [49, 50] and its release onto the anterior pituitary gland induces the release of adrenocorticotropic hormone (ACTH) and subsequently the release of glucocorticoids from the adrenal cortex [51].

CRF serves as the primary mediator in the HPA response to stress in addition to its independent roles in brain stress systems [52–55]. It binds to two types of G-protein coupled receptors, CRF receptor type 1 (CRFR1) and CRF receptor type 2 (CRFR2), with high and moderate potency respectively [56, 57]. CRF activates the HPA axis stress response via its actions at CRFR1 in the anterior pituitary but CRF receptors are widely distributed throughout the brain with particularly high concentrations in the cell bodies of the paraventricular nucleus of the hypothalamus, the basal forebrain and the brainstem [58]. While CRFR1 is widely expressed throughout the brain, distribution of CRFR2 is more restricted, with the highest density in the olfactory bulb, lateral septum, bed nucleus of the stria terminalis (BNST), ventral hippocampus, and the amygdala [59].

One clear mechanism by which chronic drug use can alter stress response is via actions on CRF signaling. Acute administration of cocaine, morphine, nicotine, cannabinoids and alcohol lead to increases in CRF release, mRNA, and/or immunoreactivity [60–65]. While transient increases are seen following acute drug administration, chronic drug administration leads to sustained increases in CRF release [66, 67] and CRF immunoreactivity [68]. Furthermore, withdrawal from drugs of abuse leads to persistent activation of CRF release and immunoreactivity [68–73]. Further, CRF antagonists block many withdrawal-mediated anxiety-like and addictive behaviors [74]. As CRF administration enhances stress related behaviors such as acoustic startle, conditioned fear and stress-induced freezing behavior [75, 76], the increase in activation of stress systems following chronic drug use provides a mechanism by which addiction leads to a dysregulation of stress responding in addicts.

This dysregulation of CRF activity impacts a number of downstream targets. For example, chronic cocaine leads to an increase in excitatory signaling within the bed nucleus of the stria terminalis and this increase is dependent upon CRF activation [77]. Another downstream target of CRF that has been implicated in addiction is dynorphin and the kappa opioid system [78]. The kappa opioid system has been demonstrated to be critically involved in the ability of stress to initiate drug relapse as well as withdrawal-induced increases in stress responsivity [79–83].

Clinical Studies of Substance Use and Stress Responsivity

The high rates of comorbidity in SUD and PTSD diagnoses clearly suggest that there is a relationship between substance use and stress. As we have discussed, much of the work examining this relationship has focused on the influence of chronic stress and trauma exposure on the likelihood of an individual becoming an addict [35, 84]. However, the relationship between stress and addiction does not end there. Along with increasing the vulnerability to developing SUD, stress exposure also triggers relapse in abstaining addicts [85]. Furthermore, abstinence from drugs of abuse can lead to increased anxiety [86], making addicts even more vulnerable to the effects of stress. Therefore, understanding how addicts respond to stress, and how this differs from non-addicts, could provide us with valuable information for the development of therapeutics for SUD as well as comorbid PTSD.

The link between stress and relapse may be due, in part, to the ability of stress to activate the HPA axis. Baseline activity of the HPA axis, specifically levels of plasma adrenocorticotropic hormone (ACTH) and cortisol, is increased in individuals with SUD compared to healthy controls [87–89]. When presented with stressful stimuli, heroin addicts exhibit higher levels of cortisol (both saliva and serum levels) as well as ACTH [90]. These increases in stress-induced cortisol seem to persist after longer periods of abstinence [91]. Furthermore, acute administration of the stress hormone, cortisol, leads to increased cocaine craving in addicted individuals compared to a placebo injection [92].

Activation of the HPA axis is often accompanied by noradrenergic activation of the sympathetic nervous system, including increases in heart rate and blood pressure. Heroin and cocaine addicts both exhibit an increase in plasma levels of norepinephrine that parallels their duration of use [93]. A similar increase in plasma norepinephrine is seen in recently abstinent alcoholics compared to healthy controls in response to a yohimbine challenge [94] (which increases norepinephrine release by blocking alpha-2 adrenergic receptors [95]). As expected, these changes in noradrenergic signaling are paralleled by changes in cardiovascular measures of stress reactivity. When exposed to stress, male cocaine addicts exhibit greater increase in heart rate and blood pressure compared to controls [96]. Even further, increases in noradrenergic signaling, induced by a yohimbine challenge lead to increased craving in alcoholics [97].

Along with these physiological differences in the response to stress, there appear to also be behavioral differences in the stress reactivity of individuals with SUD. For example, when presented with fearful faces, heroin addicts report higher levels of anxiety compared to healthy controls [90]. Additionally, when given a yohimbine challenge, heroin addicts reported higher levels of subjective anxiety than healthy controls [98]. The severity of drug use may contribute to an addict’s response to stress. When high frequency cocaine abusers are presented with stressful stimuli they exhibit higher levels of craving and anxiety than low frequency abusers. Additionally, the high frequency abusers exhibit higher increases in heart rate and blood pressure in response to these stressful stimuli [99].

In contrast to what is seen with other abusive substances, smokers exhibit a blunted cardiovascular and decreased salivary cortisol levels in response to stress [100]. However, this decrease in stress reactivity may reverse during withdrawal, with former smokers exhibiting higher responses to stress than healthy controls [101, 102].

This brings up the important consideration of withdrawal state when examining the clinical literature. During acute withdrawal, addicts exhibit an increase in anxiety [103, 104]. Accompanying this behavioral response is an increase in CRF and this dysregulation can persist after longer periods of abstinence [105–108]. For example, during acute withdrawal, heroin addicts exhibit an increased stress-potentiated acoustic startle response, accompanied by an increase in circulating cortisol [109]. Similar increases in acoustic startle have been seen in alcoholics during acute withdrawal [110]. However, after more prolonged periods of abstinence, cocaine addicts exhibit decreased acoustic startle compared with healthy controls, suggesting a dampened stress response [111]. Additionally, stimulant dependent individuals exhibit decreased cortisol response to a stressful situation, as do alcoholics after

longer periods of abstinence [94, 112, 113]. However, when marijuana dependence is added to the equation, the results are quite different. In a sample of treatment seeking individuals dependent upon cocaine and alcohol, those who were also marijuana dependent showed an increase in basal anxiety as well as stress-induced cortisol and ACTH compared to those who were not marijuana dependent as well as healthy controls [114]. Despite these decreases in peripheral markers of stress reactivity seen in alcoholics, post mortem microarray analysis of their brains reveal an upregulation of gene expression of genes that have been associated with stress signaling, suggesting that the dampened physiological response to stress may not reflect a decrease in the activity of brain stress systems [115].

As these studies were done in postmortem tissue, it is not possible to examine how substance use affects the ability of acute stress to activate stress-related genes in humans. Therefore, we must look to preclinical studies to determine how chronic drug administration affects the brain's response to stress. A focus of many of these animal studies has been the role of CRF in addiction and the response to stress after drug administration.

Preclinical studies of drug administration and stress responsivity

Preclinical studies in animal models of drug administration and addiction allow us to more directly examine how drugs of abuse modulate stress response, both behaviorally and physiologically. Furthermore, clinical studies do not allow for the examination of causality for a variety of reasons. As we know, chronic early life stress can predispose individuals towards addiction and chronic stress can alter future responses to stress, making it difficult to determine how drug administration affects stress response in human addicts. Additionally, many drug addicts are also alcoholics or polydrug users, making it difficult to determine which drugs of abuse might be causing the differences in stress responsivity. Therefore, focusing on the HPA axis and brain CRF systems, we will discuss how individual drugs of abuse alter stress responses in animal models.

Stimulants

Effect on HPA axis—Acute stimulant administration activates the HPA axis, leading to increases in corticosterone (CORT) and ACTH [116, 117]. Furthermore, chronic stimulant exposure can lead to increased basal HPA activity as seen with the increased basal CORT and ACTH levels following binge cocaine administration [117, 118]. Stimulant administration also leads to an increase in the ability of stress to elicit HPA activation. For example, repeated experimenter-administered amphetamine administration led to augmented CORT and ACTH release following a restraint stress [119]. Similar increases in restraint-induced CORT are seen following cocaine self-administration [120]. Binge cocaine exposure during adolescence leads to exaggerated CORT responses to the elevated plus maze and forced swim stress [121, 122]. Although stimulants do not cause a typical withdrawal syndrome, there are changes in the HPA axis that occur during stimulant withdrawal. For example, animals exhibit decreased ACTH and CORT responses to amphetamine challenge when withdrawn 28 days from chronic amphetamine [123]. However, there appears to be an enhanced ability for stress to activate the system during withdrawal, as evidenced by

increases in restraint-induced CORT following acute withdrawal from chronic cocaine administration [124].

Behavioral alterations—These alterations in HPA response to stress seen following stimulant administration are accompanied by alterations in behavioral stress reactivity. For example, acute cocaine administration leads to an increase in acoustic startle response in rhesus monkeys [125]. It is difficult to examine stress responsivity following stimulant administration because many behavioral paradigms are confounded by stimulant-induced increases in locomotor activity [126]. However, there is evidence from a runway model that acute cocaine administration induces anxiety-like behavior [127]. The majority of work examining anxiety-like behavior and stress responses following stimulant exposure has focused on the withdrawal period. Withdrawal from chronic cocaine leads to enhanced responsivity to forced swim stress and increased anxiety-like behavior within the elevated plus maze and defensive burying test [128–130]. This enhanced responsivity to stress may last well beyond the initial withdrawal period, as rats exhibit an increase in immobility in the forced swim test after 12 days of withdrawal from repeated cocaine administration [131].

Neurobiological underpinnings—The increases in anxiety seen during stimulant administration and withdrawal from stimulants are likely influenced by alterations in CRF signaling. Acute cocaine stimulates hypothalamic CRF release [132]. Furthermore, the ability of acute cocaine to increase anxiety-like behavior is attenuated by administration of CRF antagonists in the ventral tegmental area [133]. However, this increase in release undergoes habituation with chronic cocaine administration. During a prolonged cocaine self-administration session, CRF release decreases by ~25% in central amygdala [70]. However, this decrease is reversed during withdrawal, when there is an increase in both CRF release and immunoreactivity [70, 134]. Furthermore, levels of CRFR1 are increased in the anterior pituitary following two weeks of withdrawal from binge cocaine administration [117].

Additionally, there is evidence that this augmentation of CRF signaling following chronic stimulant use has functional consequences. For example, chronic cocaine administration leads to an increase in the ability of CRF to potentiate glutamate release and excitatory transmission within ventral tegmental area dopamine neurons [135, 136], thus demonstrating a mechanism by which stress may promote drug seeking. Additionally, chronic cocaine leads to a CRF-mediated increase in synaptic strength in the amygdala [137, 138], providing a mechanism by which cocaine could alter anxiety and stress reactivity. In fact, mice with a CRF receptor type 2 (CRFR2) deficiency do not exhibit stress-induced memory deficits seen during cocaine withdrawal, suggesting that downregulating the CRF system could decrease cocaine-induced increases in stress responsivity [139].

Opiates

Effect on HPA axis—Heroin and other opiate agonists have a complex interaction with the HPA axis, as acute exposure in naïve animals results in elevated levels of CORT and ACTH, while animals that have received chronic administration and withdrawal show decreased CORT and ACTH in response to a heroin challenge [140, 141]. This may be due, in part, to the increases in basal ACTH and CORT seen following chronic opiate

administration and acute withdrawal [140, 142]. These increases in CORT have been seen as early as two hours after cessation of chronic opiate administration, but seem to disappear after long periods of abstinence [143]. Along with these alterations in basal and drug-induced HPA responses, opiates also affect the HPA response to stress. Chronic morphine increases the ACTH and CORT response to a mild novelty stress in juveniles [144]. During acute withdrawal (12hr), animals exhibit a heightened CORT and ACTH response to restraint stress [142].

Behavioral alterations—These alterations in the physiological responses to stress are paralleled by behavioral alterations following opiate administration. Despite the ability of acute opiates to activate the HPA axis, acute opiate administration can lead to decreased anxiety-like behavior in the elevated plus maze following restraint stress as well as decreased fear potentiated startle responses [145–147]. In contrast, chronic morphine leads to increased response to forced swim stress and tail suspension stress during both short (24hr) and long (1 week) withdrawal periods [143, 148]. These increases in stress responsivity seem to persist through even more prolonged periods of withdrawal as animals show augmented responses to tail suspension and forced swim stress after 4 weeks of withdrawal [143, 149].

Neurobiological underpinnings—These behavioral and physiological responses to opiates are accompanied by regionally specific alterations in brain stress systems. Within the hypothalamus, acute morphine triggers the release of CRF [141, 150, 151]. However, this release is attenuated in animals that have received chronic morphine [141]. Within the BNST, chronic morphine leads to a decrease in transport of CRF to the cell membrane, suggesting decreased CRF release [152]. However, this potential decrease in synaptic CRF may be countered by an engagement of more individual neurons, as chronic morphine increases activation of CRF+ cells with the BNST [153]. Within the central nucleus of the amygdala, chronic morphine upregulates CRF mRNA and increases the ability of morphine to activate CRF+ cells [153, 154]. Within the dorsal raphe the morphine-induced alterations in the CRF system occur at the receptor level. After chronic morphine exposure there is a decrease in CRFR1 mRNA within the dorsal raphe during both acute (3hr) and prolonged (7d) withdrawal [155]. In contrast, increases in CRFR2 mRNA were seen in the raphe during prolonged withdrawal [155]. Taken together, it is clear that opiates alter the CRF system in a profound way but these regional alterations may mediate different aspects of stress responsivity and withdrawal.

Alcohol

Effect on HPA axis—Acute alcohol administration has been clearly shown to activate the HPA axis in both humans and laboratory animals [65, 156]. However, work in laboratory animals has allowed us to determine that this increase in ACTH secretion is mediated through activation of CRF, as inhibiting CRF blocks this effect [65]. Furthermore, chronic alcohol administration has been shown to lead to alterations in the HPA axis. For example, binge-like alcohol administration leads to an increase in basal plasma CORT levels [157]. However, alcohol dependence seen after self-administration leads to a relative dampening in alcohol-evoked CORT and ACTH, suggesting a habituation in these animals [158].

Behavioral alterations—Despite this attenuated HPA response to alcohol following chronic alcohol use, behavioral and physiological responses to stress are sensitized. For example, chronic alcohol exposure leads to a sensitization of the stress response to a forced swim stress [159, 160]. Furthermore, there is a correlation between animals that exhibit higher behavioral reactivity to stress and those that self-administer more alcohol [161]. However, alcohol administration may dampen the response to stress in alcohol dependent animals, as seen in fear potentiated startle paradigms [162]. The anxiogenic effects of alcohol withdrawal may in part, mediate this effect. During withdrawal from ethanol, animals exhibit an increased responsiveness to external stimuli, as shown by an increased acoustic startle response [163]. Animals exhibit other signs of anxiety-like behavior during withdrawal as well, such as decreased open arm exploration in the elevated plus maze and decreased social interaction [164–166].

Neurobiological underpinnings—These increases in anxiety-like behavior may be due to alterations in the CRF system. Alcohol withdrawal leads to an increase in extracellular CRF release within the central amygdala [167–169] and the BNST [170]. This increase in CRF activity within the BNST is normalized by alcohol administration [170], paralleling the behavior on fear potentiated startle [162]. Along with these baseline alterations in signaling seen following alcohol administration, there is also an effect of chronic alcohol on neuronal responses to stress. When exposed to a forced swim stress, animals with a history of chronic alcohol intake exhibit increased neuronal activation, as indicated by increased c-Fos immunoreactivity, within the central nucleus of the amygdala [159]. Double-labeling revealed that this increase in stress-induced activation following chronic alcohol is mediated by CRF-positive cells [159], suggesting that stress engages the CRF system more following chronic alcohol. This is consistent with data demonstrating an increase in CRFR1 mRNA following chronic alcohol use and may be due, in part, to a decrease in basal CRF release [158, 171]. Taken together this would suggest an increased signal to noise in the CRF system that could be the cause of the increased stress reactivity seen in alcoholics. In support of this, neuropeptide Y (NPY) activity is decreased following binge alcohol drinking and NPY activation within the extended amygdala leads to an inhibition of CRF neurons [172].

Nicotine

Effect on HPA axis—Acute nicotine leads to an activation of the HPA axis, as evidenced by a dose-dependent increase in ACTH and CORT [173–175]. Furthermore, nicotine can enhance the ability of stress to activate the HPA axis, leading to a further increase in stress-induced CORT and epinephrine [176]. Chronic nicotine also has the ability to augment stress-induced HPA activation. Following nicotine self-administration, rats exhibit a greater increase in ACTH and CORT following a mild stressor [177, 178]. Additionally, nicotine self-administration augments stress-induced activation of the paraventricular nucleus, a central player in the HPA axis [179].

Behavioral alterations—These nicotine-induced changes in HPA activity are accompanied by changes in behavior. Acute nicotine leads to enhanced anxiety-like behavior in the elevated zero maze, particularly in adult females and adolescent males [73]. However, there is also evidence that nicotine can decrease stress responsivity in the forced swim test

and marble-burying test [180, 181]. Similarly, chronic nicotine can decrease the behavioral response to a forced swim stress as well as stress response to novelty [180, 182, 183]. In contrast, withdrawal from nicotine can also lead to increased anxiety-like behavior as well as enhanced stress responsivity. For example, after 1 day of withdrawal from chronic nicotine, mice exhibit higher levels of anxiety-like behavior in the novelty-induced hypophasia test [184]. Similar effects are also seen in the elevated plus maze and forced swim test, with animals exhibiting augmented responses to these stressors [185–188]. These withdrawal induced increases in anxiety-like behavior and stress responsivity are persistent; animals withdrawn from nicotine exhibit an augmented response to swim stress after 30 days of withdrawal [189].

Neurobiological underpinnings—As seen with other drugs of abuse, the behavioral effects of nicotine on stress may be mediated by changes within the brain CRF system. Chronic nicotine self-administration leads to a basal decrease in the number of CRF positive cells as well as a decrease in CRF mRNA within the paraventricular nucleus [179]. However, withdrawal from nicotine leads to an increase in CRF immunoreactivity and CRF mRNA within the amygdala [72, 74]. This increase in CRF mRNA is also seen within the nucleus accumbens during nicotine withdrawal [73]. Furthermore, CRFR1 antagonists blunt nicotine withdrawal-induced anxiety-like behavior and dysphoria [74, 190]. This suggests that while chronic nicotine may lead to a decrease in HPA activity, brain CRF systems remain sensitized. This sensitization of the CRF system is likely responsible for the changes in stress reactivity and normalizing these differences could provide therapeutic relief [191].

Marijuana

Effect on HPA axis—Systemic injections of delta(9)-tetrahydrocannabinol (THC, the main psychoactive component of marijuana) do not alter HPA activity on its own and subchronic THC seems to decrease HPA activity [192]. This may be due, in part, to peripheral effects, as centrally administered THC (intracerebroventricular injections) leads to a marked increase in plasma ACTH and CORT at multiple doses [193]. Along with these changes in basal HPA activity, it seems clear that higher doses of THC can potentiate the ability of stressors to activate the HPA axis. For example, THC and/or other CB1 agonists can potentiate CORT release in response to forced swim stress [194], restraint stress [195] and footshock stress [196]. Chronic THC has also been shown to potentiate the CORT response to restraint stress [197].

Behavioral alterations—Similar to the dose dependent effects of cannabinoids on HPA activity, the behavioral effects of THC can be both anxiolytic and anxiogenic. There is evidence that low doses of THC and other CB1 receptor agonists can reduce anxiety-like behavior and stress responsivity [198–200], while higher doses of the drug have the opposite effect [201–204]. High doses of a CB1 agonist lead to increased anxiety-like behavior in the elevated plus maze [205]. Additionally, acute administration of a highly potent cannabinoid agonist led to an increased stress response in a defensive burying task [64]. Similarly, systemic injections or direct infusion of THC into the amygdala increases anxiety in the elevated plus maze [203, 206]. Further, acute THC potentiates the behavioral response to forced swim stress and systemic administration of a CB1 agonist also increases the ability of

chronic stress exposure to potentiate anxiety-like behavioral responses [194, 202]. Although there is much less work examining the effects of chronic THC exposure, there is evidence that it too can lead to increased anxiety. For example, chronic cannabinoid administration leads to greater anxiety-like behavior in the open field test and the light-dark test [197, 207].

Neurobiological underpinnings—Just as with other drugs of abuse, both acute and chronic THC leads to alterations in brain CRF systems that may help explain the behavioral effects. Acute administration of the endogenous cannabinoid agonist anandamide leads to increased hypothalamic CRF release [208]. Chronic THC treatment leads to a decrease in CRF mRNA in the central amygdala [205], while increasing CRF mRNA in the hypothalamus [209]. However, during withdrawal from chronic cannabinoid administration, an increase in CRF mRNA and CRF release is seen within the amygdala [71, 205]. These withdrawal-induced changes in the CRF system may explain the increased reactivity to stressors seen after chronic THC use. In support of this, increases in behavioral response to stress seen following cannabinoid agonist administration are blocked by a CRF receptor antagonist [64].

Development of Novel Drug Therapies

The large body of literature suggesting the involvement of the CRF system in addiction has led researchers to examine the possibility of targeting this dysregulated stress system in the development of therapeutics. In support of this, small molecule CRFR1 antagonists can reduce alcohol withdrawal induced increases in anxiety without altering anxiety in non-dependent controls [169, 210–213]. Similarly, anxiogenic withdrawal responses from cocaine, nicotine, cannabinoids, and opiates have been reversed by CRFR1 antagonists [71, 74, 214–218]. This has led to the examination of small molecular CRF antagonists for the treatment of addiction and alcoholism. However, to date, the studies examining these compounds have not yielded promising results. A recent examination of pexacerfont, an orally available and brain-penetrant CRFR1 antagonist, for the treatment of alcoholics found no evidence for therapeutic efficacy. The treatment group failed to exhibit a decrease in craving or subjective distress responses [219]. However, CRFR1 antagonists with different receptor kinetics have yielded promising results for the treatment of depression [220], so it is possible that more drug development is needed to find a compound that will be effective. However, these compounds have been developed to affect brain CRF activity without affecting the HPA axis to aid in their therapeutic safety. Therefore, the sympathetic response to stress remains increased in these alcoholics. It is possible that for a therapy to be effective it must dampen both brain and sympathetic responses to stress.

Interestingly, recent studies suggest that manipulating the HPA axis could be a more effective treatment option. Within a small sample of addicts, Walter et al. [221] found that cortisol administration led to a decrease in craving within low dose heroin addicts while not affecting heavier users. Additionally, clonidine, which decreases noradrenergic activity through presynaptic activation of alpha-2 receptors [222], is currently used in the treatment of opiate withdrawal [223], further supporting an idea that peripheral stress responsivity may be critically involved in addictive behaviors. The use of another antihypertensive drug, prazosin, which decreases noradrenergic activity via inhibition of postsynaptic alpha-1

receptors, may be effective in reducing stress reactivity in alcoholics. Whereas four weeks of placebo treatment caused an increase in stress and cue-elicited alcohol craving and anxiety, this was not seen in individuals treated with prazosin [224]. Further, the blunted cortisol response to stress seen in the placebo group was not seen in the prazosin group suggesting this drug was able to normalize HPA axis activity. As such, a clinical trial is currently underway to test the efficacy of prazosin in patients with comorbid PTSD and SUD (NCT007440055; clinical trials.gov).

It is also possible that the failure of CRFR1 antagonists in clinical trials is because other stress-related neurotransmitters play a more critical role in addictive phenotypes. One such neurotransmitter is substance P, which binds preferentially to the neurokinin 1 receptor (NK1R). A small trial in recently detoxified alcoholics demonstrated that an NK1R antagonist blunted spontaneous craving as well as stress and cue-elicited craving [225]. These decreases in craving were accompanied by a decrease in cortisol, further supporting the idea that therapeutics that also act on the peripheral HPA axis may be more effective.

Conclusion

These studies clearly demonstrate that drugs of abuse and alcohol alter the stress response, behaviorally, neurochemically, and physiologically. These changes may be linked to the CRF system, however clinical trials of CRF antagonists have not been effective. Although preclinical data suggest that dampening the CRF system should decrease craving and relapse, it is clear that there are differences in basal tone that have to be considered as well as stimulus-evoked responses of the system. Furthermore, there seem to be differences between how drugs of abuse affect the central and peripheral CRF systems and any current therapeutics are hitting both of these systems equally. Perhaps most importantly, it is clear that although there are similarities in how different drugs of abuse affect the CRF system, the alterations are not identical. The majority of drug addicts use more than one drug, including alcohol and nicotine and therefore more work into how different drug combinations might affect the system are needed. More research into the interplay between these systems and the development of more targeted therapies is necessary to best treat the alterations in the stress system that occur following drug addiction.

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Highlights

- Drugs of abuse and alcohol alter behavioral & physiological responses to stress
- Drug use leads to altered CRF response to stress
- CRF antagonists have not been effective in treating SUD
- Therapies targeting both central and peripheral stress responses may be more effective

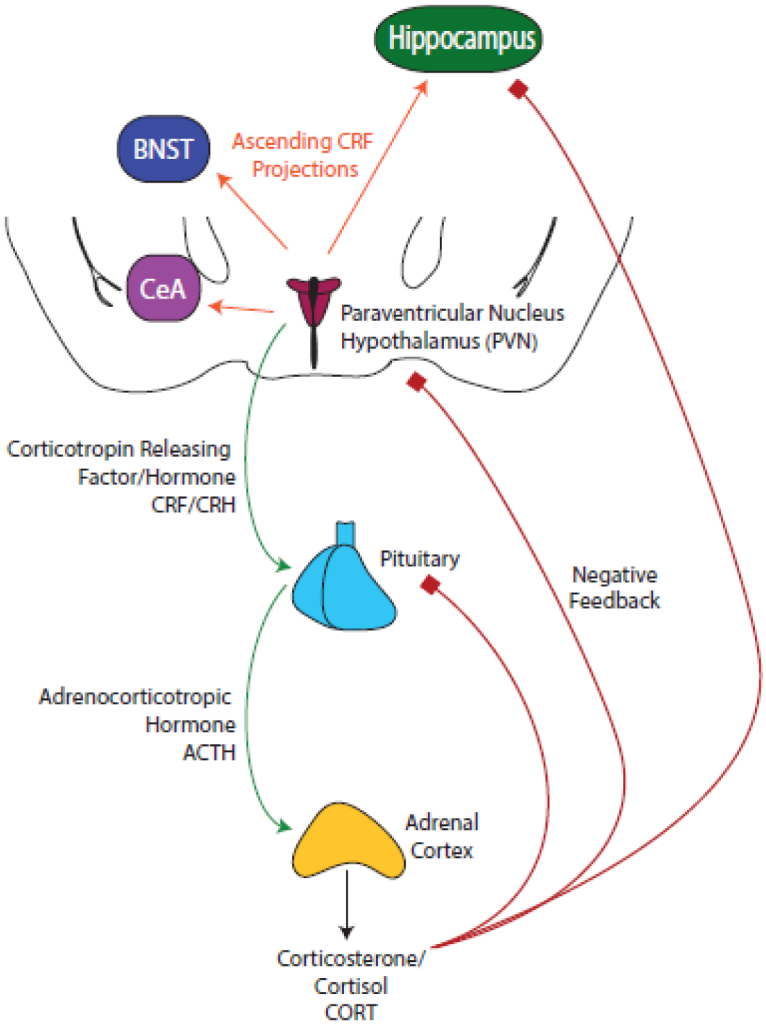

Fig. 1.