Drug-induced stress responses and addiction risk and relapse

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A B S T R A C T

A number of studies have assessed the effects of psychoactive drugs on stress biology, the neuroadaptations resulting from chronic drug use on stress biology, and their effects on addiction risk and relapse. This review mainly covers human research on the acute effects of different drugs of abuse (i.e., nicotine, cannabis, psychostimulants, alcohol, and opioids) on the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). Responses are reviewed in the literature on acute peripheral stress responses in naive or light recreational users and binge/heavy or chronic drug users. We also discuss evidence of alterations in tonic levels, or tolerance, in the latter relative to the former and associated changes in the phasic stress responses. We discuss the impact of the stress system tolerance in heavy users on their response to drug- and stress-related cue responses and craving as compared to control subjects. A summary is provided of the effects of glucocorticoid responses and their adaptations on brain striatal and prefrontal cortices involved in the regulation of drug seeking and relapse risk. Finally, we summarize important considerations, including individual difference factors such as gender, co-occurring drug use, early trauma and adversity and drug use history and variation in methodologies, which may further influence the effects of these drugs on stress biology.

1. Introduction

Substance use disorders (SUDs) incur a significant burden to society in the United States and worldwide. In the United States alone, SUDs are estimated to cost $400 billion across a variety of domains, including crime, poor health outcomes, and lost productivity (US Department of Health and Human Services, 2016). There have been alarming shifts in the clinical presentation where young people are increasingly experiencing more consequences from use as demonstrated by the increases in alcohol-related liver disease (Tapper and Parikh, 2018), opioid use disorder (Martins et al., 2017), and marijuana-related vehicle crashes (Brady and Li, 2014). These trends collectively point to the importance of targeting specific mechanisms that may facilitate the transition from occasional use to chronic, problematic substance abuse.

Early life stress and cumulative adversity, including child maltreatment, are key factors that play a critical role throughout the cycle of addiction, from the development of addictive disorders, to maintenance, relapse, and recovery from SUDs (Enoch, 2011; Le Moal and Koob, 2007; Sinha, 2008, 2001). There has been limited focus on the potent effects of drug use itself on the acute stress response. Although several studies have pointed to an altered setpoint in these systems, less has focused on effects of these adaptations on cue reactivity, drug motivation, and relapse risk. For this reason, we uniquely focus on the effects of acute and chronic drug use on the biological stress pathways and their related effects on stress, reward, craving, and relapse risk. Previous work has investigated the acute effects of different drugs of abuse in animal models of acute and chronic use (Armario, 2010) and translational research on addiction course (Lijffijt et al., 2014). Thus, we focus primarily on human studies and the peripheral stress response and include central reward and motivation pathways when discussing the effects of altered peripheral stress biology on drug motivation and intake. Furthermore, this review covers the most commonly used drugs of nicotine, alcohol, cannabis, psychostimulants (i.e., cocaine and amphetamines), and opioids.

1.1. Relationship between peripheral and central neuroadaptations to drug use

The most frequently studied biological stress responses in relation to SUDs include the two branches of the peripheral autonomic nervous system (ANS), specifically the physiologic responses of the sympathetic and parasympathetic arms, and the neuroendocrine responses of the hypothalamic-pituitary-adrenal (HPA) axis (see Milivojevic and Sinha, 2018 for review of stress biomarkers). For this review, we will focus on specific measures of ANS (i.e., epinephrine/norepinephrine, heart rate variability [HRV]) and HPA axis responses (i.e., adrenocorticotropic...
Fig. 1. The dynamic interplay between peripheral stress response and central stress circuitry. Autonomic and HPA axis arousal (1) occurs in response to stress and drug use. This arousal causes a peripheral feedback (2) into limbic circuits as well as central activation to initiate adaptive emotional, cognitive and behavioral responses to regulate stress, emotion and reward states (3). Sensory regions provide information to the amygdala, hippocampus, and locus coeruleus (LC), which facilitates adaptation to central emotional, cognitive, behavioral responses. AMY = Amygdala, HP = Hippocampus, HYP = Hypothalamus, PFC = Prefrontal Cortex, THAL = Thalamus, VTA = Ventratal Tegmental Area. Templates were used from Servier Medical Art (www.smart.servier.com).

2. Acute and chronic psychoactive drug effects on peripheral stress responses

2.1. Nicotine

2.1.1. Acute effects of nicotine in non- and light smokers

The acute effects of nicotine on the HPA axis in non-smokers or light smokers ("chippers") have not been as well-documented, particularly in human samples, as compared to chronic users. Nevertheless, consistent with evidence in non-dependent animals, nicotine increases corticosterone levels particularly at high levels of nicotine dosing (Acri, 1994; Chen et al., 2008; Donny et al., 2000; Lutfy et al., 2012; Okada et al., 2003). Both nicotine-naive and regular nicotine users show dose-dependent increases in cortisol, ACTH and prolactin have been reported (see Mello, 2010 for review). Studies of the mechanism in animal models suggest that the effect of nicotine on the HPA axis is primarily through the nicotine-induced release of norepinephrine and CRH in the paraventricular nucleus of the hypothalamus (Fu et al., 1997; Matta et al., 1990; Okada et al., 2003). These collective findings indicate nicotine activates the HPA axis via its direct effects on the catecholaminergic and cholinergic stimulation of the ANS.

Regarding the ANS, naïve or light smokers' catecholamine response has been mostly documented in animal models, but several human studies have studied the cardiovascular effects of nicotine in non-smokers. Epinephrine has been reliably shown to increase in a dose-dependent fashion in response to nicotine (Grunberg et al., 1988; Mello, 2010; Morse, 1989; Watts, 1960), particularly under conditions of nicotine self-administration (Donny et al., 2000). Nicotine also increases cardiovascular output in animals (Watts, 1960), a finding that has been replicated in non-smoking humans (Foulds et al., 1997; Perkins et al., 2009). In human models, several studies have demonstrated that nicotine increases cardiovascular activity as measured by increases in low frequency (LF; an index of sympathetic activity), and decreases in high frequency (HF; parasympathetic activity) HRV, both in response to nicotine and when co-administered with a stressor (Karakaya et al., 2007; Sjoberg and Saint, 2011).

2.1.2. Acute effects of nicotine in chronic, heavy smokers

Chronic nicotine administration dysregulates tonic levels of the HPA axis. Chronic smokers show greater basal cortisol levels relative to non-smokers (al’Absi, 2006). In chronic users, acute nicotine administration further increases cortisol and ACTH levels (Chen et al., 2008; Mendelson et al., 2008; Pomerleau and Pomerleau, 1990; Seyler et al., 1984; Wilkins et al., 1982) in a dose-dependent manner (Fill and Wynder, 1974; Mendelson et al., 2005). Animal models show that nicotine elevates corticosterone and ACTH early in use but, although nicotine still induced a rise, this response to nicotine was attenuated after successive administration (Chen et al., 2008); a comparison that has been replicated in a correlation study of humans where chronic users are compared to chippers (Shiffman et al., 1992). Nicotine withdrawal is associated with a higher basal HPA axis tone and blunted response to nicotine at varying lengths of acute abstinence (Cohen et al., 2004; Frederick et al., 1998). Thus, the HPA axis adapts to the stimulating effects of chronic smoking (see al’Absi, 2006 for review) and, during early abstinence, these changes result in an increase of activity that worsens withdrawal.

Heavy smokers also display disruptions in ANS system functioning. Like the HPA axis, acute nicotine administration increases heavy smokers’ epinephrine, norepinephrine, blood pressure, and heart rate (DeVito et al., 2014; Foulds et al., 1997; Hill and Wynder, 1974; Mendelson et al., 2008; Minami et al., 1999; Sofuoglu et al., 2012, 2001; Tsuji et al., 1996; Wilkins et al., 1982). Acute administration of nicotine also increases LF HRV, decreases HF HRV, and increases the ratio of LF/HF HRV (Ashare et al., 2012; Barutcü et al., 2005; Karakaya et al., 2007; Kobayashi et al., 2005; Minami et al., 1999). Cigarette chippers have a more robust blood pressure response to nicotine than was noted in heavy smokers (Shiffman et al., 1992). Sustained abstinence appears to normalize ANS activity as evidenced by decreased epinephrine and norepinephrine levels and reduction in the LF/HF HRV (Minami et al., 1999). Nicotine, therefore, activates the peripheral ANS stress system in both acute response and overall tone that normalizes over sustained abstinence.

2.2. Cannabis

2.2.1. Acute effects of cannabis in light users

Δ1-tetrahydrocannabinol (THC) is the psychoactive component of cannabis. Administration of THC activates corticosterone/cortisol and ACTH in both animal (Kubena et al., 1971; Martín-Calderón et al., 1998; Puder et al., 1982) and human samples (DSouza et al., 2004;
Hollister et al., 1970; Ranganathan et al., 2009). The action of exogenous cannabinoids on the HPA axis is complex, exerting both direct effects (Puder et al., 1982) on both the paraventricular nucleus of the hypothalamus and via other brain areas, including the basolateral amygdala (Armario, 2010). Acute smoked cannabis or oral THC stimulate cardiovascular arousal with increases observed in HR and plasma epinephrine (Hollister et al., 1970) and increases heart rate (Lindgren et al., 1981; Strogou et al., 2008; Zuurman et al., 2010).

2.2.2. Acute effects of cannabis in heavy users

Acute administration of smoked cannabis or oral THC in chronic users has also been shown to stimulate both the ANS and the HPA axis. With regard to the HPA axis, cortisol increases in response to either smoking marijuana or receiving intravenous THC has been reported (Cone et al., 1986; D’Souza et al., 2008; Ranganathan et al., 2009). However, the THC-induced rise in disordered users was blunted when it was compared to the cortisol increase in healthy controls (D’Souza et al., 2008; Ranganathan et al., 2009). Prolonged exposure to THC over the course of two weeks blunted the cortisol rise expected after administration (Benowitz et al., 1976). This previous finding combined with observed higher basal cortisol levels in heavy cannabis users (Cuttler et al., 2017; King et al., 2011) and sustained higher levels even after six months of abstinence (Somaidi et al., 2012) suggest that continued cannabis use is associated with lasting adaptations in the HPA axis. It should be noted that based on these studies, it is unclear if chronic cannabis use alters stress function or vice versa. While some studies have found that THC does not impact epinephrine and norepinephrine concentration (Dumont et al., 2009), THC does induce a marked increase cardiovascular response in chronic users (Dumont et al., 2009; Haney et al., 2016; Lindgren et al., 1981; Ramesh et al., 2013; Vandrey et al., 2013), but this response does not differ between heavy and light cannabis smokers (Haney et al., 2016). Thus, acute exposure to the psychoactive components of cannabis increases HPA axis activity and cardiovascular arousal, but its effects on peripheral catecholamines are not clear and more research is needed. Abrupt cessation of smoking also caused blood pressure to increase dramatically (Vandrey et al., 2011); however, the abstinence-related increases in heart rate are delayed (Haney et al., 2018).

2.3. Stimulants

2.3.1. Acute effects of stimulants in naïve or light users

Cocaine increases corticosterone and cortisol in cocaine-naïve rodents (Borowsky and Kuhn, 1991; Levy et al., 1991; Moldow and Fischman, 1987; Saphier et al., 1993; Sarnyai et al., 1992) and humans (Heesch et al., 1995) in a dose-dependent fashion. Similarly, cocaine also increases ACTH in male rodents (Borowsky and Kuhn, 1991; Kuhn and Francis, 1997; Levy et al., 1991; Moldow and Fischman, 1987), although this was not replicated in the one human study (Heesch et al., 1995). Furthermore, it appears that CRF may play an important role in the mechanism of action of cocaine. One study found that CRF, when peripherally administered, blocks the effects of HPA response (Sarnyai et al., 1992). Gender may be an important moderator as indicated by one study that found female rats had a larger corticosterone response to cocaine than male (Kuhn and Francis, 1997). This finding is particularly important since most cocaine administration studies in naïve populations have focused on male animals and humans. Cocaine also stimulates the ANS as evidenced by increased epinephrine and norepinephrine in an animal sample (Chieu and Kopin, 1978) and increased heart rate in a human sample (Vongpatanasin et al., 2004). In human models, cocaine dramatically increases HR and reduces the activity of the parasympathetic nervous system as evidenced by reduced HF HRV (Vongpatanasin et al., 2004).

Another group of stimulants, amphetamines, has similar impacts on the HPA axis and adrenergic system. Similar to cocaine, amphetamines increase cortisol responding in human (de Wit et al., 2007; dos Santos et al., 2011; Halbreich et al., 1981; Jacobs et al., 1989; Nurnberger et al., 1984; L. M. Oswald et al., 2005; Sachar et al., 1980; Söderpalm et al., 2003; Wand et al., 2007; White et al., 2006) and rodent samples (Knyc and Eisenberg, 1979; Sverdlow et al., 1993). Individuals with a history of using methamphetamine at least six times, but who were not dependent, had increased in cortisol in response to methamphetamine administration (Harris et al., 2006, 2003). CRF and other neurotransmitters mediate the cannabis-induced increase in cortisol (Armario, 2010; Sverdlow et al., 1993). In addition to its actions on the HPA axis, amphetamine also stimulates adrenergic response as evidenced by increased norepinephrine, blood pressure (Nurnberger et al., 1984), blood pressure (Nurnberger et al., 1984), and heart rate (de Wit et al., 2007). Amphetamine acutely activates the ANS of experienced, but not dependent, methamphetamine users as indexed by the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) (Harris et al., 2006).

2.3.2. Acute and chronic effects of stimulants in dependent users

Several studies have demonstrated that cocaine increases corticosterone secretion (see Marinelli and Piazza, 2002 for review). In humans, chronic cocaine users also display higher cortisol and ACTH levels when administered cocaine (see Manetti et al., 2014 for review) and elevated basal levels of cortisol (Haney et al., 2001) that either are unchanged by abstinence (McDougle et al., 1994; Mendelson et al., 1988) or reduced with sustained abstinence from cocaine (Buydens-Branchey et al., 2002). Cocaine administration also increased the adrenergic response including catecholamine levels (Sofuoglu et al., 2001), blood pressure, and heart rate (Ezel, 2001; see Foltin et al., 1995 for review; Kollins and Rush, 2002; Kosten et al., 1996; Lynch et al., 2008, 2006; Reid et al., 2006; Walsh et al., 2009) dose-dependently (Collins et al., 2007; Foltin et al., 2003; Lynch et al., 2006). Some studies have suggested that repeated exposure to cocaine sensitizes the heart rate response to cocaine with most robust responses occurring during laboratory-monitored cocaine binges (Kollins and Rush, 2002; Walsh et al., 2009, 2000). Other studies found that, after an initial rise in the subjective cardiovascular effects, the cardiovascular response flattens suggesting that individuals become tolerant to binge levels (Bitmead and Bitmead, 1984; Foltin et al., 2003; Ward et al., 1997). Reed and colleagues’ (1984) dissection of the HR response by comparing the area-under-the-curve to the overall increases suggested that the increase in the cardiovascular response may be due to the conditioned response of pairing administration with contextual cues. During acute abstinence, the norepinephrine metabolite MHPG is increased as was systolic blood pressure in response to intranasal cocaine (McDougle et al., 1994). Basal cardiovascular levels are elevated in chronic cocaine users (Sharma et al., 2016).

The effects of amphetamines on cortisol levels in chronic users is complicated. Regular 3,4-methylenedioxymethamphetamine (MDMA or “ecstasy”) users had higher hair cortisol levels than light, recent users or non-using controls (Parrott et al., 2014). One study found that amphetamine use while on placebo treatment was associated with a significantly lower cortisol level after administration relative to amphetamine-dependent individuals on naltrexone (Jayaram-Lindströ et al., 2008); however, another study found that methamphetamine-increased cortisol and ACTH in experienced non-dependent users. The effect of amphetamines on basal levels of the HPA axis is not clear-cut. Some studies have found that non-treatment seeking chronic methamphetamine users had lower (Carson et al., 2012) or no differences in basal cortisol levels (Zorick et al., 2011) as compared to controls subjects. The latter correlational study found no differences between individuals with methamphetamine dependence and control subjects after four weeks of abstinence. Methamphetamine-dependent individuals had altered sympathetic tone with increased LF HRV, decreased HF HRV, and higher LF/HF ratio, and greater use positively correlated with the latter (Henry et al., 2012). More research is necessary to understand the effects that amphetamines have in stimulant-dependent individuals fully.
2.4. Alcohol

2.4.1. Acute effects of alcohol in light drinkers/naive individuals

Alcohol acutely stimulates the HPA axis in non-dependent users. In rats, alcohol has been shown to consistently increase plasma corticosterone and ACTH levels (Allen et al., 2011; Richardson et al., 2008). In humans, similar increases in cortisol have been noted in response to acute alcohol administration (Frias et al., 2006; Gianoulakis et al., 1996; Mendelson and Stein, 1966; Välimäki et al., 1984; W.J. et al., 1995). It appears the effects of alcohol on the HPA axis occurs primarily due to alcohol’s actions on the paraventricular nucleus of the hypothalamus (Armanio, 2010). With respect to ANS activation, animal models have demonstrated elevated epinephrine and norepinephrine response to intravenous alcohol administration (Livezey et al., 1987; Perman, 1960) and, similar to the observations with the HPA axis in humans, found that alcohol blunted the expected stress response when the animals were confronted with a stressor. In humans, noradrenaline responses were also elevated and peaked about 30 min after drinking 0.9 g/kg of alcohol and remained high after 4 h (Howes and Reid, 1985). Alcohol consumption also appears to impact cardiovascular indices of increased sympathetic arousal. Acute alcohol administration in moderate to high doses consistently decreases high-frequency HRV and also increases the ratio of low frequency to high-frequency heart rate variability, an index of sympathetic to parasympathetic function (Romanowicz et al., 2011). Collectively, these results are consistent with animal studies and suggest that alcohol acutely increases HPA axis and ANS activity in naive alcohol users and may further blunt the stress response when administered in close temporal proximity to a stressor.

2.4.2. Acute effects of alcohol in binge and alcohol-dependent samples

Persistent binge drinking alters the HPA axis and ANS system via the repeated activation by frequent, heavy alcohol use. Basal cortisol levels are elevated in binge heavy men (Blaine et al., 2018; Thayer et al., 2006) and women (Wemm et al., 2013). Furthermore, the expected rise in cortisol in response to alcohol administration was blunted in heavy relative to light/moderate social drinkers (King et al., 2006). Basal HRV levels appear to significantly lower in heavy drinking males, indicating decreased functioning of the ANS (Thayer et al., 2006). Also, individuals who were heavy drinkers five years prior had a reduced cortisol response to alcohol relative to those who were light drinkers (King et al., 2016).

Alcohol stimulates cortisol levels in both dependent animals (Richardson et al., 2008) and humans (Adinoff et al., 2003; Feller et al., 2014; Mendelson and Stein, 1966; Stokes, 1973). When an individual abstains from alcohol, withdrawal is also associated with increased basal cortisol levels (Mendelson and Stein, 1966) and decreased diurnal variation (Adinoff et al., 1991; Risher-Flowers et al., 1988). Cortisol tone also tends to be increased during periods of heavy drinking (Wand and Dobs, 1991). Although basal cortisol levels decrease during longer abstinence (Motaghipanjad et al., 2015), sustained abstinence is associated with increased basal cortisol levels as compared to healthy controls (Starcke et al., 2013). Activation of the ANS system in alcohol-dependent individuals is also affected by alcohol. Acute intoxication was associated with increases in MHPG (Borg et al., 1981) and, as dependent individuals enter acute withdrawal, levels of MHPG decrease as time since their last drink increase (Hawley et al., 1994). Although not tested directly in response to acute intoxication, adaptive HRV functioning is also directly modified by alcohol dependence. A meta-analysis found that alcohol dependence, regardless of treatment setting, is associated with a decrease in basal HF HRV levels (Quintana et al., 2013). Collectively, the results from these studies point to neuroadaptations in HPA and ANS response with active binge and chronic use such that there is a blunted or lack of a phasic response but elevated tonic levels in binge/disordered users relative to controls.

2.5. Opioids

2.5.1. Acute effects of opioids in non- and light users

Unlike other drugs of abuse, opioids appear to have different effects on stress biology in rodents as compared to humans. In rats, morphine increases ACTH and corticosterone (Buckingham and Cooper, 1986; Eisenberg, 1985; Suemaru et al., 1989) whereas, in humans, morphine dampens the HPA response (Delitala et al., 1983; George et al., 1974; Rittmaster et al., 1985; Zis et al., 1984). Naloxone, an opioid antagonist, increases ACTH and cortisol levels in humans (Grossman et al., 1986; Naber et al., 1981) and pigs (Richard et al., 1986; Rushen et al., 1993). There is evidence that opioids directly impact the HPA axis (Vuong et al., 2010) to suppress HPA axis responses. The impact of opioids on the ANS is complex, with decreasing response of HPA axis to CRF, morphine had limited impact on the epinephrine and norepinephrine response (Rittmaster et al., 1985). Although opioids decrease heart rate and blood pressure (Suemaru et al., 1989), high-frequency HRV has been shown to be decreased by opioids (Latson et al., 1992).

2.5.2. Chronic effects of opioids on stress systems in dependent samples

In human samples, opioids and opioid agonists, including methadone and buprenorphine, acutely suppress cortisol levels (Camí et al., 1992; Mendelson et al., 1975; Nava et al., 2006; Walter et al., 2011, 2008) and basal cortisol levels tend to be higher in opioid-dependent users as compared to healthy controls (Walter et al., 2011). One early study found that cortisol was unchanged by heroin administration (Mendelson et al., 1975) and a more recent study found that diazepam, the pharmaceutical version of heroin prescribed for maintenance therapy, decreased cortisol levels more than methadone (Walter et al., 2011). Withdrawal from opioids corresponds with significant tonic increases in ACTH and cortisol levels regardless of whether it was induced by a naloxone challenge (Gerra et al., 2003) or occurred naturally over time (Shi et al., 2009). Acute administration of intravenous opioids is associated with an initial spike in heart rate that is followed by a delayed reduction in heart rate (Kennedy et al., 2015; Rook et al., 2006). A similar pattern of results was found for withdrawal-related effects on the SAM system. Specifically, epinephrine, norepinephrine, LF HRV, and blood pressure increase in response to naloxone-induced withdrawal (Hoffman et al., 1998; Kienbaum et al., 1998; McDonald et al., 1999).

On the basis of the review presented in the previous sections, Table 1 summarizes the direction of phasic HPA axis and ANS responses.

| Substance   | Acute Drug Response | Binge/Disordered vs. Naive/Non-Disordered* |
|-------------|---------------------|------------------------------------------|
| HPA         | ANS                 | HPA                                      |
| Nicotine    | ↑                   | ↑                                         |
| Cocaine     | ↑                   | ↑                                         |
| Amphetamine | ↓                   | ↑                                         |
| Cannabis    | ↑                   | ↑                                         |
| Alcohol     | ↑                   | ↑                                         |
| Opioids     | ↓                   | ↓                                         |

Note: In autonomic nervous system activity, LF HRV is indicative of an activated sympathetic nervous system response, whereas HF HRV is reflective of parasympathetic response. Here, we focused on activation of the sympathetic nervous system within the autonomic nervous system.

* Acute phasic effects of drugs on the HPA axis and the ANS in non-disordered/lightly using (non-weekly use at very low levels) subjects as compared to actively using binge/disordered users.

† indicates activation; ↓ indicates reduction; ↑ ↓ indicates mixed results; = indicates similar responses; ? indicates areas for future research.
to acute administration of each psychoactive drug of abuse in naïve/non-disordered and adaptations in these responses with binge/heavy and dependent users relative to controls.

3. Drug-related adaptations in stress biology, reward, craving and relapse risk

The previous sections and Table 1 highlights the potent effects of the most common psychoactive drugs on stress biology with acute effects of stimulation for nicotine, cannabis, stimulant, and alcohol, and depressive effects of acute opioids in humans. More importantly, regular, binge and chronic use of drugs alter these stress responses, signaling significant adaptations in stress biology. As substance use escalates in frequency and intensity, adaptations in HPA axis and ANS pathways manifest as changes in basal levels, but also in phasic responses to drug, stress and challenge (see al’Absi, 2006 for review of nicotine; Ashare et al., 2012; see Blaine and Sinha, 2017 for review of alcohol; McKee et al., 2011; McRae-Clark et al., 2011). In turn, withdrawal-related basal increases in cortisol are associated with cognitive impairments (Errico et al., 2002). In turn, these cognitive impairments could perpetuate the worsening of addiction (see Bernardin et al., 2014; Besson and Forget, 2016; Spronk et al., 2013 for discussion).

This cumulative evidence begs the question of whether such adaptations in stress biology are the mere consequences of drug use, or if they also serve as interoceptive drug-related adaptations that may play a role in motivating compulsive drug use and relapse risk in chronic users. There have been decades of focus on mesolimbic striatal dopaminergic pathways as critical for the reinforcing effects of psychoactive drugs. While striatal adaptation may drive compulsive drug motivation, other positron emission tomography (PET) evidence indicates that psychoactive drug-stimulated increases in cortisol is highly correlated with dopamine release in the striatum (Booij et al., 2016; Cox et al., 2009; Wand et al., 2007) and drug-induced cortisol increases are associated with the subjective intoxication in healthy volunteers (Oswald et al., 2005). Similarly, psychological stress provocation in healthy volunteers has also been shown to increase dopamine transmission in the striatum and the PFC (Nagano-Saito et al., 2013; Pruessner et al., 2004), and cortisol responses to psychosocial stressors predict reward after amphetamine administration (Hamidovic et al., 2010). In a functional magnetic resonance imaging (fMRI), a psychological stress provocation results in robust striatal activation, specifically in the ventral striatum but not the dorsal striatum relative to non-stress cues in healthy volunteers (Sinha et al., 2016). Also, activity in the ventromedial prefrontal cortex and the rostral anterior cingulate cortex was predictive of resilient coping and low levels of alcohol use. Consistent with these findings, other fMRI studies have shown blunted stress responses in at-risk individuals is predictive of blunted central brain activity in limbic-striatal and prefrontal regions (Carroll et al., 2017; Ginty, 2013) that are critical for regulating motivated behavior and resilient coping. Other PET research has reported a loss of dopamine transmission and blunted dopamine release in drug-abusing patients is correlated with severity of addiction as well as with increases in compulsive motivation for drug and treatment failure (Martinez et al., 2011; Martinez and Narendran, 2010). Whether these blunted dopamine changes are related to blunted glucocorticoid responses to drug or stress has not been fully investigated. Nonetheless, these data highlight that drug-induced activation of stress and dopaminergic pathways are highly interactive and suggest that both may jointly play a role in psychoactive drug effects, and on compulsive drug motivation.

Findings from several well-controlled laboratory studies in treatment-seeking or non-treatment seeking and acutely abstinent drug-abusing patients have shown a blunted stress cortisol and ANS axis response to stress and drug cue provocations along with higher basal cortisol and HR along with disrupted HRV responses (Table 2; see Sinha, 2008 and Milivojevic and Sinha, 2018 for review). Such responses are predictive of higher relapse risk after treatment and co-occuring with greater drug craving during stress and drug cue provocation (Ashare et al., 2012; McKee et al., 2011; Milivojevic and Sinha, 2018; Sinha, 2011; Sinha et al., 2006). Blunted cortisol arousal to stress cues is also predictive of increased alcohol motivation to drink alcohol in bing, heavy drinkers (Blaine et al., 2018). Thus, these studies consistently link adaptations and changes in peripheral and central stress responses to compulsive drug motivation and relapse risk, thereby suggesting a need to target these pathways as both markers of addiction risk and severity but also in treatment development (Milivojevic and Sinha, 2018).

On the basis of the review presented in previous sections, we present a heuristic model to illustrate the drug-stress motivation cycle in Fig. 2. The findings presented earlier suggest a feed-forward cascade of effects of drugs on stress biology. Our stress biology is wired to help us to adapt to life’s struggles but, in the face of increasing drug use and abuse, this critical biological process is handicapped and blunted. Consequently, heavy and chronic drug users are more vulnerable to negative affect, distress and poor stress coping. Furthermore, with blunted or more “tolerant” stress responses to drug use, greater levels of drug use are needed to maintain abstinence, thereby driving a cycle of increased drug use and stress disruption that further drive greater compulsive drug motivation and relapse risk.

4. Factors affecting drug effects on stress responses

4.1. Effects of drugs on responding to a stressor

We focused specifically on the effect of drugs on the activity of the HPA axis and the SAM system in the previous sections; however, anecdotal evidence from patients and several theories of substance use point to the fact that a stressor often precedes use, thus likely modifying the response to the stressor. In an experimental model of this observation, studies have shown that the simultaneous administration of a drug with a stressor disrupts the normal stress response system (Van Hedger et al., 2017). For example, when alcohol or methamphetamine is administered following a stressor, the drug impairs the cortisol response to psychosocial and pharmacological stressors (Childs et al., 2010; Söderpalm et al., 2003). Alcohol administered immediately after a stressor prolonged the negative affect and increased craving in response to the stressor (Childs et al., 2011). When low doses of THC was administered after a stressor, the subjective distress was also blunted; however, at high doses of THC, negative affect was increased, and blood pressure was blunted (Childs et al., 2017). In a human laboratory model
of smoking relapse, exposure to a stressor increased the rewarding effects of smoking, which was correlated to cortisol (McKee et al., 2011). However, these effects may depend on the type of drug administered. In opioids, cortisol administration was found to reduce craving in patients with low-dose heroin consumption (Walter et al., 2015). This finding is perhaps not surprising given that opioids have a dampening effect on the HPA axis system whereas the other substances of abuse have an activating effect. Further research is necessary to fully understand the interactive impact of a drug and stress on stress system responsivity.

4.2. Drug-related factors influencing stress responses

A host of methodological factors (e.g., frequency and amount of recent drug use, rapidity and amount of acute drug intake, the dose of the drug administered and tested, type of drug within a broad drug class, route of administration) could potentially impact the strength of the drug effects on the stress responses. Notably, Allain et al. (2015) discuss the role of frequency of drug use and rapidity of use during bouts as significant aspects of compulsive drug seeking and addiction risk. Self-motivational aspects of how often drug is used and the use topography may influence both subjective drug effects, drug-related stress responses, and drug motivation for continued drug use.

In other research, King and colleagues found that high dose alcohol (0.8 g/kg) increased cortisol levels in light drinkers whereas a low dose of alcohol (0.4 g/kg) did not and that heavy binge drinkers showed blunted cortisol responses (King et al., 2006). On the other hand, Blaine et al. (2018) showed low levels of alcoholic beer consumed under a behavioral motivation paradigm increased cortisol in both moderate non-binge and binge-heavy users. The articles reviewed here use a variety of administration methods, including intravenous, intranasal, oral, and self-administration. Each route has differences in the rate of absorption which would have different impacts on the reactivity of the stress systems (Gourlay and Benowitz, 1997). Another important methodological consideration is the impact of recent drug use history on the acute drug responses. For example, Ramchandani et al. (2002) found that increased drinking in the past month before participating in the study predicted the acute subjective and psychomotor response after an intravenous alcohol administration. Most studies that have investigated the effect of drugs on the stress systems have required that individuals remain abstinent for a certain period prior to participating in the study; however, some individuals may choose to begin abstinence in advance of their participation and, thus, may have differential responses to drug administration depending on their length of abstinence. Relatedly, given the impact of withdrawal on the HPA axis, it is also likely that the stress system response to drug administration may also vary depending on their stage of withdrawal.

4.3. Factors that influence the response to stress

**Family History:** Other studies suggest that participant factors, such as a family history of alcohol use disorder, may also play a role. Non-dependent participants with a family history of alcohol use disorders have consistently displayed an alcohol-induced reduction in cortisol and ACTH relative to individuals without such a family history (Schuckit et al., 1996; Zimmermann et al., 2004). Collectively, findings from these studies suggest that individuals who may be genetically

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**Fig. 2.** A heuristic framework for drug-induced stress and reward interactions is presented to illustrate the effects and acute and chronic drug intake on the stress biology and their effects on drug motivation and compulsive drug use. A refers to the effects of acute drug use or stress on peripheral and central stress response in light or inexperienced drug users. B describes the central striatal-prefrontal effects in these healthy individuals that encode drug learning, neuroflexibility, and resilient coping that results in controlled, low levels of drug intake in light drug users with robust stress responses. C indicates the mediating process of increased binge and heavy use that results in an altered and blunted stress and reward response in vulnerable individuals. D shows the blunted response then results in the feed-forward cascade of increased craving, neuroendocrine tolerance, and acute abstinence/withdrawal effects that play a role in compulsive drug use and relapse risk. E highlights potential moderators that make individuals more vulnerable or more resilient in each of the previous processes.
Co-Occurring Drug Use: Most of the research studies discussed in this article focused on samples that were dependent on a single drug; however, most individuals who seek treatment for substance use disorders report abusing several different types of drug or have a history of dependence on other substances. Individuals with marijuana use experience greater reinforcing effects of nicotine use (Perkins et al., 2009). Combined administration of cocaine and marijuana results in an increased cardiovascular response and poor cognitive performance as compared to the effect of either drug alone (Foltin et al., 1995, 1993; Foltin and Fischman, 1990). Other studies have found that combined use of cannabis with MDMA results in an enhanced acute subjective and stress system response to the drugs (Dumont et al., 2009; Kollins et al., 2015). Findings from our laboratory indicate that a history of marijuana dependence with alcohol or cocaine use dysregulates HPA axis responding to stress and drug-related cues (Fox et al., 2013). Nicotine increases the self-administration alcohol (Barrett et al., 2006) and, at low doses of nicotine, increases the alcohol-induced dopamine release in the VTA (Tizabi et al., 2002). Despite this, we know little about the impact of polysubstance disorders or other past drug history has on the HPA axis and ANS response to drugs.

Gender: Drug response may also differ by gender. Women, overall, tend to report greater sensitivity to drug effects as compared to men. For example, women tend to show greater sensitivity to the negative effects of intravenous nicotine administration as compared to men (DeVito et al., 2014; Sofuoglu and Mooney, 2009), and men tend to show greater initial reward sensitivity intranasal administration of nicotine (Perkins et al., 2009). In response to cocaine, women reported greater anxiety following administration (Kosten et al., 1996) and reduced high (Lynch et al., 2008) as compared to men. Men tend to have higher amphetamine-induced dopamine release in striatal regions and report correspondingly more rewarding effects of the drug as compared to women (Murro et al., 2006). The effects of these drugs in women may also vary across the menstrual cycle. Alcohol metabolism differs across the menstrual cycle, such that faster rates of elimination are noted in the mid-luteal phase as compared to the early follicular and ovulatory phases (Sunker et al., 1987). Women in the luteal phase of their cycle showed decreased responses to cocaine (Sofuoglu et al., 1999), nicotine (DeVito et al., 2014), and amphetamine (Justice and de Wit, 1999) as compared to those in their follicular cycle. Although one study found limited effects of sex and menstrual cycle on the response to intranasal cocaine (Collins et al., 2007). These collective results suggest that neuroactive steroids, such as estrogen and progesterone, play an important role in the metabolism and effects of drug administration.

Developmental Stage and Early Trauma: There is evidence that blunted stress reactivity is a predictor of earlier use of substances (Evans et al., 2012; Huizink et al., 2006), and that individuals with a blunted cortisol response to stress are at increased risk for substance use (Lovallo, 2006). However, it is unclear if this blunted responding becomes exacerbated by exposure to drugs and at what developmental periods are at-risk individuals most vulnerable. Exposure to early life adversity has known impacts on the HPA axis (Lovallo, 2013) and increases the likelihood that these individuals will develop addictive disorders later in life (Doan et al., 2014; see Enoch, 2011 for review; Gerra et al., 2014). Early life adversity is positively associated with dopamine response to amphetamine in the ventral striatum (Oswald et al., 2014) and lower gray matter volume in limbic regions in individuals in treatment for substance use disorders and also predicted a shorter time to relapse, regardless of type of drug (Van Dam et al., 2014). In cocaine-dependent individuals, early life adversity increased the cortisol response to stress although there was no healthy control to determine if this response was blunted (Flanagan et al., 2015). A recent study found that early life adversity moderated the impact of withdrawal on stress system response to a stressor (al’Absi et al., 2018). However, few studies have tested these associations systematically in response to stress, and even fewer still have assessed the impact of early life adversity in response to administration of drugs.

5. Conclusions and future directions

Intake of psychoactive drugs has significant acute effects on the peripheral stress pathways. These effects parallel drug-related effects on central stress and reward pathways to alter acute drug-related subjective, neuroendocrine, and physiological states. Regular, high levels of drug use alter stress and reward responses both in tonic and phasic responding and recent findings suggest that such alterations are significantly associated with the tolerance, withdrawal and intoxication effects of drugs as well as in predicting current drug use and future relapse. This review suggests that addictive substances, although varying in neurobiological targets of action, are similar in having a significant and potent effect on stress pathways, to affect stress responses, craving, and drug intake.

However, it should be noted that there are limits to what can be concluded from the current literature and important areas for future research. Most studies discussed here have focused entirely on either naïve participants/light users or chronic/dependent users; only a few have compared across different types of users. For those that have compared across substances, chronic use is generally associated with a blunting of the drug-induced activation of the stress systems (Holdstock et al., 2000; King et al., 2006; Stormark et al., 1998; Thayer et al., 2006); however, this has not been fully elucidated in many drugs. More research comparing light users to heavy users is necessary to understand the neuroadaptations that occur to drug administration fully. Additionally, most studies compare stress reactivity in chronic substance users to healthy controls are cross-sectional. Thus, it cannot be determined if the stress dysregulation of heavy users is caused by chronic exposure to substances or predisposes them to future drug use. It is probably, and indeed very likely, that the effect is synergistic. Individuals with a disrupted stress response, due to early trauma or family history, are more likely to abuse drugs, which in turn further dysregulates their stress response. Thus, longitudinal research, such as the massive undertaking that is the Adolescent Brain Cognitive Development (ABCD) study, is vital for determining if drug use results in adaptations to the stress response system or exacerbates pre-existing stress dysregulation. Chaplin and colleagues in this special issue address these temporal associations in an excellent overview of the developmental aspects of the link between substance use and stress response dysregulation.

Substance-related adaptations to the stress system may occur along a continuum. By artificially focusing on one end of the spectrum or the other, we may not be capturing the full spectrum of neuroadaptations in the stress response to addictive substances. Animal models to some extent can address this continuum but, such as seen in opiates (Armario, 2010), the stress system response to drug intake may differ between animals and humans. A future review should synthesize findings across species. Finally, certain individual differences, some of which have been noted above, may hasten or slow down the progression along this continuum.

Despite the gaps in the literature, these findings collectively suggest that dysregulation of the stress responses may serve as potential markers for prevention efforts and a target for the development of therapeutic interventions (Greenwald, 2018; Milivojevic and Sinha, 2018). Prevention efforts that target individuals with certain risk factors known to impact the stress system (e.g., early life adversity, genetic, family history) may reduce the likelihood that these individuals will develop a substance use disorder. Concerning treatment efforts for individuals with addictive disorders, the extent treatments are modestly effective at best. There is preliminary evidence that pharmacological interventions that target the adrenergic system may reduce craving evoked by both drugs and stress (Fox and Sinha, 2014; Fox et al., 2012; Lé et al., 2011; Milivojevic and Sinha, 2018). Behavioral treatments
that address the management of stress-related craving could enhance the efficacy of existing treatments. Thus, identifying specific biomarkers related to dysregulated stress responses might allow us to identify novel treatment approaches targeting normalizing of the stress response to improve addiction treatment efforts.

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