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Substance abuse, memory, and post-traumatic stress disorder

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Abstract

A large body of literature demonstrates the effects of abused substances on memory. These effects differ depending on the drug, the pattern of delivery (acute or chronic), and the drug state at the time of learning or assessment. Substance use disorders involving these drugs are often comorbid with anxiety disorders, such as post-traumatic stress disorder (PTSD). When the cognitive effects of these drugs are considered in the context of the treatment of these disorders, it becomes clear that these drugs may play a deleterious role in the development, maintenance, and treatment of PTSD. In this review, we examine the literature evaluating the cognitive effects of three commonly abused drugs: nicotine, cocaine, and alcohol. These three drugs operate through both common and distinct neurobiological mechanisms and alter learning and memory in multiple ways. We consider how the cognitive and affective effects of these drugs interact with the acquisition, consolidation, and extinction of learned fear, and we discuss the potential impediments that substance abuse creates for the treatment of PTSD.

Keywords

Hippocampus; Amygdala; Prefrontal cortex; Consolidation; Reconsolidation; Extinction; Stress

1. Introduction

The interaction between stress, substance abuse, and memory is complex and inter-dependent. Stress can modulate the initial rewarding effects of addictive drugs, reinstate drug seeking, and cause relapse to substance use. On the other hand, substance use can alter the biological response to stress (Brady & Sinha, 2005; Cleck & Blendy, 2008; Koob & Le Moal, 2008), thus changing stress responses in addicted individuals. Humans with substance dependence most commonly identify stress and negative mood states as reasons for relapse and ongoing substance abuse (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998), and in drug naive animals, a large range of stressors increase drug self-administration (Piazza, Deminiere, le Moal, & Simon, 1990). In addition to baseline stress, anxiety disorders, such as post-traumatic stress disorder (PTSD), are also affected by drugs, as evidenced by the high comorbidity between these disorders and drug abuse.

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These drug effects are further complicated by the many demonstrations that abused substances have effects on memory. These effects can include promoting or impairing memory, depending on the receptor systems and signaling cascades that the substance affects. In addition, drugs have powerful stimulus properties that can become associated with cues in the environment to produce drug-seeking or avoidance (Bardo & Bevins, 2000; Cunningham, Clemans, & Fidler, 2002; Le Foll & Goldberg, 2005). The same drug can have different effects on memory and reward as a function of dose, exposure duration, or withdrawal state. These effects interact with stress at multiple levels, with stress being both a consequence of drug withdrawal and a trigger for relapse. In a disease like PTSD, which incorporates both abnormal stress responses and memory impairments, the interactions with drugs become even more complex, as both the cognitive and emotional effects must be considered. In this review, we consider some of the effects of abused substances on memory and how these effects interact with stress. We focus in particular on the effects of cocaine, nicotine, and ethanol on fear conditioning and PTSD. These drugs operate through different cellular mechanisms and have both common and unique effects on learning and memory and the pathology of PTSD.

2. Fear conditioning as a tool to evaluate the interaction between stress and substance abuse

Pavlovian fear conditioning is a widely used procedure for examining the underlying mechanisms of the effects of stress and abused substances on memory. In this form of learning, an animal is exposed to pairings of a neutral conditioned stimulus (CS) such as a light or a tone, with a fear-inducing unconditioned stimulus (US), such as a mild footshock, and eventually exhibits a conditioned fear response to the CS. This response can include freezing, increased startle reflexes, autonomic changes, analgesia, and behavioral response suppression. Due to the rapid formation and longevity of these responses, fear conditioning has become a popular model for studying learning and memory mechanisms (Kim & Jung, 2006). There are many procedural variations of fear conditioning, including standard delay fear conditioning, in which the CS and US co-terminate; contextual fear conditioning, in which the US occurs in the absence of a discrete CS; and trace fear conditioning, in which the CS offset and US onset are separated by a stimulus-free interval. The extent of fear conditioning can be assessed by measuring the freezing responses to the cue or context, fear potentiated startle (FPS) responses, or suppression of ongoing operant behaviors. Additionally, in any of these procedures, subsequent nonreinforced exposure to the CS or context assesses the resistance of initial learning to change, as well as new inhibitory learning (extinction) that develops as animals learn that the cues are no longer associated with the US (Lattal & Lattal, 2012).

A large body of work, including lesion, pharmacological and neurophysiological studies, has shown that the amygdala is a key neural region for the development of fear conditioning (Davis, 1997; Fendt & Fanselow, 1999; LeDoux, 1996). This region receives sensory input from multiple brain regions and sends projections to several areas that mediate fear responses. The hippocampus, an important region for many types of learning, is also involved in certain types of fear conditioning, especially contextual learning and trace fear

conditioning (McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Phillips & LeDoux, 1992). Cortical regions, particularly the various sections of the prefrontal cortex (PFC), modulate amygdala output (Sotres-Bayon & Quirk, 2010) and response inhibition that occurs during extinction (Milad & Quirk, 2002; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011).

Drug addiction has been described as a disease of learning and memory, in which normal learning processes are essentially hijacked in order to form a resilient and maladaptive drug association (Hyman, Malenka, & Nestler, 2006; Torregrossa, Corlett, & Taylor, 2011). Drug effects on memory in fear conditioning tasks are complicated because exposure to and withdrawal from drugs of abuse can alter memory processes, but can also create an aversive internal state that may become part of the memory itself (Little et al., 2005). The well-defined neurobiological substrates of fear conditioning allow for the isolation of particular drug effects, facilitating the pharmacological dissection of the signaling pathways that are disrupted by the acute and chronic administration and withdrawal from chronic drugs of abuse. Fear conditioning allows for the assessment of how drugs alter both learning mechanisms and stress responses. As such, fear conditioning is a unique paradigm in which to study drug-stress-learning interactions within a single, well-defined model that can then be translated into models of drug abuse and anxiety disorders.

3. PTSD: a disease of stress and learning that shows high comorbidity with drug abuse

Due to the significant overlap between the underlying mechanisms, fear conditioning in rodents is commonly used to study aspects of anxiety and fear-related disorders, such PTSD (Chester, Kirchhoff, & Barrenha, 2013; Kim & Jung, 2006). Several paradigms of inescapable shock delivery in unpredictable patterns have been shown to create PTSD-like states in rodents (Foa, Zinbarg, & Rothbaum, 1992; Maier, 2001; Siegmund & Wotjak, 2007), and prior exposure to multiple shocks enhances the subsequent learning of conditioned fear (Rau, DeCola, & Fanselow, 2005). PTSD is linked to anxiety, memory impairments, and alterations in stress-responsive systems, such as the hypothalamic–pituitary–adrenal (HPA) axis (Smith et al., 1989; Yehuda, 2001; Yehuda et al., 1995).

Several aspects of PTSD indicate that this disorder is related to the formation of a fear memory that is highly resistant to extinction (Parsons & Ressler, 2013; Rau et al., 2005), suggesting that the abnormal processing or retention of a fearful memory is a key component of PTSD. For example, MRI studies have shown decreased hippocampal volumes in patients who suffer PTSD (Bremner et al., 1995; Karl et al., 2006). In addition to its key role in memory formation and modulation, the hippocampus is also involved in stress responses (Bratt et al., 2001). Thus, compromised hippocampal function can impair normal HPA function as well as memory processes (Schulkin, Gold, & McEwen, 1998).

Neuroimaging studies have also shown reduced amygdala volume in veterans with PTSD (Morey et al., 2012), and this is paralleled by data showing structural changes in the amygdala of stressed animals (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Stress-induced changes in the dendritic morphology and the spine density of neurons in the

basolateral amygdala are closely associated with deficits in extinction, suggesting that synaptic remodeling in the amygdala may be one mechanism that underlies the stress-induced impairment in extinction that is often associated with PTSD (Maroun et al., 2013).

PTSD patients also show abnormal reductions in medial PFC (mPFC) activity and enhanced amygdala engagement (Rauch et al., 2000; Shin et al., 2004). Due to the inhibitory connections between the mPFC and the amygdala, this could cause impairments in the extinction of fear, resulting in prolonged conditioned responding over time (Hariri, Bookheimer, & Mazziotta, 2000). PTSD symptoms may reflect amygdala hyper-responsivity to fear-related stimuli with a concomitant lack of prefrontal inhibition, ultimately resulting in an abnormal circuit between the mPFC, the amygdala, and the HPA axis (Akirav & Maroun, 2007).

In addition to the clear evidence for a learning and memory component of PTSD, this disease is also highly comorbid with substance abuse disorders for a wide range of drugs. Because these drugs have pronounced effects on learning, memory, and anxiety, this comorbidity must be considered in the treatment of PTSD. In the following sections, we will review drug effects on fear conditioning and PTSD for three commonly used drugs of abuse with highly disparate neurobiological effects: nicotine, cocaine, and alcohol. We will consider how these drugs affect learning and stress, and we will discuss the ways in which fear conditioning has been used to disentangle these effects. Because PTSD is often comorbid with a substance use disorder involving one or more of these drugs, we will discuss how the fear conditioning data can inform the effects of these drugs on PTSD.

4. Nicotine and fear conditioning

4.1. Introduction

Smoking rates in PTSD patients are high, and these patients have greater difficulty quitting relative to other smoking populations (Fu et al., 2007). Nicotine is the primary addictive component of tobacco (Benowitz, 1992) and exerts its pharmacological effects by binding to and activating nicotinic acetylcholinergic receptors (nAChRs). nAChRs are pentameric ligand-gated ion channels that allow the influx of sodium and calcium and modulate both neuronal activity and intra-cellular signaling cascades (Barik & Wonnacott, 2009; Vernino, Amador, Luetje, Patrick, & Dani, 1992). In the brain, nAChRs primarily occur in high-affinity heteromeric configurations of α and b subunits and a low-affinity configuration of homomeric α7 subunits (Barik & Wonnacott, 2009). The addictive effects of nicotine are thought to occur through the modulation of reward pathways, such as the medium spiny neurons in the ventral tegmantal area (VTA; Livingstone & Wonnacott, 2009). Nicotine also modulates learning and memory, and these cognitive effects may play direct and important roles in both the development and maintenance of nicotine addiction (Davis & Gould, 2008; Gould, 2006; Kenney & Gould, 2008).

4.2. Acute nicotine

The acute administration of nicotine can promote some forms of learning, but these enhancements often follow an inverted U-shaped curve, with higher doses potentially interfering with these enhancing effects (Kenney & Gould, 2008). Although the effects of

higher doses of nicotine on fear conditioning are not well characterized, the enhancing effects of lower doses of nicotine on fear conditioning are well established and clearly depend on high-affinity nAChRs. The acute administration of nicotine selectively enhances the contextual component of delay fear conditioning in mice (Gould & Higgins, 2003). This enhancement occurs in both foreground and background context learning (Davis, Porter, & Gould, 2006). Similarly, nicotine enhances the formation of trace fear learning (Davis & Gould, 2007; Gould, Feiro, & Moore, 2004; Raybuck & Gould, 2009). Importantly, at the these doses, nicotine does not affect delay fear conditioning, regardless of conditioning strength (Gould & Higgins, 2003), suggesting that nicotine enhances contextual and trace conditioning via the enhancement of learning, rather than altering anxiety or stress. However, it should be noted that higher doses of nicotine are anxiogenic and can act as stressors (Yu & Sharp, 2010). Interestingly, nicotine can also enhance cued extinction after delay fear conditioning (Elias, Gulick, Wilkinson, & Gould, 2010), a task that relies on cortical substrates similar to those that support the acquisition of trace fear conditioning (Stafford, Raybuck, Ryabinin, & Lattal, 2012).

These acute effects occur at a dose of plasma nicotine that is within the range reported in human smokers (Davis, James, Siegel, & Gould, 2005), and they are due to nicotine's action at high-affinity b2 subunit-containing nAChRs. The knockout of these subunits prevents this enhancement, as does the co-administration of high-affinity nicotinic antagonists with nicotine (Davis, Kenney, & Gould, 2007). Additionally, these acute enhancing effects appear to be downstream of the activation of the intra-cellular signaling kinases ERK and JNK (Kenney, Florian, Portugal, Abel, & Gould, 2010a; Kenney, Poole, Adoff, Logue, & Gould, 2012; Raybuck & Gould, 2007). Further isolating the acute effects of nicotine, infusion directly into the dorsal hippocampus is sufficient to enhance context or trace fear conditioning (Davis et al., 2007; Raybuck & Gould, 2010), while the infusion of a high-affinity antagonist into the hippocampus prevents the enhancing effects of systemic nicotine (Davis et al., 2007). Additionally, the direct infusion of nicotine into the medial prefrontal cortex can enhance trace fear conditioning without affecting contextual conditioning, suggesting that nicotine can enhance trace fear conditioning through multiple pathways (Raybuck & Gould, 2010). Collectively, these findings paint a clear picture for the effects of acute nicotine administration on fear learning, with selective, dose-dependent effects on hippocampus- and PFC-dependent learning via the action of high-affinity nAChRs. These studies on nicotine's acute effects serve as an excellent starting point for examining the chronic and withdrawal effects of nicotine on learning.

4.3. Chronic nicotine and withdrawal

In contrast to acute administration, chronic nicotine administration at levels that match the acute doses (approximately 13 ng/ml) fails to produce an enhancement of either contextual or trace fear conditioning (Davis et al., 2005; Raybuck & Gould, 2009). This effect has been replicated across many studies and suggests that chronic exposure to nicotine produces tolerance to its enhancing effects on learning and memory (Gould, 2006). Withdrawal from chronic nicotine produces selective deficits in context and trace fear conditioning without affecting delay fear conditioning (Davis et al., 2005; Raybuck & Gould, 2009). The removal of the osmotic pumps used to deliver chronic nicotine places the animal in a natural

abstinence state and produces robust deficits in learning for up to four days (Gould et al., 2012). Importantly, although nicotine withdrawal can cause stressful somatic withdrawal effects, these effects do not occur at these low doses (Malin & Goyarzu, 2009), suggesting that learning and memory disruption is driving these deficits rather than an alteration of systemic stress levels. These withdrawal effects do not occur in β2 nAChR subunit knockout mice, but do occur in α7 nAChR subunit knockout mice (Raybuck & Gould, 2009), suggesting that they are dependent on β2-containing high-affinity nAChRs. Additionally, in chronic nicotine-receiving mice, deficits in both contextual and trace conditioning can be precipitated by the high-affinity nicotinic antagonist epibatidine, but not by the low-affinity nicotinic antagonist mecamylamine (Raybuck & Gould, 2009). These precipitated withdrawal effects suggest that chronic nicotine critically alters the regulation or function of high-affinity nAChRs. Collectively, these studies suggest that the chronic and withdrawal effects of nicotine occur through a disregulation of high-affinity nAChRs.

Similar to the acute effects of nicotine, nicotine's chronic and withdrawal effects can be isolated to the hippocampus. Withdrawal from the chronic infusion of nicotine directly into the hippocampus is sufficient to induce learning deficits (Davis & Gould, 2009), and in mice chronically treated with systemic nicotine, the infusion of antagonists directly into the hippocampus precipitates withdrawal deficits in contextual fear learning (Davis & Gould, 2009). These findings, combined with the finding that a withdrawal-induced upregulation of high-affinity nAChRs in the hippocampus coincides with behavioral learning deficits (Gould et al., 2012), suggest that the effects of nicotine withdrawal on contextual fear conditioning are mediated through the disruption of hippocampal nAChR function. However, similar to the enhancement seen with acute nicotine, the withdrawal-induced deficits in trace fear conditioning may be mediated through medial prefrontal cortical mechanisms as well as hippocampal mechanisms (Raybuck & Gould, 2009; Raybuck & Gould, 2010).

These withdrawal-induced deficits in contextual fear conditioning can be reversed by a direct replacement of nicotine via acute administration or by the administration of the high-affinity nicotinic agonist ABT-418 (Davis et al., 2005; Kenney, Wilkinson, & Gould, 2010b). Additionally, a partial agonist for high-affinity nAChRs (varenicline) can ameliorate nicotine withdrawal-induced learning deficits (Raybuck, Portugal, Lerman, & Gould, 2008). This same drug is also used for the affective clinical treatment of nicotine addiction under the trade name Chantix (Jorenby et al., 2006; Lerman, 2006; Rollema et al., 2007). In humans, nicotine use is associated with similar learning deficits that are evident in a number of cognitive tasks, such as n-back and verbal memory tasks. Importantly, varenicline can also rescue cognitive deficits in abstaining smokers (Loughead et al., 2010; Patterson et al., 2009; Patterson et al., 2010), which may suggest that withdrawal-associated learning deficits are relevant in human drug abuse.

4.4. Conclusions

The acute enhancement of learning by nicotine and the learning deficits induced by withdrawal from chronic nicotine both critically depend on high-affinity nAChRs. Although higher doses of nicotine can act as chronic stressors (Yu & Sharp, 2010), the doses reviewed here, which match the levels reported in human smokers (Davis et al., 2005), selectively

alter learning via the modulation of hippocampal and medial prefrontal signaling, rather than by affecting general stress levels. Additionally, this work demonstrates that fear conditioning is sensitive to the different patterns of nicotine exposure that are observed in human smokers and patients diagnosed with PTSD.

5. Cocaine and fear conditioning

5.1. Introduction

As with nicotine, the abuse potential of cocaine is high, and the abuse of cocaine is often comorbid with PTSD (Dutra et al., 2008; Koob & Volkow, 2010; O'Brien et al., 1998; Penberthy, Ait-Daoud, Vaughan, & Fanning, 2010; Volkow et al., 2008). Cocaine's abusive liability is primarily due to the blockade of dopamine transporters within the reward circuitry, where it prevents the reuptake of dopamine (Hall et al., 2004). Dopamine is also involved in learning and cognition (Pezze & Feldon, 2004; Runyan & Dash, 2004), meaning that some of cocaine's addictive effects may be due to a perturbation of the mechanisms of learning and memory that are thought to underlie the long-term maladaptive changes in behavior that constitute addiction (Hyman et al., 2006). Studies investigating the effect of cocaine on fear conditioning suggest a general relation between cocaine exposure, learning, and anxiety; however, the effects vary greatly depending on the drug dosing, administration duration, and behavioral assay used.

5.2. Acute cocaine

One of the reasons for the comorbidity between cocaine abuse and anxiety disorders may be that cocaine itself can cause anxiety and exacerbate anxious symptoms. The acute administration of cocaine generally enhances fear learning, but these effects are complicated by the anxiety-inducing effects of cocaine. A clear example of this complication was reported by Blanchard and Blanchard (1999), who found that cocaine enhances the expression of defense behaviors in mice and rats, suggesting that, in some instances, cocaine can facilitate the expression of fear-induced responses.

It is possible, however, to isolate cocaine's cognitive enhancing effects. Wood, Fay, Sage, and Anagnostaras (2007) showed that acute cocaine administration dose dependently enhances fear conditioning in mice. A key finding from that study was that the enhancement in fear occurred at a lower dose of cocaine than that which generated effects on defensive behavior expression. This dose-based distinction suggests a Yerkes-Dodson-like interaction between cocaine and fear conditioning, with low doses enhancing learning, but higher doses that also enhance fear expression and anxiety interfering with the learning of the task. Indeed, in addition to enhancing the acquisition of fear conditioning, cocaine administered either before or after the reactivation of conditioned avoidance can enhance the retention of fear conditioning (Rodriguez, Phillips, Rodriguez, & Martinez, 1993). Notably, both of these effects occur in an inverted U-shaped dose response curve, with enhancing effects at 5–7 mg/kg.

The effects of acute cocaine on the extinction of fear conditioning are also in keeping with an inverted U-shaped dose curve. The administration of cocaine to rats at a high dose of 40 mg/kg produces deficits in the extinction of FPS responses (Borowski & Kokkinidis, 1998).

In general, these findings suggest that cocaine can dose-dependently enhance learning, but that fear responding may also be affected at higher doses. While the acute administration of these drugs has clear effects on the conditioning and extinction of fear, the focus on comorbidity between stimulant abuse and anxiety disorders has fostered much research on the effects of chronic cocaine exposure and withdrawal on fear conditioning.

5.3. Chronic cocaine and withdrawal

Although the ideal approach may be to contrast the effects of acute, chronic, and withdrawal from chronic cocaine administration on fear learning and extinction, relatively few studies have examined fear learning during chronic cocaine administration. Rather, most studies examine the effects of chronic cocaine on animals following a washout period. Additionally, because humans tend to abuse cocaine in binges, a standard approach is to administer repeated doses of cocaine across days, rather than maintaining animals on a constant, chronic drug dose.

The chronic administration of cocaine has been generally shown to disrupt learning and cognition (e.g., Ardila, Rosselli, & Strumwasser, 1991). However, the effects of high doses of cocaine on anxiety and fear responding complicate the interpretation of the effects of chronic cocaine on fear conditioning. A number of fear conditioning-based behavioral assays show that while exposure to chronic cocaine decreases the acquisition and extinction of fear conditioning, it also affects baseline measures of fear response. For instance, Borowski and Kokkinidis (1994) report that the administration of 40 mg/kg cocaine for seven days in rats produces deficits in FPS responding, though this effect depends on where the cocaine exposure occurred, suggesting an interaction between this task and context-drug associations. In contrast, Gordon and Rosen (1999) reported an enhancement of FPS following chronic cocaine administration, but these enhancing effects may be primarily due to shifted baseline startle responding in chronic cocaine-treated rats. These studies demonstrate the complexities inherent to evaluating the effects of chronic cocaine on cognition. There have been no studies on the effects of repeated exposure to the lower doses of cocaine that have been shown to enhance learning when administered acutely. These future studies will be informative in disentangling the cognitive-enhancing and anxiety-inducing effects of chronic cocaine exposure.

The effects of repeated cocaine on latent inhibition and the extinction of fear conditioning also suggest that deficits in learning could be masked by shifts in baseline responses. For instance, Murphy, Heidbreder, and Feldon (2001) report that chronic cocaine administration in rats (20 mg/kg for five days) enhanced CS responding following latent inhibition, even though CS pre-exposure occurred prior to the cocaine exposure. Thus, reports of conditioned response disruption by chronic cocaine exposure may reflect shifts in baseline CS responses, rather than effects on learning and memory per se. However, Willick and Kokkinidis (1995) report that the same regimen of chronic cocaine administration enhanced startle responses but caused deficits in the extinction of FPS, suggesting that chronic cocaine exposure produces cognitive deficits in rats. Supporting the general conclusions that chronic cocaine exposure disrupts inhibitory learning, Burke, Franz, Gugsa, and Schoenbaum (2006) showed

that chronic cocaine administration (30 mg/kg for 14 days) did not alter fear acquisition but did produce deficits in the extinction of fear conditioned response suppression.

The effects of cocaine abuse in humans are in keeping with these cognitive deficits in rodent learning. Human cocaine users generally show deficits in a number of cognitive domains, including verbal memory, working memory, and executive function (Lundqvist, 2005). Additionally, these cognitive deficits are diminished in individuals that have recently abused cocaine (Woicik et al., 2009). This suggests that cognitive deficits may be an effect of withdrawal from cocaine exposure. According to the opponent-process theory, homeostasis is maintained by an inhibitory process that emerges during chronic drug exposure to counteract the excitatory process induced by the drug. In line with this theory, acute drug use may ameliorate these cognitive deficits (Solomon & Corbit, 1974). Collectively, these findings suggest that fear conditioning and extinction, which can show opponent-process-like effects of cocaine, may be promising assays in which to model the cognitive disruptions induced by cocaine exposure. Novel pharmacotherapies generated with these models may show promise for treatment of the global cognitive disruption that accompanies chronic cocaine exposure, and the rescue of cognitive function may facilitate continued abstinence (Sofuoglu, DeVito, Waters, & Carroll, 2013).

5.4. Conclusions

There are multiple effects of cocaine on the regulation of learned fear that are complicated by interactions between baseline responding and the timing of cocaine exposure. The systematic examination of the effects of chronic cocaine on these behavioral tasks will continue to provide valuable insight into the mechanisms underlying the acquisition and maintenance of cocaine abuse, as well as the mechanisms underlying the comorbidity of psychostimulant addiction and anxiety disorders.

6. Alcohol and fear conditioning

6.1. Introduction

The interaction between alcohol and stress is well-established and complex. Alcoholism has high comorbidity with several anxiety disorders, including PTSD (Fein, 2013), and stress is often a major factor contributing to relapse following the cessation of drinking (Breese, Sinha, & Heilig, 2011; Liu & Weiss, 2002). The interaction between alcohol and stress is often bi-directional, with stressful events triggering alcohol intake (i.e., self-medication) and an increase in stress and anxiety following alcohol clearance (withdrawal). This cyclic nature makes it difficult to determine exactly how alcohol and stress influence each another. Alcohol also has well-documented effects on several forms of learning and memory, including fear-conditioned behaviors (Alijan-pour et al., 2012; Weissenborn & Duka, 2003; Alijan-pour et al., 2012). Genetic rodent models for drinking also show distinctive phenotypes for fear-conditioned behaviors, such as FPS (Barrenha, Coon, & Chester, 2011; Chester et al., 2013). This suggests that common genes regulate alcohol preference and the propensity toward fear-related behavior, thus implicating a shared underlying mechanism in these processes. In this section, we review the effects of alcohol intoxication and withdrawal on the formation, retrieval, and extinction of fear.

6.2. Acute alcohol

Alcohol intoxication has different effects on fear learning that depend on the timing of the alcohol administration, the dose of alcohol used, and the type of conditioning. In general, acute alcohol given prior to conditioning severely disrupts contextual learning (Kitaichi et al., 1995), while cued learning is impaired to a lesser extent (Gould, 2003; Melia, Ryabinin, Corodimas, Wilson, & Ledoux, 1996). These effects can be detected a few hours after training and last for several days (Gould, 2003), suggesting that both short- and long-term memories are affected.

6.2.1. Dose effect—Similar to both nicotine and cocaine, alcohol administered prior to training dose- dependently alters contextual and cued fear conditioning. Depending on the dose administered, ethanol can enhance or impair contextual fear conditioning, with low doses enhancing and high doses impairing responses. The enhancing effects occur at doses below those typically associated with the physical symptoms of intoxication (Gulick & Gould, 2007). Responses to a fear-conditioned tone are also disrupted, but only by higher doses (1.0 g/kg). This suggests that the processes involved in the tone-shock association are less sensitive to alcohol disruption than those involved in the context-shock association. This greater effect on context learning is reported by several groups and is generally interpreted to mean that hippocampal processes (i.e., contextual learning) are more sensitive to alcohol-induced disruption than amygdala processes (i.e., delay fear cue learning), though there are other differences between context and discrete cues (e.g., salience, temporal relation to shock) that complicate this interpretation. Consistent with the hippocampal hypothesis, c-fos induction is blocked selectively in the hippocampus by alcohol administration prior to fear conditioning (Melia et al., 1996). Additionally, the activity of hippocampal place cells, which is highly correlated with location within an environment, is reduced by ethanol (White & Best, 2000), while other hippocampal cells are unaffected.

6.2.2. Timing of administration—The previously discussed effects deal with ethanol administration prior to conditioning; thus, they can be interpreted as an effect on either (or both) memory acquisition or consolidation. Post-conditioning effects of ethanol are more variable than are pre-conditioning effects. For example, the impairing effects reported by Gulick and Gould (2007) were selective for the acquisition of the memory, not consolidation, as post-conditioning alcohol administration had no effect. This comparison between pre- and post-conditioning ethanol suggests that ethanol alters the formation of fearful memory, but not recall or expression (Gould, 2003). This distinction, however, is not always clear, as there are demonstrations that post-conditioning ethanol may affect memory (e.g., Hewitt, Holder, & Laird, 1996).

Work in humans suggests that ethanol administered after learning can actually enhance memory, suggesting some effect on the consolidation process (Bruce & Pihl, 1997; Hewitt et al., 1996). On the other hand, repeated ethanol exposure in rats for several days after conditioning resulted in learning deficits; however, this effect depended on the length of time between conditioning and ethanol administration. Ethanol given closer to conditioning reduced freezing, whereas the same doses given closer to testing showed no effect (Hunt, Levillain, Spector, & Kostelnik, 2009). This would seem to suggest that ethanol can affect

consolidation processes, but not retrieval or expression. In contrast, work on extinction processes, which would include the retrieval of the original memory as well as the formation of a new extinction memory, shows that ethanol can alter these processes (Barrenha et al., 2011; Holmes et al., 2012; Lattal, 2007). Methodological differences could partially explain these conflicting results. For example, the number of ethanol administrations and the timing of administration could affect the outcome. Thus, a single dose of post-training ethanol may not be sufficient to alter post-acquisition fear-conditioned memory when given immediately after training, while repeated administrations or administration closer to testing than training can have effects on subsequent fear expression. Interestingly, when testing occurs in the presence of ethanol, the extinction deficits are less pronounced, suggesting that ethanol may have potent internal stimulus properties that become associated with the external contingencies (Cunningham, 1979) and the absence of those internal signals could affect later recall.

6.2.3. Type of conditioning procedure—The impairing effect of pre-conditioning alcohol exposure on cued learning is reportedly independent of training type, as both delay and trace fear conditioning are impaired by intoxication. Weitemier and Ryabinin (2003) found that a high dose of ethanol (1.6 g/kg) impaired cue responses in both delay and trace fear conditioning, while a lower dose (0.8 g/kg) selectively impaired trace fear conditioning. For both paradigms, context learning was impaired in a dose-dependent manner, consistent with previous reports. A trace fear conditioning-selective effect has also been reported for chronic intermittent ethanol exposure in adolescent rats, which impairs trace, but not delay fear conditioning (Yttri, Burk, & Hunt, 2004). Rats subjected to repeated intoxication bouts after conditioning also had a deficit in trace, but not in delay fear conditioning (Hunt et al., 2009). Similar to the original contextual learning deficits, this suggests that hippocampal function (trace fear conditioning) is more sensitive to disruption by ethanol than amygdala function (delay fear conditioning; Raybuck & Lattal, 2011). However, the literature regarding ethanol and trace fear conditioning is limited, and further investigation is needed to compare across conditioning procedures and trace intervals.

6.2.4. Potential molecular mechanisms—Unlike nicotine and cocaine, ethanol has a wide range of molecular targets, and many of these targets are involved in stress responses, as well as learning and memory processes (Samson & Harris, 1992). Although the disruption of several systems no doubt contributes to ethanol's effects, the mechanisms most directly associated with fear-based learning are the opposing enhancement of GABAergic inhibition and the inhibition of excitatory glutamatergic transmission. Acute ethanol facilitates GABAergic inhibitory mechanisms (Roberto, Madamba, Stouffer, Parsons, & Siggins, 2004) while simultaneously antagonizing glutamatergic NMDA signaling (Lovinger, White, & Weight, 1989). Alcohol binds directly to $GABA_A$ receptors and enhances their response to GABA (Mihic et al., 1997), thus increasing inhibitory signaling. Alcohol also inhibits NDMA-activated currents, though whether this is through direct allosteric modulation of the channel or non-competitive antagonism via glycine signaling is unclear (Chandrasekar, 2013). Both GABA (Almada, Albrechet-Souza, & Brandao, 2013; Gafford et al., 2012) and NMDA signaling (Walker & Davis, 2008; Walker, Paschall, & Davis, 2005) are involved in

fear conditioning. Thus, these channel systems represent a possible mechanism by which ethanol could alter fear-conditioned behaviors.

In addition to their individual functions, GABA and NMDA signals both contribute critically to the development of long-term potentiation (LTP), a cellular analogue of learning that is observed in several brain regions, including the amygdala and hippocampus (Bliss & Collingridge, 2013; Muller, Albrecht, & Gebhardt, 2009). The induction of LTP in these regions has been shown to correlate with fear-conditioned behaviors (Goosens & Maren, 2002; Rogan, Staubli, & LeDoux, 1997). Ethanol inhibits the induction of LTP in the hippocampus both in vitro (Morrisett & Swartzwelder, 1993) and in vivo (Givens & McMahon, 1995), and this effect is enhanced by stress (Talani, Biggio, & Sanna, 2011). The disruption of hippocampal cells by ethanol has been shown to be dose-dependent and temporary (White & Best, 2000) and to differentially affect specific cell types within the hippocampus (Alexandrov Yu et al., 1993). Changes in GABA and NMDA neurotransmission are also seen in the amygdala following ethanol consumption (Roberto, Gilpin, & Siggins, 2012), suggesting that LTP in this region is also disrupted. In fact, chronic ethanol exposure and withdrawal induce glutamatergic changes in the amygdala that are similar to those engaged by Pavlovian fear conditioning (McCool, Christian, Diaz, & Lack, 2010). These mechanisms may be partially responsible for the enhanced anxiety-like behaviors observed in ethanol dependence.

6.3. Alcohol withdrawal

The most well-studied interactions between alcohol and stress involve effects of withdrawal, a highly stressful state induced by the absence of alcohol that is considered one of the hallmarks of alcohol dependence. Withdrawal produces an aversive state characterized by physiological signs of stress, dysphoria, and other subjective measures of discomfort (De Witte, Pinto, Ansseau, & Verbanck, 2003). A key behavioral pathology associated with ethanol withdrawal is anxiety, and the avoidance of withdrawal-related anxiety may underlie some aspects of relapse in alcoholics (Brady & Lydiard, 1993). Withdrawal signs occur within a few hours of ethanol consumption, and the various symptoms of withdrawal change in magnitude across the withdrawal timeline. In the first hours following ethanol intake in humans, tremor, anxiety, agitation, and tachycardia are observed, all of which peak around 24 h after ingestion (De Witte et al., 2003). The negative emotional effects of withdrawal make it difficult to distinguish between the changes in learning and changes in emotional processes. For example, exaggerated emotional responses are observed in animals exposed to a mild stressor during abstinence from ethanol, while the same stressor has no effect on non-ethanol exposed animals (Valdez, Zorrilla, Roberts, & Koob, 2003). In addition, withdrawal itself can also become a conditioned state, such that the exposure to alcohol-related cues leads to aversive feelings similar to those experienced during withdrawal (Little et al., 2005), further complicating the disentanglement of affective disruptions and learning effects.

The magnitudes of various withdrawal symptoms often increase with repeated withdrawal experiences (Becker, Diaz-Granados, & Weathersby, 1997b; Duka et al., 2004; Overstreet, Knapp, & Breese, 2002). For example, alcoholics who have undergone repeated

detoxifications show an increased frequency of panic attacks (George, Nutt, Dwyer, & Linnoila, 1990). In animal models, multiple rounds of withdrawal increase anxiety in rats (Overstreet et al., 2002) and the severity of withdrawal-induced seizures in mice (Becker, Diaz-Granados, & Hale, 1997a). Interestingly, other anxiety-like behaviors in animals decrease with repeated withdrawal, suggesting that some of the affective consequences of withdrawal ameliorate with repeated withdrawal experiences (Stephens, Brown, Duka, & Ripley, 2001).

Similar to changes in the magnitude of various withdrawal traits following multiple rounds of withdrawal, animal fear conditioning studies have found differences between animals exposed to a single round of withdrawal and animals that undergo repeated withdrawal exposures. A single round of withdrawal from chronic ethanol exposure increased anxiety and enhanced contextual fear conditioning in rats (Bertotto, Bustos, Molina, & Martijena, 2006), while repeated withdrawal had no effect on contextual fear conditioning (Borlikova, Elbers, & Stephens, 2006). However, animals given chronic ethanol treatment followed by multiple rounds of withdrawal showed impaired CS learning following withdrawal (Ripley, O'Shea, & Stephens, 2003; Stephens et al., 2001). These differential effects on contextual and cued learning suggest that withdrawal processes, following either a single withdrawal event or repeated withdrawal, alter hippocampus and amygdala processing differently.

As with alcohol intoxication, the effects of withdrawal are dependent on the temporal relation between withdrawal and learning. If learning occurred prior to the alcohol and withdrawal exposures, then repeated withdrawal has no effect. However, although repeated withdrawal does not alter previously learned associations, previous withdrawal experience can alter new associations (Ripley, O'Shea, & Stephens, 2003; Stephens et al., 2001). This suggests that the experience of repeated withdrawal does not impair the ability of the rats to express a previously established fear response and that withdrawal alters the learned association, but not necessarily the emotional response involved. This effect is also dependent on the exposure to withdrawal episodes. An equivalent amount of ethanol exposure in the absence of withdrawal episodes does not impair the formation of associations between a tone and an aversive event in either animals or humans (Ripley, O'Shea, & Stephens, 2003; Stephens et al., 2001; Stephens et al., 2005). One interpretation of these findings is that animals with previous withdrawal experience are less sensitive to aversive events (Stephens et al., 2001).

In agreement with the animal data, fear conditioning is also impaired in alcoholic patients and binge drinkers (Stephens & Duka, 2008). For example, binge drinkers, a group that experiences repeated withdrawal, show reduced galvanic skin responses to a fear conditioned tone compared to non-binge drinkers (Stephens et al., 2005). This may be due, in part, to long-term alterations in fear processing in these populations. When presented with fearful facial expressions, patients with repeated detoxification (withdrawal) events show inaccurate fear recognition (Townshend & Duka, 2003). These impairments are correlated with reduced activation in prefrontal areas and altered connections between the amygdala and a number of other brain regions (O'Daly et al., 2012), including increased connectivity between the amygdala and the bed nucleus of the stria terminalis (BNST), a region that is important for stress-induced relapse (Aston-Jones & Harris, 2004). These changes in

connectivity observed in alcoholic patients could contribute to altered anxiety responses and stress-induced relapse.

In addition to the increase in anxiety and baseline contextual fear conditioning, rats conditioned following withdrawal from chronic ethanol consumption show reduced extinction to contexts (Bertotto et al., 2006) and cues (Ripley et al., 2003) previously associated with shock. However, as both models presented withdrawal prior to conditioning, it is unclear if these effects are due to effects on the original encoding of the fear memory or impairments in the extinction processes themselves. Thus, these experiments are important first steps in demonstrating the effects of withdrawal on fear extinction, but much more work is needed to characterize the behavioral mechanisms underlying these effects.

6.3.1. Potential molecular mechanisms—Withdrawal from chronic ethanol results in a state of neuronal hyperexcitability induced by an increase in calcium entry into the cell (Littleton & Little, 1994; Samson & Harris, 1992). Repeated detoxification experiences result in behavioral and neurobiological changes, including an increased propensity for seizures, known as “kindling”, which is thought to be related to changes in amygdala function (Pinel, 1980). Facilitated neurotransmission within the amygdala due to kindling is also thought to underlie some of the enhanced fear responses in alcoholic patients (Townshend & Duka, 2003). However, this hyperexcitablilty is variable across different brain regions. For example, withdrawal facilitates kindling in the amygdala, but delays the development of hippocampal kindling (Veatch & Gonzalez, 1999). Thus, the adaptive changes to withdrawal could be different in different brain regions (Overstreet et al., 2002), resulting in distinct behavioral effects. Although it is tempting to make a direct connection between neuronal kindling and the deficits seen in withdrawn animals, it should be noted that kindling and withdrawal lead to different behavioral outcomes following fear conditioning (Ripley et al., 2003), illustrating that seizure and affective states are not the same. In agreement with this, repeated withdrawal enhances the kindling response (Becker & Hale, 1993; Kokka, Sapp, Taylor, & Olsen, 1993), but the affective consequences of withdrawal diminish (Stephens et al., 2001).

As might be expected from the previous discussion regarding the effects of alcohol intoxication, withdrawal symptoms are typically attributed to a disregulation of glutametergic and GABAergic signaling. Both single and repeated withdrawal reduce LTP capacity in the lateral amygdala, whereas repeated withdrawal has a more robust effect on hippocampal LTP (Stephens et al., 2005). These effects are long-lasting (up to 6 weeks post-withdrawal). Long-term alcohol exposure leads to an upregulation of glutamatergic transmission and increased glutamatergic turn over (Rossetti, Carboni, & Fadda, 1999; Trevisan et al., 1994). After withdrawal, the glutamatergic system continues to be overactive, leading to an increase in post-synaptic AMPA receptor function (Lack, Diaz, Chappell, DuBois, & McCool, 2007). This imbalance could lead to generalized synaptic strengthening, similar to that observed in the development of normal LTP. Non-specific synaptic strengthening would facilitate seizure activity but saturate the LTP development necessary for learning; thus, reduced LTP following repeated withdrawal may reflect a ceiling effect on plasticity rather than an impairment of LTP mechanisms per se (Stephens et al., 2005). In the amygdala, repeated withdrawal increases the efficiency of synaptic

transmission, which could mean that the fear-related stimuli that normally activate this pathway are now more effective in eliciting anxious responses (Stephens & Duka, 2008). This parallels the behavior seen in both humans (George et al., 1990) and animal models (Overstreet et al., 2002). Thus, the hyperexcitability that causes increased emotional responses can also account for the withdrawal-induced impairment in the development of fear-based associative learning.

6.4. Conclusions

Alcohol alters both emotional processing and learning. Effects on fear conditioning can thus occur through effects on either of these processes. The contrasting effects on GABAergic and glutamaterigc transmission nicely correlate with the observed behavioral changes; however, these mechanisms make for poor pharmacological targets due to their effect on a wide range of behaviors. Thus, the development of medications for alcoholism and the associated long-term emotional and cognitive effects should focus on the numerous other targets of ethanol.

7. Post-traumatic stress disorder and drug abuse

7.1. Introduction

PTSD is classified in the DSM-V as an anxiety disorder that is triggered by a traumatic event outside the range of usual human experience. According to the DSM criteria, there are four primary classes of symptoms: (1) re-experiencing the trauma (flashbacks), which is characterized by intrusive recollections of the trauma that are triggered by exposure to cues symbolizing the trauma; (2) avoidance of thoughts, people, places and memories associated with the trauma and emotional numbing; (3) alterations in arousal and reacitivty, which can include an exaggerated startle response, difficulty sleeping, irritability, difficulty concentrating, and hyper-vigilance; (4) negative alterations in cognition and mood, such as an inability to recall key features of the trauma, persistent negative beliefs or expectations, and negative trauma-related feelings, including fear. The major risk factors for the development of PTSD include the intensity and perceived uncontrollability of the underlying trauma, socioeconomic factors, and comorbidities, such as drug and alcohol use (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Logrip, Zorrilla, & Koob, 2012). As previously discussed, fear conditioning-based experimental paradigms are often used to investigate the underlying mechanisms of PTSD. The fear conditioning model nicely integrates stress responses with learning and memory, the two major systems thought to be impaired in PTSD. In this section, we will discuss the interactions between PTSD and nicotine, cocaine, and alcohol in light of the fear conditioning literature reviewed above.

7.2. PTSD and drugs of abuse

PTSD shows a high comorbidity with drug and alcohol use, and these comorbidities can alter the development, maintenance, and treatment of this disorder. Among individuals diagnosed with PTSD, the incidence of drug abuse and addiction is elevated, with the highest comorbidity observed for alcohol (Logrip et al., 2012). Multiple studies have shown a 3- to 5-fold increase in the development of substance abuse among PTSD patients, leading to substance abuse comorbidity in nearly half of PTSD patients (Breslau, Davis, & Schultz,

2003; Kessler et al., 1995; Mills, Teesson, Ross, & Peters, 2006). As many as 75% of combat veterans with lifetime PTSD also met the criteria for alcohol abuse or dependence (Jacobsen, Southwick, & Kosten, 2001). In addition, between 25% and 40% of the substance abusing population also meet the criteria for PTSD (Dansky, Roitzsch, Brady, & Saladin, 1997; Driessen et al., 2008). Patients with PTSD and substance disorders tend to suffer from more severe PTSD symptoms, particularly those in the avoidance and arousal clusters, compared to patients with PTSD alone (Saladin, Brady, Dansky, & Kilpatrick, 1995). Vietnam combat veterans with PTSD experienced more severe alcohol and drug problems than those without PTSD (McFall, Mackay, & Donovan, 1992), and the increase in use of alcohol and illicit drugs in PTSD patients parallels the increase in the number of PTSD symptoms (Bremner, Southwick, Darnell, & Charney, 1996).

High rates of comorbidity suggest that PTSD and substance use disorders are functionally related to one another, and twin studies suggest some common genetic factors among PTSD, alcohol, and drug use (Xian et al., 2000). Two primary pathways have been described to explain these high rates of comorbidity. In the first, substance abuse precedes PTSD. A pre-existing substance abuse disorder could impair judgment and lead some substance abusers to repeatedly place themselves in dangerous situations to support their habit, resulting in the experience of high levels of physical and physiological trauma (Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Saladin et al., 1995). In addition, chronic substance use can lead to higher levels of arousal and anxiety and the sensitization of neurobiological stress systems. Thus, substance abuse may result in a higher level of vulnerability to the development of PTSD (Aouizerate et al., 2006). In the second pathway, PTSD precedes the development of the substance use disorder. Here, the use of substances is a form of coping via self-medication. This is most likely for depressant drugs, such as alcohol, cannabis, and opioids, which acutely improve PTSD symptoms (Bremner et al., 1996). This pathway could then feed into what is known as the “behavioral theory of addiction”, in which negative emotions, like those associated with PTSD, motivate drug and alcohol consumption. As a result, drug consumption is reinforced due to its ability to dampen these negative emotional responses (Saladin et al., 1995).

Research is split over which of these two pathways is most common in PTSD comorbidities. Over half of all crime victims experienced their first traumatic victimization prior to their first alcohol intoxication or other substance use (Danielson et al., 2009), and many PTSD patients report using alcohol or drugs to overcome the distress of trauma-related events and to forget intrusive memories of the traumatic event (Joseph, Yule, Williams, & Hodgkinson, 1993). However, a history of behavioral problems (including alcohol and drug use) is a predisposing variable for the development of PTSD, and other research indicates that the onset of substance use typically precedes the onset of PTSD (Cottler et al., 1992), suggesting that the first pathway is the most common. Further, recent theories on PTSD development have suggested a complex interaction model involving genetic makeup and the number of traumatic experiences, referred to as the traumatic load. In this case, drug abuse could become a third factor influencing the development of this disorder or the persistence and severity of the disease (Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Neuner et al., 2004). It is likely that both mechanisms exist within the PTSD population, and it may be that the order of drug abuse and PTSD onset is tied to the specific drug abused.

This raises the interesting question of why drugs with highly varying effects are all commonly abused by a single disease population. The effects of cocaine and alcohol, for instance, are significantly different, but the instance of abuse for both drugs is increased in the PTSD population (Saladin et al., 1995). The most commonly accepted explanation is that the type of drug used depends on the specific set of PTSD symptoms experienced (Jacobsen et al., 2001; Saladin et al., 1995). Indeed, alcohol and cocaine-dependent individuals differ in their PTSD symptom profiles (Saladin et al., 1995). The following discussion will examine the effects of nicotine, cocaine and alcohol on the underlying mechanisms of PTSD using the previous discussion of fear conditioning as a basis.

7.3. PTSD and nicotine

Cigarette smoking is associated with many mental health disorders (Lasser et al., 2000). PTSD in particular is highly comorbid, with reports that over 45% of PTSD suffering individuals smoke (Lasser et al., 2000). As with many mental health disorders, these rates may reflect self-medication; however, the rates of smoking are higher in PTSD sufferers than are the rates of abuse of other substances (Breslau et al., 2003). Additionally, the high smoking rate in PTSD patients is problematic because they show significantly decreased odds of quitting (Hapke et al., 2005). Collectively, these statistical measures suggest an interaction between nicotine's effects and PTSD symptoms.

Interactions between nicotine abuse and PTSD could occur through multiple mechanisms. Smoking could enhance risk for development of PTSD, PTSD symptoms could drive smoking as self-medication, and smoking could generate maladaptive behaviors within PTSD that maintain both PTSD and smoking. Evidence suggests that one symptom cluster in PTSD, emotional numbing, a negative symptom similar to depression, is strongly associated with smoking frequency and difficulty quitting (Greenberg et al., 2012). Similarly, acoustic startle, which may reflect baseline arousal, isx enhanced in PTSD patients and by nicotine, but smoking cessation results in decreased startle (Vrana et al., 2013). Hyper arousal, another symptom cluster in PTSD, is shown to be reduced by nicotine (Beckham et al., 2007). Disrupted startle in PTSD may reflect an interaction between emotional numbing and hyper arousal in PTSD. Although the relations between these symptom clusters and smoking are not yet clear, it has been proposed that PTSD sufferers may smoke, in part, to alleviate emotional numbing and suppress hyper arousal (Greenberg et al., 2012). At present, there is little epidemiological evidence to suggest that cigarette smoking predisposes individuals to development of PTSD following a traumatic event. However, the self-medication hypothesis is supported by the hypothesis that smokers may be at risk for hyper arousal and self-medication (whether intentional or otherwise), and this could result in maladaptive responses to PTSD symptoms, thus exacerbating the disorder. In keeping with this idea, nicotine has been shown to acts as a chronic stressor in animals, enhancing stress responses to novel and weakly stressful stimuli via disruption of HPA axis signaling (Yu, Chen, Wu, Matta, & Sharp, 2010; Yu & Sharp, 2010).

The fear conditioning literature suggests that withdrawal from chronic nicotine impairs learning. Thus, it is possible that chronic nicotine exposure (i.e., smoking) and the subsequent withdrawal periods impair the ability of PTSD patients to form extinction

memories, which may make treatment with exposure therapy more difficult. This is speculative, but the literature on basic mechanisms of nicotine and fear suggest that the relation between smoking and treatment efficacy would be important to explore.

7.4. PTSD and cocaine

Cocaine use and PTSD are highly comorbid (e.g., Breslau et al., 2003; Khoury, Tang, Bradley, Cubells, & Ressler 2010). At least one study has shown that cocaine abuse may be predictive of traumatic exposure that can lead to PTSD (Cottler et al., 1992), suggesting that cocaine addicts place themselves in dangerous situations in order to obtain drug, leading to increased chances of developing PTSD (Cottler et al., 1992). However, this report contained a single narrow demographic and these effects could have been due to limited cohort effects.

In addition to predisposing individuals to trauma exposure, chronic cocaine can disrupt stress systems, resulting in shifted set points, leaving addicts more susceptible to stress induced relapse and possibly to PTSD precipitation or maintenance. In keeping with the idea that cocaine exposure may predispose individuals to PTSD, animals exposed to cocaine can show deficits in fear extinction (Burke et al., 2006; Willick & Kokkinidis, 1995), a putative hallmark of PTSD. Indeed, in human cocaine users with PTSD, exposure to traumatic scripts in a clinical setting increases attentional bias to cocaine cues, whereas in cocaine users without PTSD, exposure to the same scripts reduces attentional bias (Tull, McDermott, Gratz, Coffey, & Lejuez, 2011). This may suggest that in cocaine users with PTSD, the recurrent stress that is a hallmark of PTSD may drive drug seeking. Additionally, this effect of PTSD on cocaine seeking in addicts fits well with the shifted stress response curve suggested by Koob and Le Moal (2008) for psychostimulant addiction. Their model predicts that drugs of abuse act as stressors invoking a compensatory opponent process to maintain baseline stress and hormone levels. Thus, with chronic exposure, these opponent or compensatory processes shift set points downward, resulting in basal stress levels that are predisposed to disruption. These shifted stress levels could explain why addicts with PTSD react to traumatic script exposure differently than do addicts without PTSD. Collectively, these findings suggest that cocaine abuse and PTSD could interact in two ways, through increases in exposure to traumatic events during drug seeking or by predisposing a cocaine addict to PTSD development by altering their stress response systems.

The fear conditioning literature for cocaine shows an increased sensitivity to stress-inducing stimuli as well as deficits in extinction. Thus, cocaine addicts exposed to a traumatic event may be more likely to develop PTSD. In addition, PTSD patients that use cocaine may have a reduced capacity for extinction, thus impairing treatment and extending the duration of the disease.

7.5. PTSD and alcohol

As previously mentioned, alcoholism and PTSD show a high comorbidity, with one third of individuals with life-time PTSD also showing signs of alcohol disorders (Blanco et al., 2013; Kushner et al., 2005). Among men, alcoholism is the most common comorbid disorder with PTSD (Kessler et al., 1995), and more than half of Vietnam veterans with PTSD show signs of alcohol abuse (Bremner et al., 1996). Among individuals with PTSD,

heavy alcohol drinking is associated with a greater number and more severe PTSD symptoms, in addition to a prolonged course of illness (Saladin et al., 1995; Yehuda et al., 1995), and the odds of having alcohol use disorders increases with the number of PTSD criteria (Pietrzak, Goldstein, Southwick, & Grant, 2011). However, it is unclear whether the development of PTSD predates the development of alcoholism. Half of individuals with PTSD and alcohol abuse reported that the onset of alcoholism occurred in the same year or later than PTSD (Kessler et al., 1995), and accumulating evidence suggests that the risk for developing comorbid alcoholism and PTSD stems from inherited genetic and biological factors that influence the risk for both conditions (Sartor et al., 2011; Xian et al., 2000), suggesting that either one could develop first and influence the later development of the other.

Whereas the self-medicating aspect of alcohol for PTSD-related anxiety has been well documented (Saladin et al., 1995; Ullman, Filipas, Townsend, & Starzynski, 2005; Waldrop, Back, Verduin, & Brady, 2007), the interaction between alcohol and stress is much more complex. For example, in rats exposed to a long-term foot-shock paradigm, alcohol consumption was only slightly elevated on the days when shocks were administered, but increased dramatically on subsequent days (Volpicelli, Ulm, & Hopson, 1990). If alcohol is used solely to reduce anxiety, then consumption should increase during times of stress, rather than after (Volpicelli, Balaraman, Hahn, Wallace, & Bux, 1999). Thus, while the anxiolytic properties of alcohol are surely a contributing factor, they do not fully explain the interaction between alcohol and stress-related disorders, such as PTSD. As discussed in the alcohol section above, alcohol intoxication can either increase or decrease fear-based learning, depending on the dose. Low doses enhance context learning, suggesting that sub-intoxication levels of alcohol prior to a traumatic event could increase the likelihood of forming a fear memory. Conversely, high levels of alcohol might be expected to impair this memory formation, possibly having a protective effect. Unfortunately, research regarding the effect of acute alcohol intoxication during a traumatic event is lacking.

Of specific interest to this topic is the effect of alcohol on the extinction of fear. As previously mentioned, PTSD can be conceptualized as a robust, long-lasting fear memory that is resistant to extinction, and ethanol can alter previously formed associations (Lattal, 2007; Stromberg & Hammond, 1997). This effect could be due to ethanol impairing the formation of the extinction memory itself, rather than enhancing the previous association, thus simply reflecting an inhibitory effect on new memory formation. Alternatively, the stimulus properties of ethanol could create an internal context during extinction that would be absent in subsequent (non-intoxicated) extinction tests, resulting in higher freezing due to a lack of critical cues necessary to retrieve the extinction memory (Cunningham, 1979). In either case, the use of alcohol to self-medicate during PTSD-induced anxiety might further reduce extinction of fear, which could explain why high levels of drinking are associated with more severe and long-lasting PTSD symptoms.

Whereas alcohol intoxication has anxiolytic effects, alcohol withdrawal, as might be expected, has anxiogenic properties. In fact, negative emotional states, including anxiety, are a defining characteristic of abstinence in alcohol dependent individuals (Valdez et al., 2003), and this anxiety can last for years in humans (De Soto, O'Donnell, Allred, & Lopes, 1985) or

weeks in experimental animals (Rasmussen et al., 2000). Given that anxiety is a hallmark of alcohol withdrawal, one might expect the relationship to anxiety disorders to be straightforward. However, given the general cognitive deficits observed in alcoholics and following repeated withdrawal in animals (Kuzmin et al., 2012; Mann, Gunther, Stetter, & Ackermann, 1999), the ultimate effect of enhanced anxiety and reduced learning capacity are difficult to predict. For example, people with an increased genetic risk for alcoholism as well as those with PTSD show blunted cortisol responses to stress, trauma or situational reminders (de Kloet et al., 2006; Sorocco, Lovallo, Vincent, & Collins, 2006), though it is unclear whether this effect precedes PTSD or is a result of the disorder. Multiple withdrawal episodes can also result in the generalization of conditioned fear to other stimuli (Stephens et al., 2005). Repeatedly withdrawn rats show conditioned response suppression to both a conditioned and non-conditioned tone, suggesting that the fear of the conditioned tone generalized to the non-conditioned one. A common aspect of PTSD is the generalization of the anxiety from the specific trauma to other similar cues, an effect that could be exacerbated in patients with pre-existing alcohol disorders.

As previously discussed, many of the behavioral impairments seen in binge drinkers can be ascribed to alterations in the function of the amygdala and prefrontal cortical areas (Duka, Townshend, Collier, & Stephens, 2003; Duka et al., 2004). Both veterans with PTSD (Morey et al., 2012) and alcohol-dependent individuals (Wrase et al., 2008) have reduced amygdala volumes, suggesting that fear processing is altered for both populations. A possible consequence of impaired prefrontal functions, which normally modulate the output of the amygdala, might be that alcoholic patients are predisposed to recall adverse experiences that are normally suppressed (Stephens et al., 2005), thus enhancing the re-experiencing category of PTSD symptoms.

The body of work regarding alcohol abuse and PTSD shows that these two disorders are highly related and share many of the same underlying mechanisms. Although the exact nature of this relationship is complex, it is clear that the comorbidity of these diseases can influence both the severity of symptoms and treatment options for alcoholics with PTSD. However, much less is known about the effects of sub-alcoholic drinking on PTSD development. For example, does a traumatic event following a single low dose of ethanol alter the acquisition or maintenance of PTSD-like memories? The fear conditioning literature discussed above would suggest that an interaction would be likely, though the exact nature of that interaction is difficult to predict. As low dose bouts of drinking are common, the effect of such drinking patterns on PTSD development should be investigated.

8. General conclusions

This review illustrates some of the ways in which nicotine, cocaine, and alcohol can interact with learning, stress, and PTSD. These abused substances have distinct mechanisms in the brain, creating complex interactions within the cellular circuits of drug action and learning. It is clear that the effects that these abused substances have on memory mechanisms may interact with treatments for PTSD, whether they are behaviorally or pharmacologically based. Thus, a close consideration of a patient's substance abuse patterns is warranted in designing interventions for anxiety-based disorders, such as PTSD.

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