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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.

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.

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

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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), have also been implicated in fear conditioning, particularly in the modulation of 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 an incredibly 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 allows 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 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 β 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

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