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Translational and reverse translational research on the role of stress in drug craving and relapse

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Abstract

Rationale and background—High relapse rates during abstinence are a pervasive problem in drug addiction treatment. Relapse is often associated with stress exposure, which can provoke a subjective state of drug craving that can also be demonstrated under controlled laboratory conditions. Stress-induced relapse and craving in humans can be modeled in mice, rats, and monkeys using a reinstatement model in which drug-taking behaviors are extinguished and then reinstated by acute exposure to certain stressors. Studies using the reinstatement model in rats have identified the role of several neurotransmitters and brain sites in stress-induced reinstatement of drug seeking, but the degree to which these preclinical findings are relevant to the human condition is largely unknown.

Objectives and highlights—Here, we address this topic by discussing recent results on the effect of alpha-2 adreno-ceptors and substance P-NK1 receptor antagonists on stress-induced reinstatement in mice and rats and stress-induced craving and potentially stress-induced relapse in humans. We also discuss brain sites and circuits involved in stress-induced reinstatement of drug seeking in rats and those activated during stress-induced craving in humans.

Conclusions—There is evidence that alpha-2 adrenoceptor agonists and NK1 receptor antagonists decrease stress-induced drug seeking in rats and stress-induced craving in humans. Whether these drugs would also prevent stress-induced drug relapse in humans and whether similar or different brain mechanisms are involved in stress-induced reinstatement in non-humans and stress-induced drug craving and relapse in humans are subjects for future research.

Keywords

Corticotropin-releasing factor; Craving Extinction; NK1 receptor; Noradrenaline; Reinstatement; Relapse; Reverse translational research; Stress; Substance P; Translational research; Yohimbine

Introduction

The high rate of relapse to drug use following periods of forced or self-imposed abstinence is a major clinical problem in addiction treatment (Hunt et al. 1971; O'Brien and Gardner

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2005). Clinical studies suggest that stress is among the key factors contributing to these high relapse rates (Brownell et al. 1986; Sinha 2001). Prospective human studies have shown that stress exposure (either acute stressors like an argument with coworkers or more chronic adverse life events like divorce or job loss) is associated with subsequent drug relapse (Baker et al. 2004; Brown et al. 1990; Brown et al. 1995; Epstein et al. 2009a; Hyman et al. 2007; Preston and Epstein 2011; Shiffman 2005; Sinha 2001). While an important strength of these studies over previous correlational studies of stress and relapse has been the prospective assessment of drug relapse in order to predict future relapse risk, these studies have focused on varied assessment of stressful life events, which may have led to some negative results (Hall et al. 1990; O'Doherty and Davies 1987).

Human laboratory studies of stress provocation have also been conducted to provide additional psychobiological measures of stress. These studies have assessed drug use motivation by measuring drug craving (Sinha 2001). The stressors used in these studies include guided imagery stress scripts (Sinha et al. 1999), Trier Social Stress Task (Kirschbaum et al. 1993), and systemic injections of the stress neurohormone corticotropin-releasing factor (CRF) (Vale et al. 1981). These stressors induce physiological (e.g., increased cortisol release and heart rate) and psychological (e.g., increased subjective assessment of anxiety and irritability) stress responses and also increased subjective self-reports of drug craving (Back et al. 2010; Coffey et al. 2002; Sinha 2001; 2009; Sinha et al. 1999). These laboratory studies have established a clear cause–effect relationship between stress exposure and drug craving (Sinha 2001; 2009) and more preliminary evidence for a cause–effect relationship between stress exposure and relapse to drug use in the laboratory (McKee et al. 2011).

Recent studies combining the induction of stress, affect, and related drug craving in the laboratory with a prospective assessment of relapse in the drug user's environment have shown that stress-induced craving, attenuated subjective response to natural rewards, and physiological stress responses in the laboratory predict drug relapse and intake (Back et al. 2010; Lubman et al. 2009; Sinha et al. 2006; Sinha et al. 2011a, b). Additionally, ecological momentary assessment (EMA) approaches that prospectively measure the relationship between stress exposure in the drug user's environment and stress-related negative affect with subsequent drug use provide further support for the notion that stress contributes to relapse to drug use (Cooney et al. 2007; Epstein et al. 2009a; Preston and Epstein 2011; Shiffman et al. 1996; Shiffman et al. 2004).

However, while human research has identified that stress contributes to drug relapse, the underlying neurobiological mechanisms are largely unknown. Stress-induced relapse and craving can be modeled in non-humans using two procedural variations of the reinstatement model (Shaham et al. 2000a; Shaham et al. 2003). In the self-administration version, which is based on an operant conditioning paradigm (Skinner 1938), mice, rats, or monkeys are trained to respond for drug infusions (or oral solutions in the case of alcohol), typically by pressing a lever; then, following extinction of the drug-reinforced responding, non-reinforced pressing on the drug-associated lever is induced by certain stressors (Shaham et al. 2000a). These stressors include intermittent unpredictable footshock (Erb et al. 1996; Mantsch and Goeders 1999; Shaham and Stewart 1995), acute food deprivation (Carroll 1985; Shalev et al. 2001b), cold swim stress (Conrad et al. 2010), and the pharmacological stressors yohimbine (Lee et al. 2004; Shepard et al. 2004) and CRF (Erb et al. 2006; Le et al. 2002; Shaham et al. 1997). Yohimbine is a prototypical alpha-2 adrenoceptor antagonist that induces stress- and anxiety-like responses in both humans and laboratory animals (Redmond and Huang 1979); in human laboratory studies, yohimbine also induces opiate and alcohol craving (Stine et al. 2002; Umhau et al. 2011).

In the conditioned place preference (CPP) version of the reinstatement model, which is based on a classical conditioning paradigm (Pavlov 1927), CPP is induced by drug administration, extinguished, and then induced again by stress exposure (Aguilar et al. 2009; Shalev et al. 2002). Stressors reported to reinstate drug preference in the CPP reinstatement version include intermittent unpredictable footshock (Wang et al. 2002; Wang et al. 2006), restraint (Sanchez et al. 2003), conditioned fear (Sanchez and Sorg 2001), social defeat (Ribeiro Do Couto et al. 2006), swim stress (Kreibich and Blendy 2004; Redila and Chavkin 2008), tail pinch (Ribeiro Do Couto et al. 2006), and the pharmacological stressors yohimbine (Mantsch et al. 2010) and the kappa receptor agonist U50,488 (Redila and Chavkin 2008).

It should be noted, however, that stress-induced reinstatement of drug seeking is to some degree both stressor specific and procedure specific. Thus, the established stressors like social defeat (Miczek et al. 1994; Miczek et al. 2008) and restraint (Kvetnansky and Mikulaj 1970) reinstate drug preference in the CPP reinstatement version (Ribeiro Do Couto et al. 2006; Sanchez et al. 2003) but not drug seeking in the self-administration reinstatement version (Funk et al. 2005; Shalev et al. 2000). Additionally, in the case of intermittent footshock, the stressor most often used in reinstatement studies, its effect on reinstatement is dependent on several experimental parameters (Kupferschmidt et al. 2011; Lu et al. 2003), including the context of stress exposure (Shalev et al. 2000), the shock intensity (Shaham 1996), the duration of the withdrawal period (Shalev et al. 2001a), and the amount of drug intake during training (Ahmed et al. 2000; Mantsch et al. 2008).

Studies on stress-induced reinstatement of drug seeking in non-humans have provided mechanistic information on the brain sites and neurotransmitters involved in this reinstatement (Erb 2010; Kalivas and McFarland 2003; Le and Shaham 2002; Shalev et al. 2010); however, the relevance of this information to mechanisms underlying stress-induced craving and relapse in humans is unknown (Epstein et al. 2006). Therefore, an important theoretical issue is the validity of the reinstatement model as an animal model of human drug craving and relapse. This issue has been thoroughly addressed in several reviews (Bossert et al. 2005; Epstein and Preston 2003; Epstein et al. 2006; Katz and Higgins 2003), and thus we do not discuss it in the present review. Instead, we describe translational research on the role of stress in drug craving and relapse that was inspired in part from the results of studies using the reinstatement model. We also describe reverse translational research, in which a finding originally obtained in the human laboratory was assessed in the reinstatement model.

Below, we first discuss studies on the effect of alpha-2 adrenoceptor agonists on stress-induced reinstatement in laboratory animals, which have led to translational clinical studies on the effect of these agonists on stress-induced craving and relapse in heroin and cocaine addicts. We then describe studies on the effect of a neurokinin 1 (NK1) receptor antagonist on stress-induced craving and neuronal activation in alcoholics that have led to a reverse translational preclinical study on the effect of substance P-NK1 receptor blockade on stress-induced reinstatement of alcohol seeking. We subsequently review the brain sites involved in stress-induced reinstatement of drug seeking in rats and the brain sites activated during stress-induced craving in humans. We conclude by proposing future directions of translational research based on findings obtained from preclinical studies using the reinstatement model. Table 1 provides a glossary of several terms used in our review.

Effect of alpha-2 adrenoceptor agonists on stress-induced reinstatement in non-humans and stress-induced craving and relapse in humans

Central noradrenergic neurons are activated by different stressors and are thought to play an important role in the mediation of physiological and psychological responses to stress (Bremner et al. 1996a, b; Redmond and Huang 1979; Stanford 1995; Tanaka et al. 1990). There is evidence that brain noradrenaline is a critical mediator of footshock stress-induced reinstatement of drug seeking (Shaham et al. 2000b; Shalev et al. 2002). In several pharmacological studies, investigators have used alpha-2 adrenoceptor agonists (clonidine, lofexidine, guanbenz) that inhibit central noradrenaline cell firing and release (Abercrombie et al. 1988; Aghajanian and VanderMaelen 1982; Carter 1997; Mongeau et al. 1997). In an initial study, Shaham et al. (2000b) reported that systemic injections of low doses of clonidine inhibit the footshock stress-induced reinstatement of heroin seeking. This inhibitory effect of systemic injections of the alpha-2 adrenoceptor agonists on footshock-induced reinstatement of drug seeking has also been observed in rats previously trained to self-administer cocaine, speedball (a heroin–cocaine mixture), alcohol, and nicotine (Table 2) (Erb et al. 2000; Highfield et al. 2001; Le et al. 2005; Zislis et al. 2007).

The effect of the alpha-2 adrenoceptor agonists on footshock-induced reinstatement is centrally mediated. Ventricular injections of clonidine mimic the inhibitory effect of the drug's systemic injections (Shaham et al. 2000b), while systemic injections of ST-91, a charged analogue of clonidine that does not readily cross the blood–brain barrier (Scriabine et al. 1975), had no effect on footshock-induced reinstatement. Another finding from this series of studies is that systemic injections of the alpha-2 adrenoceptor agonists had no effect on reinstatement of drug seeking induced by drug priming injections or exposure to drug-associated cues (Erb et al. 2000; Highfield et al. 2001).

Additional evidence for a role of alpha-2 adrenoceptors in stress-induced reinstatement is that systemic injections of the prototypical alpha-2 adrenoceptor antagonist yohimbine, which increases noradrenaline cell firing and release (Abercrombie et al. 1988; Aghajanian and VanderMaelen 1982), reinstate methamphetamine, cocaine, heroin, and alcohol seeking in rats (Banna et al. 2010; Feltenstein and See 2006; Le et al. 2005; See and Waters 2010; Shepard et al. 2004), and cocaine seeking in monkeys (Lee et al. 2004). Yohimbine also potently reinstates palatable food seeking in rats (Ghitza et al. 2006; Ghitza et al. 2007; Nair et al. 2009; Nair et al. 2011). Surprisingly, however, the evidence that yohimbine-induced reinstatement of drug seeking is mediated by central noradrenergic systems is mixed. The alpha-2 adrenoceptor agonists clonidine and guanfacine attenuate yohimbine-induced reinstatement of alcohol seeking in rats (Le et al. 2009; Lê et al. 2011) and cocaine seeking in monkeys (Lee et al. 2004). In contrast, clonidine has no effect on yohimbine-induced reinstatement of cocaine seeking in rats (Brown et al. 2009) or yohimbine-induced reinstatement of CPP in mice (Mantsch et al. 2010). Additionally, in rats, 6-hydroxydopamine lesions of the ventral or dorsal noradrenergic bundles have no effect on yohimbine-induced reinstatement of alcohol seeking (Le et al. 2009). Furthermore, yohimbine's effect on reinstatement of alcohol seeking is not mimicked by RS79948, a selective alpha-2 adrenoceptor antagonist (Le et al. 2009). In contrast, in monkeys, yohimbine's effect on reinstatement is mimicked by RS79948 (Lee et al. 2004), and in mice this effect of yohimbine is mimicked by another selective alpha-2 adrenoceptor antagonist, BRL44408 (Mantsch et al. 2010). Mantsch et al. (2010) also reported that yohimbine-induced reinstatement of cocaine CPP in mice is attenuated by the beta adrenoceptor antagonist propranolol. Finally, Lê et al. (2011) recently reported that the alpha-1 adrenoceptor antagonist prazosin blocks yohimbine-induced reinstatement of alcohol seeking; prazosin also blocks intermittent footshock-induced reinstatement. A tentative conclusion from the above studies is that both adrenergic and non-adrenergic (possibly

serotonergic) mechanisms contribute to the potent effect of yohimbine on reinstatement of drug seeking (Le et al. 2009).

The above findings on the potent inhibitory effect of alpha-2 adrenoceptor agonists on footshock stress-induced reinstatement of drug seeking have led to several laboratory studies on the effect of these agonists on stress-induced craving and relapse in humans. The first human study on the effect of an alpha-2-adrenergic agonist (lofexidine) on stress and drug craving was conducted in opioid-dependent individuals in naltrexone treatment (Sinha et al. 2007). Naltrexone is an opiate receptor antagonist that is approved for the treatment of opioid addiction, but it is not used widely because of poor compliance and high relapse rates (Julius 1976). In rats, naltrexone has no effect on stress-induced reinstatement of heroin or alcohol seeking (Le et al. 1999; Liu and Weiss 2002; Shaham and Stewart 1996). This finding raises the possibility that high relapse rates during naltrexone treatment occur because naltrexone has no effect on stress-induced drug craving and relapse. Indeed, naltrexone-treated opioid-dependent individuals show high levels of guided imagery stress-induced drug craving, physiological arousal, and emotional distress, supporting the notion that naltrexone treatment may not be effective in decreasing stress-related drug craving (Hyman et al. 2007). In a small laboratory and clinical outcomes study, we found that daily administration of 2.4 mg of lofexidine for 4 weeks decreased the guided imagery stress-induced opiate craving, anger ratings, and basal heart rates, as well as improved opiate relapse outcomes in naltrexone-treated opioid-dependent individuals (Sinha et al. 2007).

In a follow-up study, we examined whether chronic 4-week administration of the alpha-2 adrenoceptor agonist guanfacine (up to 3 mg/daily dosing) would decrease guided imagery, stress, cue, and stress + cue-induced drug craving, anxiety, and physiological arousal in cocaine-dependent individuals who also use alcohol and nicotine (Fox et al. under review). Guanfacine (extended release) has been recently approved for attention deficit hyperactivity disorder in children (Sallee and Eaton 2010). Guanfacine decreased basal heart rate and blood pressure. While the placebo group reported significant increases in cocaine and nicotine craving and anxiety following drug cue-related compared with stress-related imagery, such increases were not observed in the guanfacine group. Subjects treated with guanfacine also reported lower nicotine craving, fear, and arousal following drug cue and combined stress + drug cue imagery. These preliminary findings have led to a large scale dose–response study with guanfacine in cocaine-dependent individuals who are also nicotine dependent, which is currently under way.

In another recent study, Jobes et al. (2011) assessed the effect of clonidine on stress- and cue-induced craving in cocaine users that were randomly assigned to three groups receiving clonidine 0, 0.1, or 0.2 mg orally under double-blind conditions. The stress and cue manipulations were standard auditory imagery scripts of stress-related and drug cue-related situations. Each subject received clonidine or placebo followed 3 h later by exposure to two pairs of scripts (neutral/stress and neutral/drug). Jobes et al. (2011) reported that both clonidine doses decreased stress-induced cocaine craving while only the high clonidine dose decreased cue-induced craving.

In conclusion, studies using the reinstatement model in rats and mice indicate that stress-induced activation of central noradrenaline systems mediates stress-induced reinstatement of drug seeking. These preclinical studies have led to three human laboratory studies that demonstrated that alpha-2 adrenoceptor agonists (clonidine, lofexidine, and guanfacine), which decrease brain nor-adrenaline cell firing and release, decreased stress-induced drug craving in drug addicts. A question for future research is whether chronic treatment with alpha-2 adrenoceptor agonists would also prevent stress-induced relapse in the addict's environment. Ongoing studies at both Yale and National Institute on Drug Abuse (NIDA)

intramural research program will provide an answer to this question in the near future. Finally, a surprising dissociation has emerged between the rat reinstatement studies and the human laboratory studies. In the rat studies, the alpha-2 adrenoceptor agonists selectively decreased footshock stress-induced reinstatement of drug seeking but not cue or drug priming-induced reinstatement (Erb et al. 2000; Highfield et al. 2001). In contrast, in the human studies, the alpha-2 adrenoceptor agonists consistently decreased cue-induced drug craving (Fox et al. under review; Jobes et al. 2011; Sinha et al. 2007). A possible reason for these different findings is that in the rat, cue exposure likely primarily causes an appetitive motivational state with little or no stress component (Feltenstein and See 2006; See 2005). In contrast, in the human, laboratory cue exposure primarily induces an alpha-2 adrenoceptor agonist sensitive stress-like physiological (e.g., increased cortisol and heart rate) and psychological (e.g., increased subjective ratings of anxiety, anger, and irritability) states that are very similar to those induced by exposure to stressors like guided imagery stress or the Trier Social Stress Test (Back et al. 2010; Sinha et al. 1999; Sinha et al. 2000).

Role of NK1 receptors in stress-induced reinstatement in non-humans and stress-induced craving in humans

Substance P (SP) is an 11 amino acid peptide originally isolated from intestinal extracts in 1931 (Euler and Gaddum 1931); this peptide is known to be involved in pain transmission (Payan 1989). SP and its preferred NK1 receptors are expressed in brain areas involved in stress responses, including the hypothalamus and amygdala (Mantyh et al. 1984; Nakaya et al. 1994). Central injection of SP or related peptide agonists is anxiogenic in the elevated plus maze (Teixeira et al. 1996) and causes conditioned place aversion (Elliott 1988). The release of endogenous SP is similarly linked to enhanced stress responses (Ebner et al. 2004; Ebner et al. 2008; Ebner and Singewald 2007). Conversely, NK1 receptor antagonism or genetic deletion of the receptor causes anxiolytic-and antidepressant-like effects in animal models of anxiety and depression (Ballard et al. 2001; File 1997; Kramer et al. 1998b; Papp et al. 2000; Rupniak et al. 2000; Rupniak et al. 2001; Santarelli et al. 2001; Teixeira et al. 1996; Varty et al. 2002).

George et al. (2008) observed that mice with a genetic deletion of the gene encoding the NK1 receptor showed decreased intake of home–cage alcohol drinking after prolonged access to the drug and progressive increases of alcohol concentrations. This finding and the previously established role of the SP–NK1 system in stress responses described above led these investigators to assess the effect of the NK1 receptor antagonist LY686017 (50 mg per day over 3 weeks) on several outcome measures in recently detoxified anxious alcohol dependent subjects. These included alcohol craving and physiological responses after combined exposure to alcohol-related cues (Monti et al. 1993) + the Trier Social Stress task (Kirschbaum et al. 1993). LY686017 suppressed spontaneous alcohol cravings and had a beneficial effect on global measures of well-being in the absence of effects on general psychopathology. LY686017 treatment also reduced both the subjective craving response to the combined cue + stress challenge and the concomitant cortisol response (George et al. 2008).

Additionally, George et al. (2008) used functional magnetic resonance imaging (fMRI) to study the effect of LY686017 treatment on brain responses to standardized affective stimuli from the International Affective Picture System (IAPS) (Lang et al. 1995). Subjects treated with LY686017 showed less brain activation in response to the negative images than the placebo group in several regions associated with emotional response to visual stimuli, including the insula, a part of the brain recently implicated in drug craving and relapse in humans (Naqvi and Bechara 2009; Naqvi et al. 2007). Surprisingly, the LY686017-treated group also showed greater brain activation in the nucleus accumbens and anterior cingulate

cortex in response to positive IAPS images than the placebo-treated group, normalizing the deficit in brain responses to positive affective stimuli otherwise found in alcoholics (George et al. 2008). Together, the attenuation of responses to negative affective stimuli and the restoration of responses to positive affective stimuli may reflect an overall shift in the balance between positive and negative emotionality reflected in the subjective improvement detected by the clinical ratings.

The human data by George et al. (2008) on the effect of the NK1 receptor antagonist LY686017 on stress-induced craving and negative affective states inspired us to perform a reverse translational study to determine the role of NK1 receptors in stress-induced reinstatement of alcohol seeking (Schank et al. 2011). In this study, we used a different NK1 receptor antagonist (L822429) that was synthesized to bind with high affinity to the rat NK1 receptor (Ebner et al. 2004; Singewald et al. 2008). We found that systemic injections of L822429 block footshock stress-induced reinstatement of alcohol seeking.

In summary, NK1 receptor antagonism has emerged as a candidate treatment mechanism in alcoholism and illustrates the feasibility of bidirectional translation in developing novel pharmacological treatments for alcohol and drug addiction. A word of caution, however, is that NK1 receptor antagonists were previously assessed for the treatment of depression with mixed results (Ebner and Singewald 2006). While results from some studies were promising (Kramer et al. 1998a; Kramer et al. 2004), results from others were not (Keller et al. 2006). As discussed by Ebner and Singewald (2006), patient selection may be an important factor for these mixed results because it is currently unknown which subpopulation/s of depressed patients may benefit from NK1 receptor antagonist treatment. For example, this treatment may be more suitable for depressed patients with comorbid anxiety, because the administration of an NK1 receptor antagonist decreases social phobia symptoms during a stressful public speaking task (Furmark et al. 2005). We predict that similar mixed results will be obtained in clinical trials with heterogeneous populations of drug addicts in which an unknown proportion of the subjects is prone to stress-induced relapse. On the other hand, more favorable results with NK1 receptor antagonists may be obtained if these drugs are used to treat a subset of drug addicts who are highly anxious and prone to stress-induced relapse.

Brain mechanisms of stress-induced reinstatement in rats and stress-induced craving in humans

Results from neuroanatomical studies have identified brain sites and anatomical projections that are critical for foot-shock stress-induced reinstatement of drug seeking (Kalivas and McFarland 2003; Shaham et al. 2000a; Shalev et al. 2010). An early neuroanatomical model was proposed by Erb et al. (2001b) in which footshock causes initial activation of lateral tegmental (but not locus coeruleus) noradrenergic neurons (Shaham et al. 2000b), which in turn activate CRF projection neurons from the central nucleus of the amygdala to the bed nucleus of stria terminalis (BNST) as well as local CRF interneurons in the BNST (Erb et al. 2001a; Erb and Stewart 1999). Subsequently, CRF-induced activation of excitatory projection neurons from BNST (which possibly contain CRF as a neurotransmitter or cotransmitter) that act in distal brain areas [including dopamine or non-dopamine ventral tegmental area (VTA) neurons] to initiate appetitive approach behaviors that lead to reinstatement of drug seeking.

Neuropharmacological support for this model is provided by the finding that blockade of postsynaptic adrenoceptor antagonists or stimulation of alpha-2 adrenoceptors in BNST or central amygdala decrease footshock stress-induced reinstatement of drug seeking or drug preference (Leri et al. 2002; Wang et al. 2001; Yamada and Bruijnzeel 2011). Anatomical

support for this model comes from the identification of glutamate and CRF projection neurons from BNST to VTA (Georges and Aston-Jones 2001; 2002; Rodaros et al. 2007). Potential functional support for the model is provided by the discovery that in the VTA, both CRF and glutamate transmission are critical for footshock-induced reinstatement of cocaine seeking (Wang et al. 2005; Wang et al. 2007). Results from other studies suggest that the neuroanatomical model should be expanded to include the dopaminergic projection from the VTA to dorsal medial prefrontal cortex (mPFC), which interacts with glutamatergic projections from the dorsal mPFC to the nucleus accumbens (Capriles et al. 2003; McFarland et al. 2004; Sanchez et al. 2003; Xi et al. 2004). Results from a comprehensive study, in which discrete brain areas were reversibly inactivated by a mixture of gamma-amino-butyric acid (GABA)a and GABAb agonists, confirm the findings discussed above on the role of the dorsal mPFC, BNST, central amygdala, accumbens, and VTA in foot-shock stress-induced reinstatement, and further indicate that the ventral pallidum plays a role in this reinstatement (McFarland et al. 2004). Finally, the results from two recent studies indicate that BNST neurons of unknown origin and dopamine in the dorsal mPFC play a role in yohimbine-induced reinstatement (Buffalari and See 2011; Nair et al. 2011).

Several recent studies have examined the effect of guided imagery stress, which causes cocaine craving, as well as other stressors (e.g., mental arithmetic subtraction task) on brain activation in humans. These studies demonstrate that with these psychological stressors, healthy individuals show increased medial prefrontal and anterior and posterior cingulate activation along with insula, dorso-medial thalamus, midbrain regions, including the VTA and periaqueductal gray, and in some cases hippocampus and striatal activation (Dedovic et al. 2009; Goldstein et al. 2010; Seo et al. 2011; Sinha et al. 2004; Soufer et al. 1998). On the other hand, there is evidence that with chronic stress, there is a decrease in prefrontal activity during an attention-shifting task (Liston et al. 2009), suggesting that there is an adverse impact of chronic stress on prefrontal regulatory function during stressful and cognitive challenge states (Seo and Sinha 2011).

To apply this research to guided imagery stress-induced drug craving in drug users, brain activation during stress and neutral imagery was examined in an fMRI study. During stress exposure, cocaine users showed decreased activity in the anterior cingulate cortex, hippocampus and parahippo-campus, and insula regions (Sinha et al. 2005). On the other hand, the cocaine users showed increased activity in the caudate and dorsal striatum region during stress and this activation was associated with stress-induced cocaine craving ratings. Thus, guided imagery stress-induced craving is associated with greater activity in the striatum, but decreased activity in the prefrontal cortex and insula.

In the recent study on the effect of guanfacine in cocaine-dependent individuals described above (Fox et al. under review), we also tested patients in an fMRI session to assess guanfacine's effects on stress-induced brain activation. During guided imagery stress exposure, guanfacine in contrast to placebo treatment increased brain activation in the ventromedial and dorsolateral prefrontal cortex and the insula, while also increasing ventrolateral prefrontal and anterior cingulate activation during drug cue imagery exposure. These data suggest that guanfacine's positive effects may include reversing the previously documented hypofrontality and insula deficits in drug addicts (Goldstein and Volkow 2002; Naqvi and Bechara 2009).

The literature reviewed above may lead to the counterintuitive conclusion that dissociable neuronal mechanisms mediate stress-induced reinstatement of drug seeking in rats and stress-induced craving in humans. Specifically, in rats, footshock stress exposure activates glutamatergic projection neurons in dorsal mPFC (dorsal prelimbic area and cingulate area) and pharmacological inhibition of dorsal mPFC prevents footshock stress-induced

reinstatement of cocaine seeking (Capriles et al. 2003; McFarland et al. 2004). In contrast, in humans, guided imagery stress exposure that induces cocaine craving causes decreased neuronal activity in the anterior cingulate cortex as assessed by BOLD fMRI signal (Sinha et al. 2005). This neuroanatomical dissociation is particularly surprising because as mentioned above, studies using systemic injections of alpha-2 adrenoceptor agonists and NK1 receptor antagonists suggest substantial overlap between the neuronal mechanisms of stress-induced reinstatement in non-humans and stress-induced craving in humans.

At present, we can only speculate on potential reasons for the findings that stress-induced mPFC activation in cocaine-experienced rats and stress-induced mPFC hypo-activation in human cocaine users. One such speculation relates to the nature of the cortical BOLD fMRI signal, which primarily reflects activity of input and local neurons rather than spiking output of projection neurons (Logothetis et al. 2001). Thus, it is often difficult to predict from local BOLD fMRI signal the nature of the activity of output projection neurons. In this regard, the cingulate cortex hypoactivity in cocaine users might reflect decreased local intracortical processing that results in disinhibition of glutamatergic projection neurons. The decreased activity of GABAergic interneurons might be invoked to account for these observations, but this notion is highly speculative, because cortical energy utilization, which correlates with synaptic transmission, is primarily due to glutamatergic neuronal activity (Pan et al. 2000; Sibson et al. 1998). However, the observation that the decreased BOLD fMRI signal in response to stress in cocaine users was associated with a parallel increase in BOLD fMRI signal in the dorsal striatum (Sinha et al. 2005), a major glutamatergic (excitatory) projection area of the cingulate cortex (Voorn et al. 2004), is potentially consistent with our speculation.

Finally, two other factors may contribute to the differential brain response to stress-induced brain activation in cocaine-experienced rats during reinstatement tests and human cocaine users exposed to a craving–inducing stress manipulation. The first is the type of stressor: intermittent footshock in the rat and guided imagery stress in humans. It is well established that even within species, different stressors induce different patterns of brain activation (Sawchenko et al. 2000; Van Loon et al. 1989). The second is the baseline level of stress, which may interact with the individual's response to stress. Here, it is reasonable to speculate that in the rat, baseline stress levels are very low because they are well habituated to the experimental procedures and the self-administration chambers before footshock exposure during the reinstatement tests. In contrast, for human cocaine users, basal stress levels are likely very high in a novel laboratory environment and novel fMRI magnet procedure that can make subjects quite apprehensive.

Conclusions and future directions

The notion that stress makes people initiate or resume drug use is intuitively appealing to patients, clinicians, and the lay public alike. Yet, clinical observations suffer from major limitations, making it difficult to establish a causal relationship between stress and drug relapse. This is because retrospective recall is biased, and relapse episodes are often associated with the stress related to the resumption of drug use during abstinence (Hall et al. 1990; O'Doherty and Davies 1987). Recently, major advances have been made in parsing out prospective versus retrospective correlative associations between stress and relapse through the use of the EMA methodology (Epstein et al. 2009b; Shiffman and Waters 2004). Another major advance in this line of research is that the magnitude of stress-induced craving in the laboratory can predict both drug relapse in the laboratory (McKee et al. 2011) and future relapse risk in the drug user's environment (Back et al. 2010; Sinha et al. 2006; Sinha et al. 2011a, b). This finding and recent EMA results on the close temporal relationship between stress-induced drug craving and stress-induced drug relapse (Preston

and Epstein 2011) suggest that measures of stress-induced craving can serve as relapse-predictive factor, and that its reduction can offer both a surrogate marker for medication development as well as an objective of novel treatments in its own right.

A future direction of major importance will be to further establish whether results from studies in which stress reinstates drug seeking in mice, rats, and monkeys "translate" to the human condition. The finding that alpha-2 adrenoceptor agonists and NK1 receptor antagonists decrease stress-induced reinstatement in rats and decrease stress-induced craving in humans is encouraging. However, a critical missing piece concerning the "translational" value of these findings is whether alpha-2 adrenoceptor agonists and NK1 receptor antagonists would prevent stress-induced drug relapse in the drug user's environment. Results from clinical studies currently conducted at Yale University and the NIDA–IRP in which the effects of alpha-2 adrenoceptor agonists on drug relapse are being assessed will provide this missing piece.

Another promising future research direction is the assessment of the effect of small molecule CRF1 receptor antagonists, which passed phase I toxicity screening and can be given to humans (Zorrilla and Koob 2010), on stress-induced craving and relapse in drug addicts. Data from these studies will be informative on the utility of translational research based on the reinstatement model as well as other preclinical addiction models. This is because multiple studies have shown that blockade of CRF receptors decreases both footshock-induced reinstatement (Bruijnzeel et al. 2009; Erb et al. 1998; Gehlert et al. 2007; Le et al. 2000; Shaham et al. 1997) and yohimbine-induced reinstatement (Marinelli et al. 2007) of drug seeking. Additionally, extended access to cocaine and alcohol upregulates the expression levels of CRF and CRF1 receptors in the amygdala (Sommer et al. 2008; Zorrilla et al. 2001), and CRF1 receptor antagonists decrease alcohol dependence induced increases in alcohol consumption (Funk et al. 2007; Gehlert et al. 2007; Heilig and Koob 2007), as well as escalation of heroin, cocaine, or nicotine self-administration in rats given extended access to these drugs (George et al. 2007; Greenwell et al. 2009; Specio et al. 2008).

An important future research direction that is only in its infancy is the understanding of individual differences in medication response. Genetic as well as experiential factors are likely to be the determinants of treatment response for drugs targeting the stress mechanisms reviewed here. For example, in both laboratory animals and humans, some individuals may be more sensitive to CRF blockade as a means of preventing stress-induced relapse or excessive alcohol and drug intake than others. This may be related to genetic factors, as suggested by human (Blomeyer et al. 2008; Nelson et al. 2010; Treutlein et al. 2006), rat (Hansson et al. 2006), and non-human primate (Barr et al. 2009) studies. Unless these individual differences are understood, treatment studies targeting unselected patient populations may dilute any effects and fail, leading to discontinuations of development efforts with treatments that would have the potential to be successful in the right patient population. Assessing the drug user's vulnerability to stress may be particularly important in future studies assessing the effect of CRF1 receptor antagonists on drug craving and relapse, because these compounds failed in double-blind phase II clinical trials of depression using non-selected patient populations (Binneman et al. 2008).

Another important future issue from the perspective of translational research is concerned with medication effects in males versus females. In this regard, there is evidence from many non-humans studies for sex differences as well as a role of ovarian hormones in reinstatement of drug seeking induced by cues or drug priming (Becker and Hu 2008; Carroll et al. 2004; Kippin et al. 2005; Lynch 2006) and stress responses (Bale 2006; Becker et al. 2007; Shors 2006). However, with the exception of the first publication on stress-induced reinstatement of drug (heroin) seeking that included both male and female rats

(Shaham and Stewart 1995) and a very recent report (Feltenstein et al. 2011), to our knowledge, preclinical research on the mechanisms of stress-induced reinstatement has primarily been performed in male rats. Additionally, while there is evidence for gender differences in physiological and psychological responses to stress in drug addicts (Fox et al. 2009; Fox and Sinha 2009), systematic studies on the effect of potential medications on stress-induced craving and relapse in males and females are yet to be conducted.

In summary, we reviewed data that support the notion that the frequently observed association between stress and relapse in patients with addictive disorders is causal rather than correlational. We further reviewed evidence that despite the numerous differences between the experimental conditions used to assess stress-induced reinstatement of drug seeking in non-humans and stress-induced craving in humans, there is a good concordance between the pharmacological agents that decrease stress effects across species. We conclude with a word of caution that in all likelihood, stress-related medication will not be effective in preventing relapse in all patients; however, the translational research reviewed here suggests potential pharmacological targets that may have considerable potential in selected stress vulnerable patient populations whose drug use and relapse is driven by stress.

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Table 1

Glossary of terminology

Reinstatement: In the learning literature, reinstatement refers to the recovery of a learned response (e.g., lever-pressing behavior) that occurs when a subject is exposed non-contingently to the unconditioned stimulus (e.g., food) after extinction (Bouton and Swartzentruber 1991). In studies of reinstatement of drug seeking, reinstatement typically refers to the resumption of drug seeking after extinction following exposure to drugs, drug cues, or stressors (Shaham et al. 2003)
Relapse (to drug use): A term used to describe the resumption of drug-taking behavior during periods of self-imposed or forced abstinence in humans (Wikler 1973)
Stress: A complex psychological construct that, despite many years of research (Cannon 1935; Selye 1956), has yet to be adequately operationally defined (Chrousos and Gold 1992; Cohen et al. 1982). In the context of animal models of psychiatric disorders, stress can be defined broadly as forced exposure to events or conditions that are normally avoided (Piazza and Le Moal 1998). In humans, the definition may be extended to incorporate cognitive and emotional responses—for example, “stress is a condition in which the environmental demands exceed the coping abilities of the individual” (Cohen et al. 1986). In non-humans, the precipitating events or conditions can be divided into two categories (Lu et al. 2003). The first category includes environmental events such as restraint, footshock, tail pinch, and defeat, as well as pharmacological events such as administration of a normally avoided drug (e.g., yohimbine, CRF). The second category includes food deprivation, social isolation, and maternal deprivation; each of these entails the removal of an environmental condition that is important for maintaining the animal’s normal physiological and psychological steady-state conditions, a state that the subject will attempt to ameliorate by seeking food, conspecific partners, or the dam
Translational (research): According to an NIH definition, translational research refers to the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease (http://grants.nih.gov/grants/guide/pa-files/PAR-05-158.html). In the context of the present review, translational research refers to the assessment of whether neuropharmacological findings from studies on stress-induced reinstatement in non-humans generalize (or translate) to the human condition as assessed in laboratory studies on stress-induced craving and stress-induced drug relapse in the drug user environment
Reverse-translational (research): There is no formal definition of this relatively novel concept in the psychiatry field (Perry et al. 2009). In the context of the present review, this concept refers to the assessment of whether neuropharmacological findings from studies on stress-induced craving in humans can provide new insight (or reverse-translated) on the mechanisms of stress-induced reinstatement of drug seeking in the non- human model

Table 2

Alpha-2 adrenoceptor agonists that decrease footshock-stress-induced reinstatement of drug seeking or footshock-induced reinstatement of drug CPP in non-humans and stress-induced or stress + cue-induced craving in humans

Alpha-2 adrenoceptor agonist	Non-human studies	Human studies
Clonidine	Heroin (Shaham et al. 2000b) Morphine (Wang et al. 2001) Cocaine (Erb et al. 2000; Mantsch et al. 2010) Nicotine (Zislis et al. 2007)	Cocaine users (Jobes et al. 2011)
Lofexidine	Cocaine (Erb et al. 2000) Alcohol (Le et al. 2005) Speedball (Highfield et al. 2001)	Opiate users (Sinha et al. 2007)
Guanfacine	Alcohol (Lê et al. 2011)	Cocaine users (Fox et al. under review)
Guanabenz	Cocaine (Erb et al. 2000)	