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Norepinephrine and Stimulant Addiction

Mehmet Sofuoglu and R. Andrew Sewell

Yale University, School of Medicine, Department of Psychiatry and VA Connecticut, Healthcare System, West Haven, CT 06516, USA

Abstract

No pharmacotherapies are approved for stimulant use disorders, which are an important public health problem. Stimulants increase synaptic levels of the monoamines dopamine (DA), serotonin (5-HT), and norepinephrine (NE). Stimulant reward is attributable mostly to increased DA in the reward circuitry, although DA stimulation alone cannot explain the rewarding effects of stimulants. The noradrenergic system, which uses NE as the main chemical messenger, serves multiple brain functions including arousal, attention, mood, learning, memory, and stress response. In preclinical models of addiction, NE is critically involved in mediating stimulant effects including sensitization, drug discrimination, and reinstatement of drug seeking. In clinical studies, adrenergic blockers have shown promise as treatments for cocaine abuse and dependence, especially in patients experiencing severe withdrawal symptoms. Disulfiram, which blocks NE synthesis, increased the number of cocaine-negative urines in five randomized clinical trials. Lofexidine, an α_2 -adrenergic agonist, reduces the craving induced by stress and drug cues in drug users. In addition, the norepinephrine transporter (NET) inhibitor atomoxetine attenuates some of d-amphetamine's subjective and physiological effects in humans. These findings warrant further studies evaluating noradrenergic medications as treatments for stimulant addiction.

Keywords

norepinephrine; Cocaine; amphetamine; adrenergic; methamphetamine; pharmacotherapy; clinical trials

INTRODUCTION

Although an estimated 2.9 million Americans aged 12 or older regularly use stimulants, cocaine, or methamphetamine (SAMHSA, 2004), there are no proven pharmacotherapies for the treatment of stimulant addiction. The consequences of stimulant use are significant and include an increased risk of HIV and hepatitis C infection, detrimental effects on the unborn and newborn, increased crime and imprisonment, and other medical, financial, and psychosocial problems (Schempf, 2007; Stein, 1999; Tyndall et al., 2003). Thus, development of an effective treatment for stimulant addiction would provide significant benefits both for society and individual patients.

The noradrenergic system, which uses norepinephrine (NE) as its main chemical messenger, consists of both central noradrenergic and peripheral sympathetic pathways, serving multiple brain functions including arousal, attention, mood, learning, memory, and the stress response (Huether, 1996; Sved et al., 2001). Although the contribution of NE in mediating reward has been recognized for forty years (Poschel and Ninteman, 1963; Stein, 1964, 1975; Wise,

1978), NE received little attention as a potential treatment target for stimulant addiction. Over the past 2 decades, parallel to better characterization of the anatomical and functional complexity of the noradrenergic system, new medications targeting NE via different mechanisms became available (Ordway et al., 2007). These advances spurred renewed interest in the noradrenergic system as a target for medication development for stimulant addiction (Aston-Jones and Harris, 2004; Stewart, 2000; Weinshenker and Schroeder, 2007), and recently clinical trials have started to evaluate noradrenergic medications as treatments for stimulant addiction (Kampman et al., 2006; Kampman et al., 2001; Sofuoglu et al., 2000a). In this paper, we will briefly describe the noradrenergic system, discuss the contributions of DA and NE to the neurobiology of stimulants, then summarize preclinical and clinical studies that have evaluated the noradrenergic system as a treatment target for stimulant addiction. A more detailed reviews of NE and reward function can be found elsewhere (Ordway et al., 2007; Weinshenker and Schroeder, 2007; Wise, 1978).

A BRIEF OVERVIEW OF THE NORADRENERGIC SYSTEM

The noradrenergic (NE-containing) neurons are localized in brainstem nuclei such as the locus ceruleus (LC), but noradrenergic axons project diffusely to almost every part of the brain (Smythies, 2005). In these neurons, NE is synthesized from the amino acid tyrosine, which is supplied by the blood and extracellular fluid (Cooper et al., 2003). The first, rate-limiting step in NE synthesis is conversion of tyrosine to dopa by the enzyme tyrosine hydroxylase; the second step is conversion of dopa to dopamine (DA) by dopa decarboxylase, and the last step is conversion of DA to NE by dopamine hydroxylase (Cooper et al., 2003). A vesicular monoamine transporter (VMAT-2) carries the cytoplasmic NE into synaptic vesicles, where it is stored then released from nerve terminals into the synapse when the noradrenergic neuron fires (Cooper et al., 2003).

The activity of NE in the synapse is terminated either by rapid uptake of NE into presynaptic terminals by the norepinephrine transporter (NET) or by the monoamine oxidase (MAO-A) enzyme (Bonisch and Bruss, 2006; Dostert et al., 1989). Catechol-O-methyl transferase (COMT), another enzyme that metabolizes monoamines, contributes to NE inactivation when NE levels are high (Huotari et al., 2002).

Synaptic NE concentrations can be affected by medications that target NE synthesis or degradation. For example, MAO and COMT inhibitors, which increase synaptic monoamine levels, are used to treat many neuropsychiatric disorders (Keating and Lyseng-Williamson, 2005), and NET inhibitors have been used to treat depression. The recent availability of highly selective NET inhibitors such as reboxetine and atomoxetine have stimulated new interest in the function of NET in neuropsychiatric disorders (Bonisch and Bruss, 2006).

Adrenergic receptors

NE's effects are mediated by three families of adrenergic receptors: α_1 , α_2 , and β (Bylund et al., 1994). The α_1 -adrenergic family is mostly postsynaptic and excitatory. Alpha₁-adrenergic receptors are coupled to phospholipase C and phosphoinositol secondary messengers through G_q proteins; they mediate contraction of vascular smooth muscle, and can therefore increase blood pressure. In the CNS, α_1 receptors are found in both neurons and glial cells and are involved in motor control, learning, memory, and fear (Tanoue et al., 2003). Prazosin, an α_1 -adrenergic blocker, is used to treat high blood pressure and has also shown promise as a treatment for post-traumatic stress disorder (Raskind et al., 2000).

The α_2 -adrenergic family includes the α_{2A} , α_{2B} , and α_{2C} subtypes, which are located both pre- and post-synaptically (Bylund et al., 1994). Alpha₂-adrenergic receptors are coupled through G_{i/o} proteins to the second messenger adenylate cyclase, which changes the concentration of

cyclic adenosine monophosphate (cAMP). Alpha_{2A} receptors are associated with diverse effects, including analgesia, hypothermia, sedation, and control of noradrenergic activity (Crassous et al., 2007). Alpha_{2B} receptors mediate vascular contraction. While the role of α_{2C} receptors is poorly understood, they may play a role in motor behavior, mood, and memory processes (Starke, 2001). Alpha₂ agonists such as clonidine, guanfacine, and lofexidine are used in diverse conditions including hypertension, opioid withdrawal, and attention-deficit hyperactivity disorder (ADHD)(Posey and McDougale, 2007; Raistrick et al., 2005).

Beta-adrenergic receptors include the β_1 , β_2 , and β_3 subtypes (Bylund et al., 1994), and are coupled via G_s to adenylate cyclase. Stimulation of β_1 -adrenergic receptors increases heart rate and cardiac contractility. Stimulation of β_2 -adrenergic receptors, which are located in smooth muscle, causes vasodilatation and bronchial relaxation. These receptor subtypes are also found in the brain, but their functions there are less well-defined (Ramos and Arnsten, 2007). Medications that block the β -adrenergic receptors are commonly used for a wide variety of conditions including hypertension, ischemic heart disease, migraine, and performance anxiety (Limmroth and Michel, 2001; Ong, 2007).

NEUROBIOLOGY OF STIMULANTS

Cocaine and amphetamines are powerful CNS stimulants that cause euphoria, heightened alertness, increased energy, and intensified emotions. These effects are mediated by increased synaptic concentrations of monoamines—DA, 5-HT, and NE (Bardo, 1998; White and Kalivas, 1998). The interaction of stimulants with the DA system has been better studied than their effects on NE and 5-HT. The rewarding and powerfully addictive effects of stimulants are attributed to their capacity to increase DA levels in the nucleus accumbens (NAc), an essential component of the mesocorticolimbic dopaminergic pathway (Koob, 1992; Tzschentke and Schmidt, 2000). This pathway, which originates from the ventral tegmental area (VTA) of the mid-brain, targets a number of limbic and cortical structures, including the NAc, amygdala and prefrontal cortex, and plays a critical role in stimulant reward (Tzschentke and Schmidt, 2000).

Stimulants increase monoamine levels through several different mechanisms. Cocaine mainly binds to monoamine transporters, which are located in presynaptic terminals, preventing binding of monoamines to the transporter and leading to increased synaptic concentrations of DA, NE, and 5-HT (Piffl et al., 1995; White and Kalivas, 1998). The relative affinities of cocaine and amphetamines for different monoamine transporters differ. For example, while cocaine has a similar affinity for transporters of all three monoamines (Han and Gu, 2006), amphetamines have negligible binding to the serotonin transporter (SERT)(Rothman and Baumann, 2003), and are five to nine times more potent at the NET than at the dopamine transporter (DAT). Amphetamines also disrupt storage of monoamines in synaptic vesicles by interacting with VMAT-2 (Partilla et al., 2006; Sulzer and Rayport, 1990), causing the release of vesicular contents into the neuronal cytoplasm. This increased intracellular DA, when converted into reactive oxygen species, may be the cause of the neurotoxicity that is frequently associated with methamphetamine use and less so with cocaine use (Giovanni et al., 1995; Larsen et al., 2002; Miyazaki et al., 2006). The subjective effects of amphetamines in humans seem to be correlated with their capacity to release NE rather than DA (Rothman et al., 2001), suggesting that NE contributes more to the subjective effects of amphetamine than it does to those of cocaine. As we shall discuss, this differential contribution of NE and DA to stimulant effects may have implications for medication development.

NE AND DA INTERACTIONS

While DAT inhibition and the resultant synaptic DA increase plays a crucial role in mediating stimulant reward, stimulant effects on the DAT alone do not explain the full range of addictive

processes. Even DAT- knockout mice continue to experience DA release in the reward circuit in response to stimulants and consequently still self-administer cocaine (Carboni et al., 2001; Rocha et al., 1998). In contrast, α_{1b} -adrenergic receptor-knockout mice do not show behavioral sensitization to d-amphetamine as expected (Drouin et al., 2002), nor increased DA release in the NAc (Auclair et al., 2002). This suggests that NE contributes to stimulant effects independently of the DAT.

Many regions of the mesolimbic DA system, including the NAc, VTA, amygdala, and the bed nucleus of stria terminalis receive noradrenergic input (Alheid and Heimer, 1988; Liprando et al., 2004; Ungerstedt, 1971). Lesioning of noradrenergic neurons in the LC decreases DA release in the NAc (Grenhoff et al., 1993) and conversely, activation of the LC's noradrenergic neurons increases the activity of dopaminergic neurons in the VTA (Lategan et al., 1990). This regulation is mediated by the α_1 -adrenergic receptor subtype. Stimulation of the α_1 -adrenergic receptors on the VTA dopaminergic neurons increases firing rate of these neurons (Paladini and Williams, 2004). Similarly, stimulation of α_1 -adrenergic receptors in the prefrontal cortex increases the activity of dopaminergic neurons in the VTA (Blanc et al., 1994). These studies suggest a close functional connection between DA and NE in the brain.

The dopaminergic and noradrenergic systems also interact at the transporter level. While the monoamine transporters have substrate specificity, there is also a significant overlap between their function. For example, the NET shows equal affinity for NE and DA and depending on DAT distribution, NET may contribute to DA reuptake, a characteristic more prominent in the prefrontal cortex than the striatum or NAc (Carboni et al., 1990). In the prefrontal cortex, where DAT is scarce, the NET binds to both DA and NE. Inhibition of the NET increases the concentration of both DA and NE, further supporting a functional coupling between the DA and NE systems (Wee and Woolverton, 2004).

NE AND STIMULANT ADDICTION-PRECLINICAL STUDIES

In this section, we will briefly summarize studies that evaluate noradrenergic compounds in preclinical models of addiction. More comprehensive reviews on this topic can be found elsewhere (Shaham et al., 2000; Weinshenker and Schroeder, 2007).

Stimulant-induced behavioral sensitization and psychomotor activation

Sensitization is defined as increased locomotor activity and stereotyped behavior in response to repeated administration of a drug, and is a characteristic of stimulants. It has been suggested that sensitization contributes to both initiation and maintenance of drug addiction (Robinson and Berridge, 2001). Many studies have shown that NE is critically involved in stimulant sensitization. For example, mice lacking the α_{1b} -adrenergic receptor do not develop sensitization (Drouin et al., 2002), which can also be prevented by lesioning noradrenergic neurons in the LC or depleting NE centrally (Archer et al., 1986; Kostowski et al., 1982; Mohammed et al., 1986). In a recent study, the psychomotor stimulant effect of d-amphetamine, but not that of cocaine, was dose-dependently inhibited by the α_2 -adrenergic agonist clonidine and α_1 -adrenergic agonist prazosin (Vanderschuren et al., 2003). These findings suggest that NE may be a crucial component in amphetamine-induced sensitization.

Discriminative stimulus

The subjective effect of drugs in humans can be modeled in animals through the use of *discriminative stimuli*. Animals can be trained to provide different responses to different drugs, presumably by identifying the drugs' different subjective effects, so two drugs that provoke the same response in an animal so trained can be presumed to cause a similar subjective effect in humans. NET inhibitors partially mimic the discriminative effects of amphetamines and

cocaine in pigeons, rats, mice, and monkeys (Evans and Johanson, 1987; Kamien and Woolverton, 1989). Both the discriminative stimulus effects of cocaine and the cocaine-like effects of NET are blocked with α_1 -adrenergic blockers (Johanson and Barrett, 1993; Spealman, 1995).

Stimulant Self-Administration

In animals trained to self-administer cocaine, lesioning of the noradrenergic neurons does not alter cocaine self-administration (Roberts et al., 1977). In pharmacological studies, NET inhibitors have not altered the maintenance of cocaine self-administration (Wee et al., 2006; Wee and Woolverton, 2004; Woolverton, 1987). Similarly, adrenergic blockers have not consistently reduced cocaine self-administration (Yokel and Wise, 1978).

Reinstatement

Reinstatement procedure, an animal model for relapse, measures the role of priming doses of drugs or stress in drug-seeking behavior (Shaham et al., 2000; Shalev et al., 2000; Stewart, 2000). In this model, an animal is trained to self-administer a drug, and then the behavior is extinguished through non-reinforcement. A new stimulus is then presented, and the stimulus is said to cause reinstatement if the animal demonstrates renewed drug self-administration without any further response-contingent drug reward. Many studies implicate the noradrenergic system in mediating stress-induced reinstatement. For example, both clonidine and lofexidine, medications which inhibit the adrenergic activity by stimulating α_2 receptors, attenuate stress-induced reinstatement of cocaine seeking in rats (Erb et al., 2000; Highfield et al., 2001). Conversely, α_2 -adrenergic antagonists reinstate cocaine seeking in monkeys (Lee et al., 2004). Beta-adrenergic receptors may also participate in stress-induced reinstatement since both β_1 - and β_2 -adrenergic receptor antagonists block stress-induced reinstatement in rats (Leri et al., 2002).

Initial studies suggested unitary involvement of the noradrenergic system in stress-induced but not in cocaine-induced reinstatement of cocaine seeking. However, other studies have shown that cocaine-induced reinstatement may be reduced by co-administration of prazosin in rats (Zhang and Kosten, 2005) or clonidine in monkeys (Platt et al., 2007). NET inhibitors mimic cocaine's effects by inducing cocaine-seeking behavior in monkeys (Platt et al., 2007) but not in rats (Schmidt and Pierce, 2006).

Altogether, preclinical studies suggest that while NE transmission may not be crucial in the induction of stimulant self-administration, it may mediate the subjective-rewarding effects of stimulants as well as the relapse to stimulant use precipitated by stress or by drug cues.

THE NORADRENERGIC SYSTEM AND STIMULANT EFFECTS: CLINICAL STUDIES

Clinical studies are summarized in Table 1

Dopamine β -hydroxylase inhibitors

Disulfiram—Disulfiram is approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence and has also shown promise as a treatment for cocaine addiction. Its therapeutic effect on alcohol dependence is likely mediated by the unpleasant symptoms experienced when acetaldehyde levels increase following ethanol ingestion because of disulfiram-induced aldehyde dehydrogenase inhibition (the “Antabuse reaction”) (Hughes and Cook, 1997). Disulfiram also inhibits dopamine β -hydroxylase (DBH), the enzyme that converts DA to NE (Karamanakos et al., 2001; Vaccari et al., 1996). As a result, synaptic NE

levels decrease relative to DA. This DBH inhibition has been suggested to explain disulfiram's therapeutic effects in cocaine addiction (Cubells and Zabetian, 2004).

Five randomized, controlled clinical trials have shown that disulfiram increases cocaine-free urines more than either placebo or an active comparison agent such as naltrexone (Carroll et al., 1993; Carroll et al., 2004; Carroll et al., 1998; George et al., 2000; Petrakis et al., 2000). In one 12-week study with 122 cocaine-dependent subjects who had concurrent alcohol abuse or dependence, disulfiram reduced cocaine use more than placebo (Carroll et al., 1998). Another study of 67 opioid- and cocaine-dependent subjects who were maintained on methadone, showed that disulfiram treatment reduced cocaine use in this population also (Petrakis et al., 2000). In a more recent study, Carroll and colleagues replicated their earlier findings in a cocaine-dependent sample, finding greater reduction of cocaine use with disulfiram (250 mg/day) than with placebo treatment (Carroll et al., 2004). When these studies are pooled and analyzed, the average number of cocaine-free urines in the disulfiram group is 55% compared to 40% in the comparison group, a significant difference.

Given that cocaine and alcohol are commonly used together, It is possible that the reduction in cocaine use with disulfiram is secondary to reduced alcohol intake (Pennings et al., 2002). Alcohol attenuates some of the negative effects of cocaine, and also serves as a "conditioned cue" for cocaine self-administration in those who take both, as well as combining with cocaine to form cocaethylene, which enhances and extends cocaine euphoria (McCance-Katz et al., 1998a; Pennings et al., 2002). Consequently, decreased alcohol use as a result of disulfiram treatment should be expected to lead to decreased cocaine use. However, several of these trials demonstrated that disulfiram is an effective treatment for cocaine dependence regardless of whether patients are alcohol-dependent (Carroll et al., 1998; George et al., 2000; Petrakis et al., 2000), and one found that disulfiram was more effective in decreasing cocaine use in those patients who were not alcohol-dependent than those who were, (Carroll et al., 2004) arguing for an effect of disulfiram on cocaine abuse that is independent of its effects on alcohol consumption.

Clinical studies have suggested other ways in which disulfiram may reduce cocaine use through mechanisms other than decreased alcohol consumption. While disulfiram does not affect the "high" from intranasal cocaine, it increased "nervousness" and "paranoia" from cocaine (Hameedi et al., 1995; McCance-Katz et al., 1998b). Another more recent study also found that disulfiram treatment enhanced IV-cocaine-induced anxiety, also attenuating the "high" (Baker et al., 2007). In these studies, disulfiram administration resulted in significantly higher plasma cocaine levels, likely due to the inhibition of cocaine metabolism by disulfiram and its major metabolite, diethyldithiocarbamate (Baker et al., 2007). The contradictory effects on "high" ratings were hypothesized to result from disulfiram's blockage of cocaine-induced vasoconstriction, enhancing absorption in the intranasal studies. These results suggest that disulfiram's efficacy in reducing cocaine use may be due its attenuation of the cocaine-induced euphoria and enhancement of cocaine-induced aversive subjective effects.

Although the findings with cocaine seem promising, disulfiram's efficacy for amphetamine addiction has not been examined until recently. Disulfiram enhanced both amphetamine-induced pleasurable ("high" and "drug liking") as well as unpleasant ("anxious" and "bad drug effects") subjective effects, but did not affect d-amphetamine-induced increases in heart rate or blood pressure (Sofuoglu et al., 2008b). The differences in disulfiram's effects on cocaine responses compared with amphetamine responses could be from increased cocaine serum levels caused by disulfiram, an effect that has not been examined for amphetamines. Another possibility is that disulfiram, through inhibition of the enzyme dopamine β -hydroxylase, may increase the amount of dopamine in the brain by blocking dopamine's conversion to norepinephrine and thereby increasing the amount of dopamine that amphetamine can release

(Karamanakos et al., 2001). While cocaine depends on simple reuptake blockade, the active release of dopamine from noradrenergic neurons terminating on the nucleus accumbens would likely increase amphetamine's positive and negative subjective effects, as observed. From a treatment perspective, although disulfiram might reduce amphetamine abuse by amplifying amphetamine-induced anxiety and "bad drug effects", making the experience aversive in the same way it does the experience of alcohol intoxication, it might also increase abuse potential by enhancing "high" and "craving". How these disulfiram-induced increases in both positive and negative subjective responses to amphetamine affect actual drug use remains to be determined empirically in future studies.

Nepicastat

Another DBH inhibitor is nepicastat (Hegde and Friday, 1998), which does not inhibit aldehyde dehydrogenase and therefore does not cause the "Antabuse reaction." Nepicastat has been evaluated for heart failure and may also show promise for stimulant addiction given the promising findings with disulfiram.

Adrenergic Blockers

The use of adrenergic blockers for the treatment of substance abuse has been examined in both clinical trials and human laboratory studies. In two clinical trials, a β -adrenergic blocker, propranolol, showed promise as a treatment of cocaine dependence. In an eight-week study, Kampman and colleagues reported that propranolol was equivalent to placebo in reducing cocaine use when all 108 subjects were examined. However, among the subset with a high withdrawal severity (defined as the CSSA score in the upper third of the sample), propranolol was more effective than placebo. The authors suggested that the utility of propranolol for cocaine dependence could be because it reduces adrenergic activity during early cocaine abstinence (Kampman et al., 2001). This finding was replicated by the same authors in a more recent clinical trial that tested the efficacy of amantadine, propranolol, or a combination of the two versus placebo for the treatment of cocaine dependence (Kampman et al., 2006). In their primary analysis, they found that none of the treatments was more effective than placebo in reducing cocaine use. However, in the highly adherent group, defined as those who took more than 80 % of the study medication, propranolol (100 mg/day) was more effective than placebo in improving treatment retention and reducing cocaine use.

The presence of cocaine withdrawal enhances the rating of "high" in response to cocaine administration in cocaine users, suggesting that enhanced rewarding effects of cocaine during the state of cocaine withdrawal may maintain cocaine use and increase the likelihood of relapse (Sofuoglu et al., 2003). Furthermore, cocaine-dependent users who endorse having experienced withdrawal symptoms (which can be part of, but are not necessary for, the diagnosis of cocaine dependence) have more severe drug-associated problems (such as emergency-room visits, emotional, and psychosocial problems) than those who have not experienced withdrawal symptoms (Schuckit et al., 1999; Sofuoglu et al., 2003). Since noradrenergic system activation is associated with stimulant withdrawal (Harris and Aston-Jones, 1993; Weiss et al., 2001), medications that dampen adrenergic activity, such as propranolol and other adrenergic blockers, may be especially effective in reducing both cocaine use and associated problems in those with high withdrawal severity. That being said, reduction of withdrawal symptoms may not necessarily lead to long-term abstinence; likewise, reduction in the severity of withdrawal symptoms may not fully account for the efficacy of established treatments for other drugs of abuse (Arendt et al., 2007; Ferguson et al., 2006; Hughes et al., 1994).

In a series of studies in our laboratory, we have investigated the potential utility of α - and β -adrenergic blockers for treating cocaine dependence (Sofuoglu et al., 2000a, b). We selected

labetalol and carvedilol, which block both α - and β -adrenergic receptors, because both have a better cardiovascular safety profile than propranolol (Lange et al., 1990). In our studies, acute treatment with labetalol (100 or 200 mg) or carvedilol (25 or 50 mg) dose-dependently attenuated cocaine-induced increases in both blood pressure and heart rate. Carvedilol at 25 mg also decreased cocaine self-administration, when compared to the 50 mg dose or placebo, a finding with implications for medications development. Since carvedilol was more effective than labetalol in attenuating both the physiological effects of cocaine and cocaine self-administration (Sofuoglu et al., 2000a), it was chosen as an adrenergic blocker to be tested in an ongoing clinical trial evaluating the efficacy of carvedilol for cocaine addiction. This trial is also examining whether the promising results observed in laboratory studies will lead to increased effectiveness of carvedilol for cocaine users with high withdrawal severity in an outpatient setting.

NET inhibitors

Many antidepressants, such as desipramine and nortriptyline, inhibit the NET (Deupree et al., 2007). Desipramine, a tricyclic antidepressant, has been evaluated for cocaine addiction, showing effects in initial studies (Levin and Lehman, 1991) that were not replicated in later studies (Arndt et al., 1992).

However, desipramine is nonselective; in addition to its NET-blocking effects, it also binds to adrenergic and non-adrenergic receptors, suggesting the need to study more selective NET inhibitors. Recently, two highly selective drugs, reboxetine and atomoxetine, have been introduced. Reboxetine, an antidepressant medication, was evaluated in an open label study for cocaine addiction, with promising findings (Szerman et al., 2005). However, no double-blind studies of reboxetine for stimulant addiction have been conducted, and it has not been approved in the United States.

Atomoxetine, the other selective NET inhibitor, has been approved for the treatment of ADHD (Simpson and Plosker, 2004). In recent study, Stoops and colleagues examined whether atomoxetine treatment affects subjective and physiological responses to cocaine in cocaine users. Atomoxetine treatment attenuated the systolic blood pressure increase, enhanced the heart rate increase, and did not change the subjective effects of intranasal cocaine (Stoops et al., 2008).

Recently, our laboratory examined atomoxetine's effects on the acute physiological and subjective responses to d-amphetamine in healthy volunteers (Sofuoglu et al., 2008a). Four days of atomoxetine treatment attenuated the increases in systolic and diastolic blood pressure, and cortisol induced by 20 mg/70 kg d-amphetamine compared to placebo. Atomoxetine also attenuated some of the subjective effects, including ratings of "stimulated", "good drug effects", and "high". Our findings are consistent with preclinical studies that suggest that NE contributes to acute amphetamine responses, including its subjective effects. The contrast between atomoxetine's effects on cocaine compared its effects on the amphetamine high could be due to the greater contribution of the NE system to the production of amphetamine's effects, compared with cocaine.

How does atomoxetine attenuate the subjective, physiological, and endocrine effects of d-amphetamine? As many preclinical and clinical studies indicate, NET inhibitors acutely increase NE activity. However, whereas tonic NE activity stays elevated with prolonged treatment, the noradrenergic response to pharmacological and behavioral challenges is attenuated, possibly due to increased stimulation of inhibitory α_2 -adrenergic autoreceptors as well as down-regulation of the post-synaptic noradrenergic receptors by tonic NE elevation (Szabo and Blier, 2001).

Alpha₂-adrenergic agonists

The α_2 -adrenergic agonists clonidine, lofexidine, and guanfacine inhibit noradrenergic activity by stimulating α_2 -adrenergic receptors. Alpha₂-adrenergic agonists have been evaluated for the treatment of opioid, alcohol, and nicotine withdrawal with some positive findings (Adinoff, 1994; Akhondzadeh et al., 2000; Baumgartner and Rowen, 1991; Glassman et al., 1984). Clonidine attenuates withdrawal symptoms from all three drugs (Dawe and Gray, 1995; Svensson, 1986). These findings suggest that withdrawal symptoms for drugs of abuse, irrespective of their primary mechanism of action, involve noradrenergic activation. Whether α_2 -adrenergic agonists attenuate stimulant withdrawal symptoms has not been examined.

As discussed above, in preclinical studies, the α_2 -adrenergic agonists clonidine and lofexidine attenuate stress-induced reinstatement of cocaine seeking (Erb et al., 2000; Highfield et al., 2001). These findings have important clinical implications, because many clinical studies suggest that stress is associated with relapse to drugs of abuse (Brady and Sinha, 2005; Sinha, 2001). To evaluate the efficacy of α_2 agonists in mitigating stress responses, Sinha and colleagues examined lofexidine's effects on the response to laboratory-induced stress in opioid-dependent patients maintained on methadone. For stress induction, they used guided imagery, drug cues, and neutral situations. Those who were on lofexidine had attenuated craving response to stress and drug cues (Sinha et al., 2007) compared to those taking placebo. These preliminary studies further support the potential utility of noradrenergic medications in ameliorating stress- and cue-induced drug seeking.

SUMMARY

The noradrenergic system subserves multiple brain functions including arousal, attention, mood, learning, memory, and the stress response. Cocaine and amphetamines are powerful CNS stimulants and their effects are mediated by increased synaptic concentrations of the monoamines DA, 5-HT, and NE. DA plays a crucial role in mediating stimulant reward, and studies suggest a close functional connection between DA and NE. While NE may not be crucial to stimulant self-administration, it mediates the subjective rewarding effects of stimulants as well the relapse to stimulant use that is precipitated by stress or by drug cues.

Clinical studies indicate that adrenergic blockers may be especially effective in reducing cocaine use in those with high withdrawal severity. Disulfiram, which inhibits NE production, is effective in reducing cocaine use in clinical trials, but its side effects, especially the Antabuse reaction, has limited its clinical use. Lofexidine, an α_2 -adrenergic agonist, reduces the craving induced by stress and drug cues in drug users, suggesting utility as a treatment for stimulant addiction. In addition, the norepinephrine transporter (NET) inhibitor atomoxetine attenuates some of d-amphetamine's subjective and physiological effects in humans. These findings warrant further studies evaluating noradrenergic medications as treatments for stimulant addiction

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Table 1
Clinical studies examining noradrenergic medications for stimulant addiction.

Medication	Subjects	Study Type	Results	Authors
DBH Inhibitors				
Disulfiram (250 to 500 mg) and psychotherapy	Cocaine dependent + alcohol-abusing or dependent (N=122)	Single-blind, randomized, 12-week clinical trial	Disulfiram increased treatment retention and abstinence from alcohol and cocaine	Carroll <i>et al.</i> , 1998
Disulfiram (250 mg)	Cocaine- and opioid-dependent (N=20)	Double-blind, placebo-controlled, 12-week clinical trial	Increases number of cocaine free urine and length of abstinence from cocaine	George <i>et al.</i> , 2000
Disulfiram (250 mg)	Cocaine- and opioid-dependent with and without alcohol abuse (N=67)	Double-blind, placebo-controlled, 12-week clinical trial	Decreased quantity and frequency of cocaine use	Petrakis <i>et al.</i> , 2000
Disulfiram (250 mg) ± Cognitive Behavior Therapy	Cocaine-dependent (N=121)	Double-blind, placebo-controlled, 12-week clinical trial	Both disulfiram and CBT reduced positive cocaine urine toxicologies	Carroll <i>et al.</i> , 2004
Disulfiram (62.5, 250 mg) + Cocaine (0.25, 0.5 mg/kg intravenous)	Cocaine-dependent (N=9)	Double-blind, placebo-controlled, crossover study	Attenuated subjective "high" but not cardiovascular response to cocaine	Baker <i>et al.</i> , 2007
Disulfiram (250 mg, 500 mg) + Cocaine (1, 2 mg/kg intranasal)	Cocaine dependent+ alcohol-abusing or dependent (N=7)	Double-blind, placebo-controlled, crossover study	Increased plasma cocaine levels and cocaine-induced heart rate, blood pressure increases. No effects on subjective responses	McCance-Katz <i>et al.</i> , 1998
Disulfiram (250 mg) + Cocaine (2 mg/kg, intranasal)	Cocaine dependent+ with or without alcohol abuse (N=8)	Double-blind, placebo-controlled, crossover study	Increased plasma cocaine levels. Increased rating of "nervousness" and "paranoia"	(Hameedi <i>et al.</i> , 1995)
Disulfiram (250 mg) + D-amphetamine 20 mg/70 kg, orally	Healthy volunteers (N=10)	Double-blind, placebo-controlled, crossover study	Enhances subjective effects of d-amphetamine	Sofuoglu <i>et al.</i> , 2008a
Adrenergic Blockers				
Propranolol (β antagonist, 100 mg)	Cocaine-dependent (N=108)	Double-blind, placebo-controlled, 8-week clinical trial	No difference from placebo overall; better treatment retention and increased cocaine free urines in subset with high withdrawal symptom severity	Kampman <i>et al.</i> , 2001
Amantadine (300 mg), propranolol (100 mg), amantadine (300 mg)+ propranolol (100 mg)	Cocaine dependent+ alcohol-abusing or dependent (N=199)	Double-blind, placebo-controlled, 10-week clinical trial	No difference between any treatment group and placebo; improved treatment retention in the high adherence to propranolol group	Kampman <i>et al.</i> , 2006
Labetalol (α ₁ - and β-adrenergic antagonist, 100, 200 mg)+ Cocaine (0.4 mg/kg, smoked)	Cocaine users (N=12)	Double-blind, placebo-controlled, crossover study	Labetalol attenuates heart rate and blood pressure but not subjective effects of cocaine	Sofuoglu <i>et al.</i> , 2000b
Carvedilol (α ₁ - and β-adrenergic antagonist, 25, 50 mg)+Cocaine (0.4 mg/kg, smoked)	Cocaine users (N=12)	Double-blind, placebo-controlled, crossover study	Carvedilol attenuated heart rate and blood pressure but not subjective effects of	Sofuoglu <i>et al.</i> , 2000a

Medication	Subjects	Study Type	Results	Authors
Norepinephrine Transporter Inhibitors			cocaine, reduces self-administration	
Reboxetine (8 mg)	Cocaine-dependent (N=26)	Open-label, 12-week clinical trial	50% cocaine abstinence, 61.5% treatment retention, improvement in psychopathology	Szerman <i>et al.</i> , 2005
Atomoxetine (0 mg, 20 mg, 40 mg, 80 mg) + Cocaine (4, 20, 40 and 60mg intranasal)	Cocaine-dependent (N=7)	Double-blind, placebo-controlled, crossover study	Attenuated cocaine-induced blood pressure but enhanced heart rate, did not change subjective effects of cocaine.	Stoops <i>et al.</i> , 2008
Atomoxetine (0, 40 mg) + D-amphetamine 20 mg/70 kg, orally	Healthy volunteers (N=10)	Double-blind, placebo-controlled, crossover study	Attenuated amphetamine-induced systolic and diastolic blood pressure. Attenuated subjective and cortisol responses to d-amphetamine	Sofuoglu <i>et al.</i> , 2008b
Alpha₂-Adrenergic Agonist				
Lofexidine (4.8 mg) and naltrexone (50 mg)	Opioid-dependent (N=18)	Double-blind placebo-controlled 4-week discontinuation study	Higher abstinence, lower physiological and subjective response to stress and drug cues in lofexidine group	Sinha <i>et al.</i> , 2007