

MINIREVIEW

# Adrenaline Rush: The Role of Adrenergic Receptors in Stimulant-Induced Behaviors

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Received October 15, 2013; accepted February 5, 2014

## ABSTRACT

Psychostimulants, such as cocaine and amphetamines, act primarily through the monoamine neurotransmitters dopamine (DA), norepinephrine, and serotonin. Although stimulant addiction research has largely focused on DA, medication development efforts targeting the dopaminergic system have thus far been unsuccessful, leading to alternative strategies aimed at abating stimulant abuse. Noradrenergic compounds have shown promise in altering the behavioral effects of stimulants in rodents, nonhuman primates, and humans. In this review, we discuss the contribution of each adrenergic receptor (AR)

subtype ( $\alpha 1$ ,  $\alpha 2$ , and  $\beta$ ) to five stimulant-induced behaviors relevant to addiction: locomotor activity, conditioned place preference, anxiety, discrimination, and self-administration. AR manipulation has diverse effects on these behaviors; each subtype profoundly influences outcomes in some paradigms but is inconsequential in others. The functional neuroanatomy and intracellular signaling mechanisms underlying the impact of AR activation/blockade on these behaviors remain largely unknown, presenting a new frontier for research on psychostimulant-AR interactions.

## Introduction

For many years, medication development efforts for psychostimulant abuse therapies revolved around understanding and modifying dopamine (DA) transmission. Because DA mediates the primary rewarding/reinforcing effects of psychostimulants, the focus on DA was understandable. However, after decades of research, dopaminergic compounds have failed to gain Food and Drug Administration approval or general acceptance as treatments for stimulant dependence. Several reasons likely contribute to this lack of efficacy. For example, dopaminergic drugs showed abuse liability themselves (Mariani and Levin, 2012). In addition, experienced drug abusers often report that, although the drug may no longer produce a subjective euphoric effect, they continue to use the drug for other reasons, rendering medications that

alter the positive subjective effects of psychostimulants impotent. Accordingly, recent research has shifted focus from altering primary reward/reinforcement to preventing relapse. Although DA transmission does contribute to relapse-like behavior, other neurotransmitter systems have been implicated and may actually be more influential, revealing new possibilities for therapeutic targets (Weinschenker and Schroeder, 2007).

Although it is generally accepted that the abuse-related effects of psychostimulants occur primarily through dopaminergic activity, this class of drugs alters several neurotransmitter systems. In particular, both cocaine and amphetamine-like compounds also increase extracellular levels of norepinephrine (NE) and serotonin by preventing reuptake by their respective plasma membrane transporters (i.e., DAT, NET, and SERT) and/or inducing release. On the basis of recent studies implicating NE in relapse-like behavior, interest in the contribution of this neurotransmitter to addictive processes has reemerged (Weinschenker and Schroeder, 2007; Gaval-Cruz and Weinschenker, 2009). Some noradrenergic compounds have already shown promise in human laboratory

This work was supported by the National Institutes of Health National Institute of Drug Abuse [Grants R01-DA027535, R03-DA034867, R01-DA017963]; and the National Institutes of Health National Institute of Mental Health [Grant 5T32-MH087977-05 to K.T.S.].  
dx.doi.org/10.1124/mol.113.090118.

**ABBREVIATIONS:** AR, adrenergic receptor; BLA, basolateral amygdala; BMY 7378, 8-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-8-azaspiro[4.5]decane-7,9-dione; BNST, bed nucleus of the stria terminalis; BRL-44408, 2-[[4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole; CPP, conditioned place preference; DA, dopamine; FR, fixed ratio; ICI-118,551, 3-(isopropylamino)-1-[(7-methyl-4-indanyl)oxy]butan-2-ol; NE, norepinephrine; PFC, prefrontal cortex; PKA, protein kinase A; SDZ NVI 085, (-)-(4aR, 10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine hydrogen malonate; SR58611A, ethyl [(7S)-7-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydronaphthalen-2-yl]oxy]acetate; SR59230A, (2S)-1-(2-ethylphenoxy)-3-[[1S)-1,2,3,4-tetrahydronaphthalenyl]amino]propan-2-ol; ST 587, 2-(2-chloro-5-trifluoromethylphenylimino)imidazo[1,2-a]pyridine; UK 14304, 5-bromo-6-(2-imidazolyl-2-yl)-6-quinoxaline, 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine; WB-4101, 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane hydrochloride.

studies and initial clinical trials (Gaval-Cruz and Weinshenker, 2009; Fox et al., 2012; Haile et al., 2012; Newton et al., 2012; Shorter et al., 2013; K. Cunningham, personal communication). Yet, our knowledge of how the NE system reacts to, and interacts with, psychostimulants is remarkably incomplete, and the neurobiological mechanisms underlying the effects of these compounds are not well understood.

Because the contribution of DAT, NET, and SERT to stimulant-induced behaviors has been extensively discussed elsewhere (e.g., Sora et al., 1998; Hall et al., 2004), we will focus this review on how adrenergic receptors (ARs) influence responses to psychostimulants, and how these systems could be targeted for novel addiction therapies. We will also highlight the nearly complete absence of data concerning the relevant neuroanatomical substrates and the intracellular signaling components downstream of AR activation within the context of psychostimulant responses, which severely hampers our current understanding of these processes and represents a fertile frontier for future research.

## Adrenergic Receptor Subtypes and Compounds

ARs are G protein-coupled receptors that bind, and are activated by, NE and its derivative transmitter epinephrine. Because epinephrine levels in the brain are very low (Mefford, 1988), it is likely that NE mediates most of the effects discussed in this review, although some evidence for epinephrine regulation of motor activity exists (Stone et al., 2003). Included in this family of receptors are 9 subtypes encoded by separate genes: three  $\alpha$ 1ARs ( $\alpha$ 1a,  $\alpha$ 1b, and  $\alpha$ 1d), three  $\alpha$ 2ARs ( $\alpha$ 2a,  $\alpha$ 2b, and  $\alpha$ 2c), and three  $\beta$ ARs ( $\beta$ 1,  $\beta$ 2, and  $\beta$ 3).  $\alpha$ 1ARs are  $G\alpha_q$  coupled, and their activation stimulates phospholipase C activity to cleave phosphatidylinositol 4,5-bisphosphate and increase inositol triphosphate and diacylglycerol, causing an increase of intracellular calcium and activation of protein kinase C.  $\beta$ ARs are typically  $G\alpha_s$ -coupled and activate protein kinase A (PKA) via stimulation of adenylate cyclase activity and cAMP production.  $\alpha$ 2ARs are  $G\alpha_i$ -coupled and function as inhibitory autoreceptors on noradrenergic neurons, although both pre- and postsynaptic  $\alpha$ 2AR heteroreceptors on NE target neurons are also abundant in the brain. Activation of these receptors decreases PKA activation by suppressing cAMP production by adenylate cyclase. In addition, the  $G\beta\gamma$  protein complex associated with ARs is capable of modulating intracellular signaling molecules and ion channels, including phospholipase C, G protein receptor kinase, inwardly rectifying potassium channels, and calcium channels, among others (Lin and Smrcka, 2011). However, the functional consequences of  $\beta\gamma$  signaling in the context of stimulant-induced behaviors have not been well investigated.

Although ARs typically signal via these molecules, several noncanonical AR signaling pathways that are independent of G proteins and cAMP exist. For example,  $\beta$ 2AR activation stimulates a glycogen synthase kinase  $\beta$ /Akt pathway via  $\beta$ -arrestins, which previously were thought only to be important for G protein-coupled receptor internalization and sensitization but are now known to be scaffolds for multiprotein complexes and signaling (Yamamoto et al., 2007; Beaulieu et al., 2009). Additionally,  $\beta$ 1ARs can signal through  $G\alpha_{olf}$  to activate a receptor tyrosine kinase, which in turn stimulates the Ras/Raf/mitogen-activated protein kinase kinase/mitogen-activated protein kinase/mitogen- and stress-activated protein

kinase pathway to produce cAMP response element-binding protein phosphorylation and gene transcription (Meitzen et al., 2011).  $\beta$ 2ARs can switch coupling from  $G\alpha_s$  to  $G\alpha_i$  via PKA-mediated phosphorylation of the receptor, leading to mitogen-activated protein kinase pathway activation (Daaka et al., 1997).  $\beta$ 2AR activation can cause G protein receptor kinase phosphorylation, which activates a  $\beta$ -arrestin and phosphodiesterase-4 feedback circuit to decrease cAMP activity and PKA phosphorylation of the receptor (Baillie et al., 2003). Without this  $\beta$ -arrestin/phosphodiesterase-4 feedback, an enhanced switch from  $G\alpha_s$  to  $G\alpha_i$  coupling is observed. This  $\beta$ 2AR- $G\alpha_i$  signaling also occurs in the brain and is reported to mediate learning and memory, potentially via phospholipase C (Schutsky et al., 2011a, b; Ouyang et al., 2012). The mechanisms underlying ligand-induced activation of these pathways are understudied and could provide critical insights into AR-mediated effects.

## Pharmacologic Compounds Targeting Adrenergic Receptors

Because many compounds targeting these ARs with varying degrees of selectivity for one subtype versus another are used to determine the roles of each receptor in stimulant-induced behaviors, we provide a brief description of these compounds.

The prototypical  $\alpha$ 1AR antagonist is prazosin, but it is limited by its equal affinity for each of the  $\alpha$ 1AR subtypes (Zhong and Minneman, 1999). Terazosin is similar to prazosin but is favored in intracranial infusion studies because it is more soluble in artificial cerebrospinal fluid, which is often used as a vehicle for these experiments (Stone et al., 1999). WB-4101 [2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane hydrochloride] was the first subtype-selective  $\alpha$ 1AR antagonist, with an affinity for the  $\alpha$ 1aAR approximately 20-fold greater than the  $\alpha$ 1bAR; however its binding affinity does not differentiate the  $\alpha$ 1dAR (Morrow and Creese, 1986). Two compounds that are selective for  $\alpha$ 1a over  $\alpha$ 1b and  $\alpha$ 1d are 5-methylurapidil and (+)-niguldipine (Boer et al., 1989; Hanft and Gross, 1989). BMY 7378 [8-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-8-azaspiro[4.5]decane-7,9-dione] has a 100-fold greater affinity for  $\alpha$ 1d than  $\alpha$ 1a or  $\alpha$ 1b but also acts as a partial 5HT<sub>1a</sub> receptor agonist (Goetz et al., 1995; Zhong and Minneman, 1999). Epinephrine activates  $\alpha$ 1ARs with the highest affinity, followed by NE and phenylephrine, respectively (Morrow and Creese, 1986). As measured by radioligand binding, epinephrine, NE, and phenylephrine show the highest affinities for  $\alpha$ 1d (Minneman et al., 1994), and only phenylephrine binds with a greater affinity for  $\alpha$ 1a than  $\alpha$ 1b (Morrow and Creese, 1986). However, when measuring intracellular responses in recombinant human embryonic kidney 293 cells expressing only one subtype, similar potencies are found for epinephrine, NE, and phenylephrine regardless of the receptor subtype expressed (Minneman et al., 1994). Methoxamine, ST 587 [2-(2-chloro-5-trifluoromethylphenylimino)imida-zolidine], and SDZ NVI 085 [(–)-(4aR, 10aR)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-methylthio-2H-naphth[2,3-b]-1,4-oxazine hydrogen malonate] also activate  $\alpha$ 1ARs (Speelman, 1995; Munzar and Goldberg, 1999).

Agonists at  $\alpha$ 2ARs include clonidine, UK 14304 [5-bromo-N-(2-imidazolyl)-6-quinoxaline, 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine], lofexidine, guanabenz, and dexmedetomidine (Aghajanian and VanderMaelen, 1982;

Carter, 1997; Kleven and Koek, 1997; Sallinen et al., 1997; Erb et al., 2000). Guanabenz/guanfacine is preferential for  $\alpha_2a$ , but clonidine and dexmedetomidine have equal affinity at  $\alpha_2$  subtypes (Gobert et al., 1998).  $\alpha_2AR$  antagonists include yohimbine, efaroxan, BRL-44408 (2-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1*H*-isoindole), dexefaroxan, idazoxan, and atipamezole (Dickinson et al., 1988; Villegier et al., 2003; Juhila et al., 2005; Jimenez-Rivera et al., 2006; Doucet et al., 2013). Yohimbine and atipamezole show equal affinities at all three receptor subtypes, but atipamezole has a 200-fold greater selectivity than yohimbine for the  $\alpha_2AR$  over the  $\alpha_1AR$  (Schwartz and Clark, 1998). Because yohimbine interacts with a number of non-noradrenergic systems in addition to acting at the  $\alpha_2AR$ , its effects should be interpreted with caution (Feuerstein et al., 1985; Millan et al., 2000; Conrad et al., 2012).

The prototypical  $\beta AR$  antagonist is propranolol, and like prazosin, it is not selective for any of the  $\beta$  subtypes. Timolol and nadolol act equally at  $\beta_1$  and  $\beta_2$  ARs, but nadolol cannot cross the blood-brain barrier (Colussi-Mas et al., 2005). Selective  $\beta_1AR$  antagonists include atenolol, which also only acts peripherally, and betaxolol (Harris et al., 1996; Bernardi et al., 2009). ICI-118,551 [3-(isopropylamino)-1-[(7-methyl-4-indanyl)oxy]butan-2-ol] has high affinity for the  $\beta_2AR$  (O'Donnell and Wanstall, 1980; Bilski et al., 1983). SR58611A [ethyl [(7*S*)-7-[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydronaphthalen-2-yl]oxy]acetate) and SR59230A [(2*S*)-1-(2-ethylphenoxy)-3-[[[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]amino]propan-2-ol] are selective agonists and antagonists, respectively, for the  $\beta_3AR$  (Consoli et al., 2007).

Although not an exhaustive list of AR activators and inhibitors, these are some of the most commonly used compounds in psychostimulant studies that we will refer to later in this review.

### Stimulant-Induced Locomotor Activity

A characteristic trait of stimulant drugs, such as cocaine and *D*-amphetamine, is the ability to increase locomotor activity in rodents. This hyperactivity is robust and provides a reliable metric for assessing the contribution of different systems to simple drug effects. In these studies, subjects are placed in an open field-like chamber, and activity is measured via a grid of infrared photobeams across the chamber. The animal's position is monitored by beam breaks or by visual tracking software that uses contrast between the animal and the floor to identify location and movement. When initially placed in the chamber, animals will typically show an increased level of locomotion induced by the novelty of the chamber that is subject to habituation. Drug administration can occur either prior to this exploratory period or after habituation. Additionally, repeated administration of stimulants leads to behavioral sensitization in which the same dose results in greater levels of activity. Although the face validity of this behavioral measure for drug addiction per se is poor, locomotor activity can be a predictor of abuse liability (Marinelli and White, 2000; Simmons et al., 2013), and it has been suggested that the sensitization paradigm reflects the incentive salience value of drugs and models drug craving (Robinson and Berridge, 2001).

Manipulations of NE receptor subtypes indicate opposing roles of  $\alpha_1AR$  and  $\alpha_2AR$ , with blockade of  $\alpha_1AR$  decreasing

and antagonism of  $\alpha_2AR$  increasing the acute locomotor response to stimulants. Numerous studies have shown that  $\alpha_1AR$ s antagonists such as prazosin, terazosin, and WB-4101 decrease drug-induced motor activity and behavioral sensitization (Snoddy and Tessel, 1985; Dickinson et al., 1988; Blanc et al., 1994; Darracq et al., 1998; Drouin et al., 2002; Weinschenker et al., 2002; Wellman et al., 2002; Vanderschuren et al., 2003; Auclair et al., 2004; Salomon et al., 2006; Alsene et al., 2010). Importantly, the effects seen with  $\alpha_1AR$  antagonism appear to be specific to drugs with abuse liability because prazosin did not impair basal locomotion or hyperactivity induced by the muscarinic antagonist scopolamine (Blanc et al., 1994; Wellman et al., 2002; Alsene et al., 2010). Compared with the wild type, mice genetically lacking the  $\alpha_1bAR$  subtype ( $\alpha_1b$  KO) had a decrease in acute and sensitized responses to amphetamine and cocaine despite normal basal dopaminergic function and DA receptor populations (Auclair et al., 2002, 2004; Drouin et al., 2002; Villegier et al., 2003). Furthermore, the effects of prazosin on drug-induced hyperactivity were abolished in the  $\alpha_1b$  KO mice, indicating that the  $\alpha_1b$  subtype is the most important mediator of this psychostimulant response (Drouin et al., 2002).  $\alpha_1d$  KO mice showed a decreased locomotor response to amphetamine, suggesting a contribution of this subtype. However, spontaneous wheel running and novelty-induced rearing were also reduced in these animals, indicating a nonspecific effect on motor activity (Sadalg et al., 2003). Intracerebroventricular administration of the  $\alpha_1a$  receptor antagonist, 5-methylurapidil, failed to suppress cocaine hyperlocomotion (Clifford et al., 2007). The location of the  $\alpha_1AR$ s regulating stimulant-induced activity appears to be the prefrontal cortex (PFC; Blanc et al., 1994; Darracq et al., 1998) and nucleus accumbens shell (Mittrano et al., 2012), because local infusions of  $\alpha_1AR$  antagonists into these regions reduced cocaine and/or amphetamine-induced locomotion.

Antagonism of  $\alpha_2AR$ , on the other hand, which facilitates NE transmission by blocking autoreceptor function, increased both acute stimulant-induced locomotion (Dickinson et al., 1988; Villegier et al., 2003; Jimenez-Rivera et al., 2006) and sensitized responses (Doucet et al., 2013) in mice and rats. Conversely, the  $\alpha_2AR$  agonist clonidine, which suppresses NE release via autoreceptor stimulation, produced a decreased acute response to cocaine (Vanderschuren et al., 2003; Jimenez-Rivera et al., 2006) and prevented amphetamine sensitization (Doucet et al., 2013). None of these studies provided evidence for the neuroanatomical substrates mediating these  $\alpha_2AR$  responses.

Fewer studies have examined the role of  $\beta AR$ s on locomotor responses to stimulants. Propranolol, a nonselective  $\beta AR$  blocker, increased the acute effects of cocaine in rats (Harris et al., 1996) but not mice (Al-Hasani et al., 2013). Mixed results have been reported with amphetamine; low doses of propranolol (1.0–3.0 mg/kg) increased activity induced by amphetamine (1.0 mg/kg) in rats (Vanderschuren et al., 2003), but much higher doses of both drugs (30 mg/kg propranolol and 3.2 mg/kg amphetamine) produced decreased locomotion compared with mice treated with amphetamine alone (Snoddy and Tessel, 1985). Administration of a centrally acting  $\beta AR$  antagonist blocked the development of sensitization to amphetamine or cocaine, whereas peripherally acting antagonists did not (Colussi-Mas et al., 2005; Bernardi and Lattal, 2012a). These studies implicated the bed nucleus of the stria terminalis

(BNST), which displayed induction of the immediate early gene *c-fos* after amphetamine administration, and intra-BNST infusion of the  $\beta$ AR antagonist timolol prevented sensitization (Colussi-Mas et al., 2005).

In summary, it appears that NE transmission has an overall facilitatory effect on stimulant-induced locomotion, and blocking postsynaptic ARs attenuates this behavior.

### Place Preference and Aversion

The conditioned place preference (CPP) procedure is a popular paradigm used to measure the rewarding effects of addictive drugs (Tzschentke, 2007; Aguilar et al., 2009). This procedure uses a two- or three-compartment apparatus in which daily conditioning sessions pair the effects of a drug to one compartment and vehicle to the other. In the three-chamber version of the CPP paradigm, the third compartment is a neutral middle partition that is not paired with any stimuli and can be used as a “start box.” To determine whether the animal has an initial bias toward one side, a preconditioning test occurs during which the subject can freely explore all compartments. Ideally, the paradigm follows a balanced design in which no initial side preference is observed. If the subjects show a preconditioning preference, the experimental design can be described as “biased” or “unbiased.” In a biased design, the drug pairing is made with regards to the animals’ initial preference. For example, to increase the probability of observing a place preference on the final test, drug is paired with the compartment each animal prefers less during preconditioning. In the preferred unbiased design, the drug-compartment pairing is random: some animals receive the drug on the “preferred” side, others on the “nonpreferred” side. Alternatively, one compartment can be designated as the drug-paired chamber for all animals regardless of initial preference. After repeated pairings, a test session is used to assess the rewarding or aversive properties of the drug in question by allowing the animal to freely move between the compartments in a drug-free state. An increased amount of time spent in the drug-paired chamber is thought to reflect drug reward, whereas decreased time indicates a drug aversion. Because the paradigm requires learning, the conditioned effect can be extinguished, is subject to retrieval and reconsolidation processes, and can be reinstated after a drug-prime or stress exposure, which are believed to model aspects of relapse in human drug abusers.

**Place Preference Induction.** In general, drugs that modulate NE activity specifically are ineffective at creating conditioned preferences or aversions on their own. Neither the  $\alpha$ 1AR agonist phenylephrine nor the  $\alpha$ 1AR antagonist prazosin supported the formation of a place preference (Zarrindast et al., 2002; Sahraei et al., 2004). Similarly,  $\alpha$ 2AR antagonists have also showed either no effect (Morales et al., 2001; Sahraei et al., 2004; Tahsili-Fahadan et al., 2006) or a conditioned aversion (File, 1986). In contrast, the  $\alpha$ 2AR agonist clonidine elicited a CPP (Asin and Wirtshafter, 1985; Cervo et al., 1993), but this effect was only observed at specific doses and when paired with the less preferred compartment, and other  $\alpha$ 2AR agonists have not mimicked this effect (Sahraei et al., 2004; Tahsili-Fahadan et al., 2006). The  $\beta$ AR antagonist timolol also did not produce a preference on its own (Robledo et al., 2004). These results indicate that neither AR agonists nor antagonists per se have rewarding properties or abuse liability.

Despite a thorough search of the literature, surprisingly few studies were found that examined the effects of AR antagonists on the development of a psychostimulant CPP. One study reported that propranolol (10 mg/kg) failed to alter cocaine CPP (Al-Hasani et al., 2013), and two others showed that mice lacking the  $\alpha$ 2aAR or both the  $\beta$ 1AR and  $\beta$ 2AR had normal amphetamine and cocaine CPP (Juhila et al., 2005; Vranjkovic et al., 2012). Surprisingly, no published studies have examined the influence of  $\alpha$ 1ARs on stimulant CPP. Considering the substantial evidence indicating a role for  $\alpha$ 1AR signaling in stimulant-induced locomotor activity, discussed above, and certain aspects of stimulant self-administration, discussed below, future efforts to determine the influence of  $\alpha$ 1ARs on the rewarding effects of cocaine and the neuroanatomy underlying any such findings are warranted.

**Retrieval, Reconsolidation, and Extinction.** Although the effects of NE on the extinction of fear conditioning have been thoroughly investigated (Mueller and Cahill, 2010), only a few studies have examined the role of AR signaling in the extinction of conditioned drug effects. Because the neurobiological events mediating memory retrieval, reconsolidation, and extinction impact the ability to express or extinguish a CPP, care must be taken in the design and interpretation of studies to address the distinction between these processes. For the purposes of this review, we will be using the terms retrieval, reconsolidation, and extinction as the authors employed them to describe their work.

The retrieval of a cocaine CPP memory was blocked by pre-session administration of  $\beta$ -receptor antagonists (Otis and Mueller, 2011). These effects were localized to  $\beta$ ARs in the PFC or dorsal hippocampus but not basolateral amygdala (BLA; Otis et al., 2013, 2014). Furthermore,  $\beta$ ARs, specifically  $\beta$ 2ARs, mediate the reconsolidation of cocaine CPP as administration of propranolol and ICI-118,551 ( $\beta$ 2 antagonist), but not betaxolol ( $\beta$ 1 antagonist), immediately after retrieval impaired the expression of CPP in subsequent sessions (Bernardi et al., 2006, 2009; Fricks-Gleason and Marshall, 2008). Similar effects were observed with a high dose of prazosin, but not a lower dose (Bernardi et al., 2009), yet how and where these  $\beta$ AR-mediated effects occur were not determined.

In contrast to retrieval, the effects of  $\beta$ AR activation on reconsolidation were localized to the BLA; *c-fos* immunoreactivity was increased in the BLA after reconsolidation and local infusions of  $\beta$  antagonists blocked the effect (Bernardi et al., 2009; Otis et al., 2013).

Regarding extinction of CPP, a possible role of  $\alpha$ ARs has been identified, but the data are not clear-cut. Mice treated with prazosin immediately after daily drug-free test sessions extinguished at normal rates, yet reacquired cocaine CPP with a single re-exposure session that was ineffective in vehicle-treated animals (Bernardi and Lattal, 2010). However, when the data were reanalyzed to control for initial preference, a high dose of prazosin accelerated extinction in animals with a high initial preference score (Bernardi and Lattal, 2012b). Yohimbine impaired the extinction of cocaine CPP, although this effect was not replicated with a selective  $\alpha$ 2AR antagonist and may be mediated by orexin rather than NE (Davis et al., 2008; Conrad et al., 2012).

**Reinstatement.** After extinction of a drug–environment association, place preference can be reinstated with a non-contingent drug prime. Cocaine-primed reinstatement of CPP was unchanged by administration of propranolol, prazosin, or

clonidine just prior to the cocaine prime (Mantsch et al., 2010; Al-Hasani et al., 2013), yet  $\beta$ AR antagonism during retrieval and extinction sessions prevented subsequent reinstatement (Fricks-Gleason and Marshall, 2008; Otis and Mueller, 2011; Otis et al., 2014). The mechanisms by which these compounds alter memory to prevent future cocaine-primed reinstatement but fail to impact the acute priming effects of cocaine should be further investigated.

Stress exposure can reinstate stimulant CPP in an AR-dependent manner. Stress-induced reinstatement of CPP depended on  $\beta$ 2AR activity but was preserved after  $\alpha$ 1AR blockade (Mantsch et al., 2010). Stress-induced reinstatement could also be blocked by a cannabinoid receptor (CB1) antagonist, and a subthreshold dose of the  $\alpha$ 2AR antagonist BRL-44408 reinstated cocaine CPP when combined with a CB1 agonist (Vaughn et al., 2012), indicating an interaction of the NE and cannabinoid systems in this paradigm. Moreover,  $\beta$ 2AR agonists and  $\alpha$ 2AR antagonists produced reinstatement on their own (Mantsch et al., 2010; Vranjkovic et al., 2012).  $\kappa$ -Opioid receptors were necessary for stress-induced reinstatement, and  $\kappa$ -agonist-induced reinstatement of cocaine CPP required  $\kappa$  expression in the noradrenergic locus coeruleus and was enhanced by clonidine, propranolol, or betaxolol, but not ICI-118,551, at doses that did not reinstate on their own (Al-Hasani et al., 2013). These results indicate that diverse stress-inducing compounds act via noradrenergic mechanisms, specifically  $\beta$ 2AR activation, to facilitate reinstatement of a CPP.

### Drug-Induced Anxiety

In addition to the rewarding effects of stimulants, drugs like cocaine also have anxiogenic properties. The elevated plus maze can be used as a behavioral readout of anxiety-like behavior. In this task, an animal is placed in a plus-shaped apparatus raised a few feet from the floor. Two of the four arms are enclosed with walls, and the other two arms are open. Time spent in the closed arms is thought to represent anxiety-like behavior because (1) restriction to the open arms causes greater behavioral and physiologic responses consistent with anxiety than closed arm restriction, (2) compounds that cause anxiety in humans increase time spent in the closed arms, and (3) clinically effective anxiolytic drugs selectively increase time spent in the open arms (Pellow et al., 1985).

With the elevated plus maze, mice injected with cocaine decreased the amount of time spent in the open arms. This anxiety-like behavior was blocked by propranolol, but not prazosin or yohimbine, implicating  $\beta$ ARs (Schank et al., 2008). Thus, the noradrenergic system may act as a brake to limit the intake of cocaine by inducing negative side effects and suggests a therapeutic avenue to decrease drug use.

Additionally, withdrawal from chronic cocaine induced anxiety-like behavior in the elevated plus maze and the defensive burying task, another preclinical measure of anxiety, that was attenuated by the  $\beta$ 1AR antagonist betaxolol and the  $\alpha$ 2AR agonist guanfacine, respectively (Rudoy and Van Bockstaele, 2007; Buffalari et al., 2012).  $\beta$ 1AR protein levels and corticotropin-releasing factor transcription in the amygdala were increased during cocaine withdrawal and reduced after betaxolol administration, suggesting that

a  $\beta$ 1AR-mediated change in corticotropin-releasing factor production is important for this behavior (Rudoy and Van Bockstaele, 2007; Rudoy et al., 2009). Furthermore, betaxolol returned intracellular PKA catalytic subunit abundance after cocaine withdrawal to levels of drug-naive animals and prevented cocaine-induced cAMP response element-binding protein phosphorylation (Rudoy et al., 2009). Similarly, propranolol blocked cocaine withdrawal-induced anxiety in rats and also clinically in patients dealing with severe withdrawal symptoms (Harris and Aston-Jones, 1993; Kampman et al., 2001). Because drug-dependent individuals continue taking drugs to decrease the aversive effects of withdrawal, targeting the receptors responsible for this anxiety could have substantial therapeutic efficacy.

### Drug Discrimination

Drug discrimination is a measure of the interoceptive effects of a drug. In this procedure, animals are trained to respond on one operandum (drug appropriate) after an experimenter-administered injection of a training drug and another operandum (vehicle appropriate) after vehicle administration. Responses on the appropriate lever are reinforced by food, water, shock termination, or other stimuli that maintain high, stable rates of behavior, but typically appetitive reinforcement is used. Once animals meet training criteria in which responses are made on the appropriate operandum with high selectivity (typically greater than 80–90%), a session occurs to test whether various doses of the training drug, other drugs, or pretreatments plus the training drug can alter the discriminative stimulus properties. When the test treatment produces interoceptive effects similar to the training drug, the subject responds predominantly on the drug-appropriate lever. When the test treatment produces interoceptive effects that are distinct from the training drug, the subject responds predominantly on the vehicle-appropriate lever. In this way, one can interrogate whether a test treatment produces a state that “feels” like that produced by the training drug. For example, when trained with cocaine, the psychostimulants amphetamine and methylphenidate engendered responding on the cocaine-appropriate lever, whereas nonstimulant drugs such as fenfluramine and mescaline elicited responding on the vehicle lever (McKenna and Ho, 1980).

The discriminative stimulus effects of psychostimulants are largely dependent on DA activity and only partially mediated by  $\alpha$ ARs, yet  $\beta$ ARs have greater influence. Cocaine and amphetamine cross-generalized, and their effects could be abolished after administration of the DA D2 antagonist haloperidol (Schechter and Cook, 1975; McKenna and Ho, 1980). Regarding  $\alpha$ ARs and discrimination, a mixed bag of results has been reported with some studies indicating effects and others failing to find significance depending on the training drug and species used. The  $\alpha$ AR antagonist phenoxylbenzamine failed to alter the discriminative effects of cocaine or amphetamine (Schechter and Cook, 1975; McKenna and Ho, 1980). Similarly, it was recently reported that the non-selective  $\alpha$ AR antagonist phentolamine had no effect on the ability of amphetamine or ephedrine to substitute for amphetamine in pigeons (Ercil and France, 2003). The  $\alpha$ 1AR antagonist dibenamine also did not change cocaine's discriminative stimulus effects in rats (Colpaert et al., 1976). Prazosin has been the most thoroughly examined  $\alpha$ AR antagonist, yet it

lacks a clear, consistent role in the interoceptive effects of stimulants. It failed to profoundly shift the dose-response curves of cocaine (Kleven and Koek, 1998), methamphetamine (Munzar and Goldberg, 1999), or amphetamine (West et al., 1995) in rats, yet produced rightward shifts in the curves of cocaine in pigeons (Johanson and Barrett, 1993) and squirrel monkeys (Spealman, 1995; Rowlett et al., 2004), methamphetamine in pigeons (Sasaki et al., 1995), and amphetamine in mice (Snoddy and Tessel, 1985). No effect on cocaine or methamphetamine discrimination was observed after  $\alpha 1$ AR agonist administration in rats or monkeys (Spealman, 1995; Kleven and Koek, 1997; Munzar and Goldberg, 1999). Because no consistent, cross-species effects of  $\alpha$ AR signaling has been observed, it appears that activity at these receptors is largely unnecessary for the interoceptive effects of stimulants.

A similar hodgepodge of results has been reported with compounds targeting  $\alpha 2$ AR. Whereas the  $\alpha 2$ AR agonist UK 14304 failed to alter the discriminative stimulus effects of cocaine (Spealman, 1995; Kleven and Koek, 1997), clonidine partially substituted for methamphetamine, amphetamine, and cocaine in rats (D'Mello, 1982; Wood et al., 1985; Munzar and Goldberg, 1999) and cocaine in pigeons (Johanson and Barrett, 1993) but not cocaine in squirrel monkeys (Spealman, 1995). Oddly, when tested in combination with methamphetamine doses higher than the training dose, clonidine decreased drug-appropriate responding (Munzar and Goldberg, 1999). Cocaine discrimination was unaffected by yohimbine or efaroxan, another  $\alpha 2$ AR antagonist (Wood et al., 1985; Spealman, 1995; Kleven and Koek, 1997). Thus, the data on  $\alpha 2$ AR compounds are inconsistent and confusing. These differential effects could be explained, at least in part, by the specificity of these drugs at different doses. At low doses,  $\alpha 2$ AR agonists and antagonists preferentially interact with the  $\alpha 2$ AR inhibitory autoreceptor, whereas at higher doses, these drugs can also engage  $\alpha 2$ AR heteroreceptors on target neurons, as well as  $\alpha 1$ ARs (Gobert et al., 1998).

Experiments using  $\beta$ AR drugs have revealed some interesting results. Several studies found no effect of propranolol on the discriminative stimulus effects of amphetamine (Schechter and Cook, 1975; Snoddy and Tessel, 1985; Eril and France, 2003), methamphetamine (Munzar and Goldberg, 1999), or cocaine (Spealman, 1995). However, propranolol and cocaine partially substituted for each other (Colpaert et al., 1979; Young and Glennon, 2009). Furthermore, in a discrimination test between 2.5 and 10 mg/kg cocaine, propranolol, tertatolol, and the  $\beta 2$ AR antagonist ICI-118,551, but not the peripherally limited  $\beta$ AR antagonist nadolol nor the  $\beta 1$ AR antagonist betaxolol, enhanced the ability of the low dose of cocaine to engender responding on the 10 mg/kg cocaine-associated lever (Kleven and Koek, 1997). When pretreated with prazosin, the enhancing effect of propranolol was blocked (Kleven and Koek, 1998; Young and Glennon, 2009). These results suggest a role for central  $\beta 2$ ARs in cocaine's discriminative stimulus effects, particularly when low doses of cocaine are used, that is modulated by  $\alpha 1$ AR activity.

In summary, the interoceptive effects of stimulants are, at best, modestly susceptible to alteration by AR agonists or antagonists. Specifically, the clearest evidence supports the ability of  $\beta$ AR antagonists to influence the discriminative stimulus effects of psychostimulants in an  $\alpha 1$ AR-dependent fashion.

## Self-Administration

The gold standard for assessing the reinforcing properties of a drug is the operant self-administration paradigm, in which an animal performs a behavior reinforced by the delivery (intravenous, oral, etc.) of a drug that is usually paired with a sensory cue (e.g., light or tone). Psychostimulants and other drugs that are abused by humans are readily self-administered by animals and produce behavioral patterns that are reminiscent of aspects of human addiction. First, in the "acquisition" phase, the animal learns the operant task (e.g., lever press, nose poke, etc.) that results in reinforcer presentation, and the "maintenance" phase commences once the behavioral rates and drug intake stabilize. Maintenance responding is thought to model ongoing drug taking in humans, and alterations in this phase have been used to determine the neurobiological basis of addiction and to test potential interventions. A variety of schedules can be employed during the maintenance phase to address specific aspects of reinforcer efficacy. For example, a fixed ratio (FR) schedule, in which the completion of a set number of responses (e.g., every response in an FR1, every 5th response in an FR5, etc.) delivers a reinforcer, is a simple schedule frequently used to determine whether an animal will self-administer a compound. By comparison, a progressive ratio schedule, in which the response requirement increases exponentially during the course of the session until a "breakpoint" is reached when the subject stops responding to earn reinforcers, determines the relative reinforcing efficacy of the drug (Richardson and Roberts, 1996). More recently, interest has piqued in two subsequent phases, "extinction" and "reinstatement." During extinction, the drug is replaced with a nonreinforcing vehicle (e.g., saline, water). The animal learns that the operant task no longer precipitates reward presentation, and the conditioned behavior declines to low levels. Once the behavior is extinguished, administration of a drug prime, restoration of cues previously associated with the drug, or stress (e.g., mild electric foot shock or pharmacological stressor like yohimbine) can "reinstatement" the operant behavior to rates comparable to maintenance levels even though the operant behavior is not reinforced by drug presentation. Thus, reinstatement represents drug seeking and is thought to model relapse behaviors of human addicts. Because many addicts try repeatedly to quit but have difficulty staying drug-free, this phase has become a prime target for recent medication development efforts.

**Maintenance.** Most noradrenergic compounds have not shown reinforcing properties on their own (e.g., Risner and Jones, 1976), although some, such as  $\beta$ AR agonists/antagonists, have not been tested. The one exception is the  $\alpha 2$ AR agonist clonidine, which was self-administered by rats (Davis and Smith, 1977; Shearman et al., 1981), macaques (Woolverton et al., 1982), and baboons (Weerts and Griffiths, 1999). Interestingly, rats self-administered clonidine even at doses that resulted in toxicity and occasionally death (Davis and Smith, 1977). However, methadone-dependent patients did not self-administer clonidine (Preston et al., 1985). Therefore, it appears that, at least in this clinical setting, the abuse liability of noradrenergic compounds is inconsequential.

With regards to the primary reinforcing effects of stimulants, AR activation or blockade is largely ineffective in altering the maintenance phase of intravenous self-administration, yet subtle effects were reported for  $\alpha 1$ ARs and  $\beta$ ARs in oral

consumption. In monkeys, the  $\alpha$ AR antagonists phentolamine, phenoxybenzamine, and prazosin failed to alter cocaine self-administration across various schedules of reinforcement (Wilson and Schuster, 1974; Woolverton, 1987; Howell and Byrd, 1991). A similar lack of effect was observed in dogs self-administering amphetamine (Risner and Jones, 1976) or cocaine (Risner and Jones, 1980). Infusion of prazosin directly into the PFC or ventral tegmental area likewise did not alter cocaine intake in rats (Ecke et al., 2012). Given the technical difficulties of intravenous self-administration in mice, the importance of ARs has not been tested in this species, although genetic ablation of the  $\alpha$ 1bAR reduced cocaine consumption in an oral self-administration paradigm (Drouin et al., 2002).  $\alpha$ 2AR agonists had no effect on amphetamine (Yokel and Wise, 1978), heroin/cocaine “speedball” (Highfield et al., 2001), or cocaine (Wee et al., 2008) intravenous self-administration.  $\beta$ AR antagonists also failed to impact long-access (6 hour/session) cocaine responding (Wee et al., 2008) but have been reported to decrease cocaine self-administration in 3-hour sessions with rats (Harris et al., 1996) and in 100-minute sessions in squirrel monkeys (Goldberg and Gonzalez, 1976). However, food-maintained responding also decreased after propranolol administration in rats, suggesting a nonspecific suppression of operant behavior (Harris et al., 1996). Combined, these results indicate that stimulants maintain their reinforcing effects through mechanisms other than ARs. With the abundance of research identifying DA as the neurotransmitter mediating the primary reinforcing effects of stimulants, these data are not surprising.

Oral self-administration of amphetamine is vastly different than intravenous self-administration, because rats develop an aversion to oral amphetamine and consume mostly water in a two bottle choice procedure. Propranolol, but not haloperidol, increased the intake of amphetamine, indicating that the aversive effects of oral amphetamine are mediated by  $\beta$ AR signaling but not DA (Kongyingyoes et al., 1988). Additional support for a role of  $\beta$ ARs in the negative effects of stimulants was observed using a runway model of self-administration in which rats must walk down an alley to a goal box to receive intravenous cocaine infusions. In this model, approach and retreat behaviors indicate the reinforcing and aversive effects, respectively, of cocaine. Combined administration of betaxolol and ICI-118,551 infused in the central amygdala or BNST decreased retreat behaviors (Wenzel et al., 2014). Therefore, it appears that the influence of NE on stimulant self-administration depends on the sensitivity of the operant task to the NE-dependent, aversive effects of the drug. Perhaps, this NE-dependent increase in the aversive effects of stimulants can be advantageous if used as a strategy to develop noradrenergic therapies that would counteract the euphoria experienced by drug abusers.

An important contribution of  $\alpha$ 1AR signaling emerged during various paradigms of escalated stimulant self-administration. For example, rats that underwent a cocaine pre-exposure regimen showed escalated cocaine self-administration that was abolished when prazosin was coadministered with cocaine during the sensitization phase (Zhang and Kosten, 2007). Furthermore, prazosin decreased breakpoint on a progressive ratio schedule of cocaine self-administration in rats under 6-hour long-access conditions that typically showed escalated drug intake (Wee et al., 2008).  $\alpha$ 1AR abundance was decreased in the BNST by high levels of cocaine exposure (Wee et al., 2008), which the

authors speculated occurred as a compensatory response to inflated NE overflow during prolonged self-administration and produced antagonist sensitivity. However, the behavioral consequences of intra-BNST prazosin infusions remain to be tested in this paradigm.

Thus, it appears that chronic drug exposure recruits  $\alpha$ 1AR-dependent pathways that are necessary for escalated drug taking in experimental animals. Because these escalation procedures are believed to more closely resemble addiction and binge drug taking in humans compared with short-access maintenance schedules, these effects of  $\alpha$ 1AR signaling may have clinical relevance. Only two human studies have examined the clinical utility of  $\alpha$ 1ARs in stimulant dependence, and the findings parallel the escalated intake effects in the rodent literature. For example, the  $\alpha$ 1AR antagonist doxazosin decreased self-report of “high,” “stimulating,” and “like cocaine” after cocaine administration (20 mg/kg i.v.; Newton et al., 2012) and increased cocaine-negative urines in treatment-seeking cocaine-dependent people compared with placebo under some dosing regimens (Shorter et al., 2013). These results indicate a need for further investigation of the promising therapeutic capabilities of  $\alpha$ 1AR antagonists.

**Extinction.** Only a few studies have examined the role of NE in the extinction of stimulant self-administration. Stemming from evidence that extinction of drug self-administration and fear conditioning requires activity in the infralimbic cortex, one study dissected the contribution of NE to the extinction of cocaine self-administration via microinfusions of GABAergic, glutamatergic, and noradrenergic compounds (LaLumiere et al., 2010). Silencing activity in the region with GABA agonists impaired extinction learning. Intrafralimbic administration of the  $\beta$ 2AR agonist clenbuterol immediately after extinction sessions enhanced the retention of extinction learning, whereas ICI-188,551 infused immediately prior to extinction sessions impaired extinction. In another study, repeated exposure to yohimbine during the first few extinction sessions slowed the rate of extinction (Kupferschmidt et al., 2009). Clearly, further studies examining other AR subtypes are needed.

**Reinstatement.** The most profound effects of AR signaling manipulations occur during the reinstatement phase of stimulant self-administration, which is thought to reflect relapse-like drug-seeking behavior in humans. Stress, cues previously associated with the drug, or the noncontingent administration of the drug itself can trigger drug-seeking behaviors. Interestingly, NE alone has been shown to reinstate cocaine seeking when administered intracerebroventricularly (Brown et al., 2009). The authors attributed this phenomenon to a stress effect because it was associated with activation of neurons in the BNST and central amygdala that are part of the brain’s stress pathway (Brown et al., 2011).

Yohimbine, an  $\alpha$ 2AR antagonist that increases NE release by blocking the primary noradrenergic inhibitory autoreceptor, is an anxiogenic drug that reinstates psychostimulant-seeking behavior in rats and monkeys (Lee et al., 2004; Shepard et al., 2004; Schroeder et al., 2013). However, it is unclear whether the effects of yohimbine occur through the noradrenergic system at all. In monkeys, the reinstating effects of yohimbine were blocked by clonidine and replicated with a selective  $\alpha$ 2AR antagonist (Lee et al., 2004), implicating the  $\alpha$ 2AR. Conversely, clonidine had no effect on yohimbine-primed reinstatement in rats (Brown et al., 2009), suggesting a contribution of nonadrenergic receptors, although the preferential

$\alpha$ 2aAR-selective agonist guanfacine did reduce yohimbine-primed reinstatement in this species (Buffalari et al., 2012).

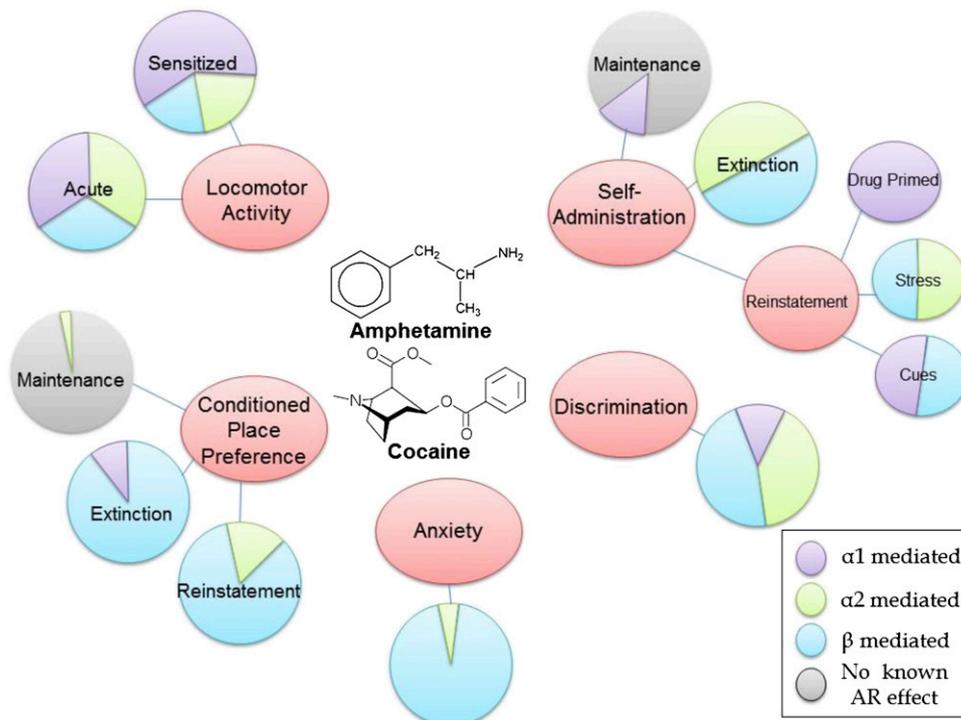
NE signaling has a critical role in stress-induced, cue-induced, and drug-primed reinstatement in rats, but through distinct combinations of receptor subtypes. Either systemic administration of  $\alpha$ 2AR agonist (clonidine, lofexidine, or guanabenz) or a cocktail of  $\beta$ 1 and  $\beta$ 2AR antagonists infused directly into the BNST or central amygdala prevented foot shock stress induced reinstatement of cocaine seeking (Erb et al., 2000; Leri et al., 2002), clonidine prevented reinstatement induced by  $\kappa$ -opioid pharmacologic stressors (Valdez et al., 2007), prazosin attenuated cocaine-primed reinstatement (Zhang and Kosten, 2005), and a combination of prazosin and propranolol modestly reduced cue-induced reinstatement (Smith and Aston-Jones, 2011). Clonidine also blocked stress-induced, but not cue-induced reinstatement of cocaine + heroin "speedball" in rats (Highfield et al., 2001). Thus,  $\beta$ ARs mediate the effects of NE on stress-induced reinstatement,  $\alpha$ 1ARs are required for cocaine-primed reinstatement, and  $\alpha$ 1ARs and  $\beta$ ARs contribute to cue induced-reinstatement but via redundant pathways.  $\alpha$ 2AR agonists appear to diminish multiple forms of reinstatement by decreasing overall NE release via inhibitory autoreceptor activation.

A somewhat different picture emerges for primates. For example, adrenergic compounds had no effect on cocaine-primed reinstatement in squirrel monkeys (Platt et al., 2007). However, reinstatement paradigms differ between rats and nonhuman primates in important ways that may affect interpretation of these results. For instance, nonhuman primate self-administration typically involves a second-order schedule of reinforcement in which cues associated with cocaine serve as conditioned reinforcers. During "cocaine-primed reinstatement," a combination of drug-prime and drug-associated cues drives cocaine-seeking behavior. Because prazosin, on its own, had no

effect on cue-induced reinstatement in rodents, the lack of effect in the monkey cocaine + cue reinstatement paradigm is not entirely surprising. The only human studies germane to this subject found that clonidine and guanfacine decreased stress- or cue-induced craving for cocaine (Jobes et al., 2011; Fox et al., 2012).

### Adrenergic Receptor Signaling Cascades and Functional Neuroanatomy: Where's the Beef?

In summary, although all ARs appear to impact stimulant responses, the relative contributions of  $\alpha$ 1,  $\alpha$ 2, and  $\beta$ AR subtypes differ depending on the behavioral paradigm employed (Fig. 1). As discussed in the introduction, ARs are G protein-coupled receptors that signal through diverse downstream effector proteins to alter neurotransmission, cell excitability, and gene transcription. We anticipated devoting a section of this review to the roles of these AR signaling cascades but found that the cupboard is bare. Despite the profound effects of adrenergic compounds on many aspects of psychostimulant responses, a detailed knowledge of AR signaling molecules, and an armament of pharmacological and genetic tools to manipulate these cascades, a vast vacuum exists downstream of ARs within the context of psychostimulant-induced behaviors. There is only one published study that has even attempted to address this issue, which we discuss in other parts of this review (Rudoy et al., 2009). Knowledge of the functional neuroanatomy underlying the role of ARs in stimulant responses is also lacking for many paradigms. With the resurgence of interest in the contribution of NE to stimulant addiction, including recent and ongoing clinical trials investigating the efficacy of compounds that alter NE signaling, the intracellular mechanisms and neuroanatomical substrates by which adrenergic drugs could be acting must be



**Fig. 1.** Relative contribution of adrenergic receptor subtypes to stimulant-induced behaviors. Stimulants, such as amphetamines and cocaine, produce behaviors including locomotor activity, conditioned place preference, drug discrimination, and self-administration. Various aspects of these behaviors are subject to control by AR signaling. Based on the available literature, it appears that each AR subtype exerts different relative effects on various stimulant-induced behaviors. Shown is a qualitative representation of the relative influences of  $\alpha$ 1 (lilac),  $\alpha$ 2 (lime), and  $\beta$  (cyan) AR subtypes to each stimulant-induced behavior, with greater influence represented by colored shading of a larger fraction of the pie graph. Gray shading indicates no known effect, which includes negative results as well as instances where the contribution of the receptor has never been tested.

elucidated. These studies would have important implications for the development of targeted therapeutics to treat stimulant, and potentially other, addictions.

#### Authorship Contributions

Wrote or contributed to the writing of the manuscript: Schmidt, Weinschenker.

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