Hypothesis-Driven Medication Discovery for the Treatment of Psychostimulant Addiction

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Abstract: Psychostimulant abuse is a serious social and health problem, for which no effective treatments currently exist. A number of review articles have described predominantly 'clinic'-based pharmacotherapies for the treatment of psychostimulant addiction, but none have yet been shown to be definitively effective for use in humans. In the present article, we review various 'hypothesis'- or 'mechanism'-based pharmacological agents that have been studied at the preclinical level and evaluate their potential use in the treatment of psychostimulant addiction in humans. These compounds target brain neurotransmitter or neuromodulator systems, including dopamine (DA), γ-aminobutyric acid (GABA), endocannabinoid, glutamate, opioid and serotonin, which have been shown to be critically involved in drug reward and addiction. For drugs in each category, we first briefly review the role of each neurotransmitter system in psychostimulant actions, and then discuss the mechanistic rationale for each drug's potential anti-addiction efficacy, major findings with each drug in animal models of psychostimulant addiction, abuse liability and potential problems, and future research directions. We conclude that hypothesis-based medication development strategies could significantly promote medication discovery for the effective treatment of psychostimulant addiction.

Keywords: Psychostimulant, addiction, reward, reinstatement, dopamine, glutamate, GABA, endocannabinoids.

1. INTRODUCTION

Psychostimulant abuse is a major medical and social problem. Cocaine, amphetamine, methamphetamine and *N*-methyl-3,4-methylenedioxymethamphetamine (MDMA, ecstasy) are the most commonly abused psychostimulants in humans. The acute rewarding effects produced by psychostimulants and craving and relapse after abstinence are the core features of addiction to these drugs [1, 2]. Currently, there are no effective medications available for the treatment of psychostimulant addiction [3-5].

The lack of effective medications has spurred increased research attention. Recently, several review articles have described the progress of a number of pharmacological agents that are believed to be possibly effective in treatment of psychostimulant addiction [3-10]. However, most of these have focused on preliminary clinical findings (or 'clinical'-based medication discovery), and none of the potentially effective agents described has yet been clearly shown to be effective in humans [4-9]. We have previously argued that knowledge of the underlying brain mechanisms of addiction, garnered from diligent and astute use of preclinical animal models relevant to addiction, provides an alternative – and arguably more rational – approach to the development of effective anti-addiction treatment medications [11, 12]. On this rationale, we focus in the present review on 'mechanism'-based medication development strategies and we evaluate the pharmacological efficacy in animal models of drug addiction of various novel pharmacological agents possibly effective for the treatment of psychostimulant addiction. Animal models of disease are, by definition, approximations of the corresponding human clinical conditions. Since no single model can fully emulate all aspects of human drug abuse, multiple animal models or paradigms have been developed to reflect different aspects of the human addictive process. Among them, drug self-administration, brain stimulation reward (BSR), conditioned place preference (CPP) and drug discrimination are the most commonly used animal paradigms for studying the acute rewarding effects of drugs of abuse. Reinstatement models of drug-seeking behavior - triggered by the addictive drug itself, drug-paired environmental cues, or stress - are the most commonly used animal paradigms to emulate drug craving and relapse to drug use in humans. Detailed descriptions of each of these animal paradigms have been reported elsewhere [1, 3, 11, 12].

Extensive studies during several decades indicate that the neurotransmitter or neuromodulator systems most critically involved in drug reward and addiction are those involving dopamine (DA), γ-aminobutyric acid (GABA), endocannabinoids, glutamate, endogenous opioids, and serotonin [13-19]. Therefore, in the present review article, we first briefly review the functional role of each neurotransmitter in psychostimulant reward and relapse, and then summarize major findings in animal models of psychostimulant addiction produced by 27 pharmacological agents that target these neurotransmitter systems. We then discuss the potential use of these compounds in the clinical treatment of psychostimulant addiction. Recent studies also suggest that acetylcholine, several neuropeptides, and other neuro-signaling systems are involved in psychostimulant addiction [20, 21]. We do not review these systems in the present article because many findings are controversial or inconclusive, or reported elsewhere.

2. DOPAMINE-BASED MEDICATION DISCOVERY – ANTAGONIST STRATEGIES

Mesolimbic DA hypothesis of drug reward: It is well documented that the mesolimbic DA system is critically involved in drug reward and addiction [13-14, 17]. This system originates from the DA neurons in the ventral tegmental area

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(VTA) in the midbrain and predominantly projects to the NAc, prefrontal cortex (PFC) and amygdala in the forebrain. A great deal of evidence supports the importance of this DA system in drug addiction. First, almost all addictive drugs, including cocaine, amphetamine, opiates, nicotine, marijuana or ethanol, increase extracellular DA in the NAc [13-14, 17, 22]. Second, almost all addictive drugs are self-administered by animals either intravenously or locally into brain DA loci, an effect that can be blocked by either selective lesions of DA terminals or by pharmacological blockade of DA receptors [23, 24]. Third, electrical stimulation of brain DA loci maintains BSR, which is enhanced by drugs of abuse and attenuated by DA receptor antagonists [25, 26]. Cocaine-induced increases in extracellular DA are mediated by blockade of DA reuptake, while amphetamine- or methamphetamine-induced increases in extracellular DA are mediated predominantly by reversal of DA transporters [14, 17, 27]. These increases in synaptic DA levels in forebrain reward loci — especially in the NAc — are thought to underlie the euphoria associated with psychostimulant use [13-14, 17, 28]. Based on these findings, much development of new medications for treatment of psychostimulant addiction has focused on manipulation of DA transmission in the reward circuitry of the brain. Two major pharmacological strategies for manipulating brain DA transmission have emerged as the basis of anti-psychostimulant medication development: one being to modulate brain DA receptors, and the other being to modulate DA transporters. The former strategy has – to date – primarily utilized DA receptor antagonists, while the latter strategy has – to date – primarily utilized indirect DA receptor agonists that can be viewed as pharmacologically substituting for the addictive psychostimulants in a manner analogous to methadone substitution for heroin. Recently, extensive studies have demonstrated that the DA agents summarized in Table **1** appear to be promising for the treatment of psychostimulant addiction.

2.1. *Levo*-tetrahydropalmatine (*l*-THP): It is well documented that both D_1 and D_2 receptors are critically involved in drug reward and addiction [3, 29, 30]. However, clinical trials with D_1- or D_2-like receptor antagonists have failed because of lack of therapeutic effect with D_1-like antagonists or severe side-effects with D_2-like antagonists - such as dysphoria, supression of natural reward or abnormal movements [3, 29-32]. In contrast to D_1- or D_2-like receptor antagonists, *l*-THP is a non-selective D_1 and D_2 (and possibly D_3) receptor antagonist [33-36], purified from the Chinese herb *Stephanie* [33]. *l*-THP has been used in China as a traditional sedative-analgesic agent for more than 40 years for the treatment of chronic pain and anxious insomnia. Recent studies have shown that *l*-THP significantly inhibits: 1) cocaine- or methamphetamine-induced CPP [37, 38]; 2) cocaine self-administration under fixed-ratio (FR) reinforcement and progressive-ratio (PR) reinforcement schedules [36, 39]; 3) cocaine-enhanced electrical BSR [39]; and 4) cocaine-triggered reinstatement of drug-seeking behavior in rats [36]. Such data support the potential use of *l*-THP in the treatment of psychostimulant dependence. The attenuation of cocaine's actions in the above cited animal models of drug addiction are unlikely due to *l*-THP-induced sedation or locomotor inhibition, because the effective doses for attenuation of

Table 1. Pharmacological Actions of DA Receptor Antagonists in Animal Models or Paradigms of Psychostimulant Addiction

	l-THP	BP-897	SB-277011A	NGB2904	S33138
Pharmacological Actions	DA (D_1, D_2, and maybe D_3) antagonist	D_3 partial agonist	D_3 antagonist	D_3 antagonist	D_3-preferring antagonist
Self-Administration (SA)	↓ Cocaine SA (FR, PR)	↓ Cocaine SA (PR, 2nd-order, not FR)	↓ Cocaine SA (PR, 2nd-order, not FR) ↓ METH SA (PR, not FR)	↓ Cocaine SA (PR, not FR)	↓ Cocaine SA (PR, not FR)
Reinstatement of Drug-Seeking (Relapse)	↓ Relapse by cocaine	↓Relapse by cocaine, by cues	↓ Relapse by cocaine, cues or stress	↓ Relapse by cocaine or cues	↓ Relapse by cocaine
Conditioned Place Preference (CPP)	↓ CPP by cocaine or METH	↓ CPP by cocaine	↓ CPP by cocaine		
Enhanced Brain-Stimulation Reward (eBSR)	↓ eBSR by cocaine	↓ eBSR by cocaine or METH	↓ eBSR by cocaine or METH	↓ eBSR by cocaine or METH	↓ eBSR by cocaine or METH
Psychostimulant-like Discriminative Stimulus Effects (DS)		↓ DS by cocaine or Amphetamine			
Behavioral Sensitization (BS)		↓ BS by cocaine Cue			
Abuse Liability	No SA by itself		No SA by itself	No SA by itself	No SA by itself
Natural Reward	↓ Sucrose-taking ↓ Food-taking	No effect on sucrose-seeking	No effect on food-taking	No effect on sucrose-seeking	↓ Sucrose-taking
Clinical Use or Trials	For pain and insomnia for 40 years	Phase II	No	No	No

***l*-THP:** *Levo*-tetrahydropalmantine; **FR:** Pixed-ratio reinforcement; **PR:** Progressive-ratio reinforcement; **2nd-order:** Self-administration under second-order reinforcement; **METH:** Methamphetamine.

cocaine's actions are much lower (3-10 fold) than those for inhibition of locomotion or sucrose self-administration [39]. In addition, *l*-THP also inhibits opioid tolerance and withdrawal syndromes in rats [40], as well as locomotor sensitization to oxycodone in mice [41], suggesting an anti-addictive utility broader than just for psychostimulants. A recent clinical trial demonstrates that *l*-THP significantly attenuates drug craving and relapse in heroin addicts [42].

In vivo microdialysis demonstrates that *l*-THP modestly elevates extracellular NAc DA by itself, and also dose-dependently potentiates cocaine-augmented DA [39], suggesting an action on presynaptic DA $D_{2/3}$ receptors. However, such presynaptic action is unlikely to mediate the antagonism by *l*-THP of cocaine's actions, suggesting a post-synaptic mechanism underlying the pharmacotherapeutic effects of *l*-THP. Although *l*-THP modestly elevates NAc DA, it can not maintain intravenous self-administration behavior in rats previously self-administered cocaine [36, 39], suggesting that *l*-THP has no abuse potential by itself. Given that chronic cocaine appears to produce a reduction in basal mesolimbic DA transmision in both humans and experimental animals after withdrawal or abstinence [23, 43-46], the *l*-THP-induced modest augmentation of extracellular DA may also contribute to its therapeutic anti-cocaine actions by correcting the hypofunctional DA state. Since *l*-THP is a natural and cost-effective substance purified from Chinese herbs, and is well-tolerated in humans with few side-effects [33], the above preclinical findings support the potential use of *l*-THP for the treatment of cocaine or other pyschostimulant addiction.

2.2. BP-897: Recent research interest in DA D_3 receptor-selective compounds in medication discovery for the treatment of psychostimulant addiction is derived from the unique anatomical distribution of D_3 receptors in the brain. D_3 receptors are preferentially localized in the mesolimbic DA system with the highest receptor densities in the NAc, islands of Calleja and olfactory tubercle [47, 48]. This restricted neuroanatomic localization suggests an important role for D_3 receptors in drug reward and addiction [49, 50]. In addition, D_3 receptors have the highest affinity for endogenous DA of all known receptors [49, 51], suggesting a crucial role for D_3 receptors in the normal functioning of the mesolimbic reward system. Based on these and other considerations, it was hypothesized that pharmacological agents that block brain D_3 receptors might be effective in the treatment of psychostimulant dependence [49, 50, 52].

BP-897 [1-(4-(2-naphthoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine] is the first developed D_3-selective pharmacological agent. It has been claimed to act as a D_3 partial agonist [53] or antagonist [54, 55]. It has modest (60-70 fold) selectivity for human D_3 *versus* D_2 receptors, and similar (60-70 fold) selectivity over other receptors such as α_1-, α_2-adrenergic, and 5-HT_{1A} receptors [53]. Several studies have assessed the efficacy of BP-897 in animal models of drug addiction [56, 57]. Briefly, it has been reported that BP-897 produces a significant dose-dependent reduction in: 1) cocaine self-administration under second-order reinforcement [53], but not under FR reinforcement [58]; 2) cocaine- or cocaine-cue-triggered reinstatement of cocaine-seeking behavior [59-61]; 3) cocaine-induced CPP [62-64]; 4) cocaine's or amphetamine's discriminative stimulus properties [65]; and 5) cocaine cue-induced increases in locomotion and behavioral sensitization [66]. These data support the potential use of BP-897 in the treatment of cocaine or other psychostimulant addiction [56, 57, 67, 68].

However, enthusiasm for BP-897 has waned due to recent findings that BP-897 also displays full antagonist properties at both DA D_2 and D_3 receptors [54, 55, 57]. Given that D_2 receptor antagonism usually produces severe unwanted side-effects, such as dysphoria, inhibition of natural reward, and abnormal extrapyramidal movements [3, 29, 30], BP-897's D_2 antagonist properties raise the possibility of unwanted side-effects at the human level. BP-897 has recently entered Phase II clinical studies, but detailed pharmacokinetic and toxicological data have not yet been reported.

2.3. SB-277011A: SB-277011A [*trans-N*-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolinecarboxamide] is the most well characterized DA D_3 receptor in antagonist to date. SB-277011A has high affinity for the human cloned DA D_3 receptor, and the ratio of *in vitro* D_3/D_2 affinity of SB-277011A for human and rat is 120 and 80, respectively [69]. SB-277011A has a 100-fold selectivity or better over 180 other receptors, enzymes and ion channels [69]. Recently, we and others have assessed the pharmacological efficacy of SB-277011A in animal models of drug addiction. We found that SB-277011A attenuates: 1) cocaine- or methamphetamine-enhanced BSR [70, 71]; 2) cocaine-induced CPP [70]; 3) cocaine or methamphetamine self-administration under PR or high FR (FR10) reinforcement schedules [72, 73]; 4) cocaine-seeking behavior under second-order reinforcement conditions [74]; 5) cocaine-, cocaine cue- or stress-triggered relapse to cocaine-seeking behavior [59-60, 70, 75]; and 6) incubation of cocaine craving in rats [76]. These data suggest that SB-277011A significantly inhibits the acute rewarding effects of psychostimulants, incubation of cocaine craving, and reinstatement of cocaine-seeking behavior [57]. However, further development of SB-277011A has been halted by GlaxoSmithKline Pharmaceuticals, due to unexpectedly poor bioavailability (~2%) and a very short half-life (<20 min) in primates [77, 78]. Therefore, development of other D_3-selective antagonists with higher bioavailability and more promising pharmacotherapeutic profiles is required [79].

2.4. NGB 2904: NGB 2904 [*N*-(4-[4-{2,3-dichlorophenyl}-1-piperazinyl]butyl)-2-fluorenylcarboxamide] is another highly selective D_3 receptor antagonist which demonstrates high binding affinities at primate and rat D_3 receptors [79-81]. NGB 2904 has been reported to have >150-fold selectivity for primate D_3 over D_2 receptors, and >800-fold selectivity for rat D_3 *versus* D_2 receptors [79, 80]. In addition, it was found to have >5000-fold selectivity over D_1, D_4, and D_5 receptors, 200- to 600-fold selectivity over α_1, $5HT_2$ receptors, and >1000-fold selectivity *versus* other CNS targets in a 60-receptor Panlabs screen [80]. These *in vitro* profiles of NGB 2904 suggest it to be a promising D_3 antagonist.

Based on this, we recently examined the pharmacological efficacy of NGB 2904 in animal models of psychostimulant addiction. We found that systemic administration of NGB 2904 inhibits: 1) intravenous cocaine self-administration maintained under PR reinforcement [82]; 2) cocaine- or cocaine cue-triggered reinstatement of cocaine-seeking behavior [60, 82]; and 3) cocaine- or methamphetamine-enhanced BSR [71, 82]. In addition, NGB 2904 inhibits nicotine- and heroin-enhanced BSR [83]. Further, NGB 2904 neither produces a dysphorigenic shift in BSR functions nor substitutes for cocaine in

maintenance of self-administration behavior, suggesting that NGB 2904 itself has no addictive liability [83].

The effectiveness of NGB 2904 on PR cocaine self-administration and reinstatement of drug-seeking triggered by cocaine or cocaine-associated cues suggests a clinical therapeutic potential, particularly for relapse to drug-seeking behavior. NGB 2904 is currently not under clinical trial and detailed data regarding bioavailability and pharmacokinetic properties must still be gathered.

2.5. S33138: As described above, the selective D_3 receptor antagonists SB-277011A and NGB 2904 are ineffective against intravenous cocaine and methamphetamine (and also nicotine or alcohol) self-administration under low fixed-ratio (FR1, FR2) reinforcement conditions. In addition, NGB 2904's antagonism of cocaine- and methamphetamine-enhanced BSR displays an obvious "dose-window effect". That is, only lower doses of NGB 2904 were effective in attenuating cocaine- or methamphetamine-enhanced BSR, and the anti- reward effects could be overcome by increasing the doses of cocaine or methamphetamine [71, 83]. These data suggest that selective D_3 receptor antagonists may have limited potential against the direct rewarding effects produced by psychostimulants. Consequently, it was proposed that preferential D_3 *versus* D_2 receptor antagonists may be an effective strategy for treating psychostimulant addiction [39, 83, 84], based upon the finding that blockade of both D_3 and D_2 receptors produces additive or synergistic effects in antagonizing drug reward, but produced fewer unwanted side-effects than selective D_2 antagonists due to opposite locomotor effects produced by blockade of D_3 (facilitation) *versus* D_2 (suppression) receptors [84, 85].

S33138 (*N*-[4-[2-[(3*aS*,9*bR*)-8-cyano-1,*3a*,4,9*b*-tetrahydro [1]benzopyrano[3,4-c]pyrrol-2(3*H*)-yl)-ethyl]phenyl acetamide) is such a preferential D_3 *versus* D_2 receptor antagonist [86], displaying 25-fold selectivity for human (h) D_3 over hD_2 receptors (pK_i, 8.7 *vs.* 7.1 and 7.3). Recently, we carried out a series of experiments to evaluate the efficacy of S33138 in animal models relating to cocaine addiction [87]. We found that systemic administration of S33138 dose-dependently attenuated cocaine-enhanced BSR, but at the highest dose S33138 produced a significant aversive-like shift in BSR reward functions. S33138 produced biphasic effects on cocaine self-administration, i.e., a moderate dose increased, while a high dose inhibited, cocaine self-administration under FR2 reinforcement. We suggest that the increase in cocaine self-administration produced by the moderate dose of S33138 could be a compensatory response to a partial reduction in cocaine reward. In addition, S33138 also dose-dependently inhibited oral sucrose self-administration at high doses. In the reinstatement model of relapse to drug-seeking behavior, S33138 dose-dependently inhibited cocaine-triggered reinstatement of drug-seeking behavior. This reduction in reward-taking/seeking behaviors is unlikely due to impaired locomotor performance, as S33138 decreased neither Ymax levels in the BSR paradigm nor locomotor activity. Finally, S33138, at doses of 0.04-0.36 mg/kg/infusion, is clained to not be self-administered intravenously in rhesus monkeys[1]. These findings suggest that the preferential D_3 *versus* D_2 receptor antagonist S33138 may be useful for the treatment of cocaine addiction, and may even show advantages relative to selective D_2 antagonists, although the aversive-like BSR effects and inhibition of natural reward at high doses is a caution. Currently, S33138 is under clinical trial as an anti-psychotic agent [84, 88].

3. DOPAMINE-BASED MEDICATION DISCOVERY – AGONIST SUBSTITUTION STRATEGIES

Agonist substitution hypothesis: Agonist substitution as a pharmacotherapy for psychostimulant addiction is based on, first, the success of methadone in the treatment of opiate dependence and the nicotine patch for smoking cessation; second, the finding that the speed with which addictive drugs enter the brain and elevate NAc DA is positively correlated with addictive potential [89, 90], with slow-onset long-acting compounds having lower addictive potential; third, the hypothesis that a compound with low addictive potential may substitute for one with high addictive potential, thereby decreasing the use of the highly addictive drug; and finally, the hypothesis that long-term increases in NAc DA may ameliorate the hypodopaminergic dysfunction believed to exist in human cocaine addicts, thereby minimizing drug craving and relapse [23, 43, 45, 46]. To achieve such DA agonist effects, medication development for anti-addiction purposes has concentrated on the development of DA reuptake or DA transporter (DAT) inhibitors rather than direct DA receptor agonists. Indeed, this strategy has been at the forefront of medication development for the treatment of cocaine addiction for more than a full decade [11, 91]. To date, a wide variety of structural classes have served as chemical templates for the development of slow-onset long-acting DAT inhibitors, including benztropines, mazindol, substituted piperazines, tropanes, indanamines and trans-aminotetralins (Table **2**).

3.1. GBR-12909 (Vanoxerine): GBR-12909, a phenyl-substituted piperazine derivative, is a relatively slow-onset long-acting DAT inhibitor [92]. To date, it is the most extensively studied DAT inhibitor proposed to be beneficial in the treatment of cocaine addiction [93-96]. GBR-12909 binds to the DAT site with high affinity, and selectively inhibits DA re-uptake [97]. GBR-12909 can also compete with psychostimulants at the DAT site, thus blocking cocaine- or amphetamine-induced increases in NAc extracellular DA [98, 99]. Compared with the same doses of cocaine, GBR-12909-induced increases in striatal DA and locomotion are relatively slow-onset (<10 min *vs.* 10-20 min) and long-lasting (1 hr *vs.* 3-4 hr) [99, 100]. Pretreatment with GBR-12909 significantly inhibits cocaine self-administration in rats and nonhuman primates at doses that have little or no effect on food self-administration [101-104]. Repeated treatment with low doses of GBR-12909 also sustains the selective suppression of cocaine self-administration *versus* food self-administration [105]. Further, a single injection of a decanoate ester slow-release formulation of GBR-12909 produced a prolonged (up to one month) suppression of cocaine self-administration in nonhuman primates [92, 106]. These findings support GBR-12909 as a potential candidate for the treatment of cocaine addiction [96]. However, there are significant cautions associated with it. GBR-12909 itself produces cocaine-like augmentment of BSR [107] and cocaine-like discriminative stimulus effects [108]. It is also self-administered and triggers reinstatement of extinguished drug-seeking behavior in both rats and primates [109, 110]. These data suggest that GBR-12909 itself may have

[1]France *et al.*, unpublished data.

Table 2. Pharmacological Actions of DA or Monoamine Transporter Inhibitors in Animal Models or Paradigms of Psychostimulant Addiction

	GBR12909	RTI-336	CTDP30,640	CTDP31,345
Pharmacological Actions	DA transporter inhibitor	DA transporter inhibitor	Monoamine transporter inhibitor	Monoamine transporter inhibitor
Self-Administration (SA)	↓ Cocaine SA (FR, PR)	↓ Cocaine SA (FR, 2nd-order)	↓ Cocaine SA (FR)	↓ Cocaine SA (FR)
Reinstatement of Drug-Seeking (Relapse)	↓ Relapse by cocaine or cues			No effect on relapse by cocaine
Enhanced Brain-Stimulation Reward (eBSR)	↓ eBSR by cocaine		↑ eBSR by cocaine	↑ eBSR by cocaine
Psychostimulant-like Discriminative Stimulus Effects (DS)	↑ DS by cocaine, by METH			
Abuse Liability	SA by itself; Sensitization by itself	SA by itself; DS effect by itself	Sensitization by itself; DS effect by itself	SA by itself
Natural Reward	No effect on food-taking	↓ Food-taking		↓ Sucrose-taking
Clinical Trials	Phase I / IIa	No	No	No

abuse potential. Finally, GBR-12909 produced rate-dependent cardiac QTc interval prolongation in five out of five subjects studied in Phase I human trials, prompting discontinuation of the trials [112].

3.2. RTI-336: RTI-336 [3beta-(4-chlorophenyl)-2beta-[3-(4'-methylphenyl)isoxazol-5-yl]tropane] is a novel slow-onset (30 min) long-acting (4 hrs) DAT inhibitor [90, 111]. It has >1000- and >400-fold selectivity for the DAT relative to the serotonin transporter (SERT) and norepinepherine transporter (NET), respectively [113]. Pretreatment with RTI-336 produced dose-dependent reduction in cocaine self-administration in both rats and nonhuman primates [114, 115]. The ED_{50} dose of RTI-336 for reducing cocaine self-administration resulted in approximately 90% DAT occupancy, suggesting that high levels of DAT occupancy by RTI-336 are required to reduce cocaine self-administration. However, co-administration of the ED_{50} dose of RTI-336 with the SERT inhibitor fluoxetine or citalopram produced robust reductions in cocaine self-administration in nonhuman primates [115], suggesting that blockade of both DAT and SERT may be more effective in attenuating cocaine's reinforcement than selective blockade of DAT alone [116]. However, RTI-336, at the doses that effectively suppressed cocaine self-administration, also inhibited food-taking behavior under multiple second-order reinforcement schedules [115]. This is different from the relative selectivity of GBR-12909 in suppressing cocaine self-administration over food-taking behavior, as noted above. As with many other DAT inhibitors, RTI-336 itself reliably maintained self-administration behavior in all non-human primates tested [115], suggesting abuse liability by itself. In addition, RTI-336 itself also produced locomotor stimulating and cocaine-like drug-discrimination effects in mice and rats. However, when compared with cocaine, RTI-336 maintained lower rates of self-administration, produced weaker locomotion and cocaine-like drug discriminative stimulus effects across a broad range of doses, and showed very low locomotor sensitization [113, 117]. These data suggest that RTI-336 may have lower abuse potential than cocaine. So far, there are no human trials with RTI-336 reported.

3.3. CTDP30,640: CTDP30,640 is an indanamine analog with slow-onset and long-acting monoamine re-uptake inhibitor properties [118, 119]. The "CTDP" terminology derives from the "Cocaine Treatment Discovery Program" of the Extramural Program of the U.S. National Institute on Drug Abuse. Our interest in such a non-selective monoamine transporter inhibitor as a potential anti-cocaine medication originally stemmed from the fact that cocaine is also a non-selective monoamine transporter inhibitor. Thus, a monoamine transporter inhibitor with a slow-onset and long-acting profile might constitute a therapeutically useful substitute for cocaine. This possiblity is supported by a recent finding that combined DAT and SERT inhibition appears more effective in suppressing cocaine self-administration than a selective DAT inhibitor (RTI-336) alone, as mentioned above.

CTDP30,640 is a prodrug, which is metabolized to active metabolites by rate-limited *N*-demethylation to achieve the desired slow-onset long-lasting pharmacological profile. CTDP30,640 itself has little or no activity [118]. We have evaluated the efficacy of CTDP30,640 in preclinical animal paradigms of drug addiction. We found that: 1) CTDP30,640 produced a cocaine like enhancement of locomotor activity, but with a slow-onset (<10 min *vs.* 20 min) and striking long duration (2h *vs* 8h) compared with cocaine [118]; 2) CTDP30,640 produced cocaine-like drug-discrimination effects in rats [118]; 3) CTDP30640 produced a cocaine-like enhancement of BSR, but with a marked slow onset and prolonged duration (up to 25-48 hrs after 3-5 mg/kg) relative to cocaine [119]; 4) CTDP30,640 dose-dependently lowered cocaine self-administration, an effect that lasted for up to 28, 50, and 90 hrs after 2.5, 5.0, 10 mg/kg, respectively [119]; and finally, 5) *in vivo* brain microdialysis demonstrated that CTDP30,640 produced a marked cocaine-like enhancement of NAc DA with a very pronounced slow onset and long duration profile relative to cocaine [119]. These findings suggest that CTDP30,640 has cocaine-like rewarding, psychomotor stimulating and neurochemical properties with slow onset and extra-long duration. The prolonged suppression of cocaine self-administration after a single dose of CTDP30,640 suggests the potential use of CTDP30,640 in the treatment of cocaine addic-

tion. However, its strong psychomotor stimulant and stereotypy-inducing effects decrease enthusiasm for its further development [118].

3.4. CTDP31,345: Based on our work with CTDP30,640, we designed, synthesized and tested additional slow-onset long-acting monoamine transporter inhibitors as candidate compounds for the treatment of psychostimulant addiction. CTDP31,345 is a *trans*-aminotetralin derivative [118, 120]. Like CTDP 30,640, CTDP31,345 is also a prodrug, which is metabolized (*N*-demethylated) to CTDP31,346, a slow-onset long-acting non-selective monoamine transporter inhibitor. *In vitro* transporter binding assays demonstrate similar binding affinities of CTDP31,345 to cloned human DAT (Ki = 18 ± 5 nM) and SERT (Ki = 23 ± 7 nM), but a lower affinity to cloned human NET (Ki = 81 ± 10 mM). Functional reuptake assays with cell lines expressing each transporter revealed the IC_{50} of CTDP31,345 for inhibition of DA, serotonin (5-HT) and NE reuptake to be 330 ± 120, 3.6 ± 0.2 and 120 ± 60 nM, respectively[2].

To determine whether CTDP31,345 is superior to CTDP30,640, Froimowitz *et al.* observed the effects of CTDP31,345 on locomotion and stereotypic behaviors in rats. They found that the locomotor stimulation effects of CTDP31,345 (3-56 mg/kg i.p.) appeared to be mild and *not* dose-dependent. CTDP31,345, at 10 mg/kg, produced the most robust increase among all the doses (3-56 mg/kg i.p.) tested, with peak effects occurring at 40 min and lasting for about 8 hr. At higher doses, CTDP31,345 lost locomotor stimulating effects in mice. In contrast to CTDP30,640, CTDP31,345 failed to produce stereotypic behaviors in the majority (~80%) of mice tested[3]. These data suggest that CTDP31,345 appears superior to CTDP30,640, at least with respect to possible motoric side effects.

Therefore, we went on to assess the actions of CTDP31,345 in animal models of drug addiction. We found that: 1) CTDP31,345 itself has cocaine-like properties in rats. Systemic administration of CTDP31,345 produced slow-onset (20-50 min) and long-lasting (at least 5-7 hrs) increases in locomotion and NAc extracellular DA, and a sustained (>24 hrs) enhancement of BSR in rats [121, 122]; 2) pretreatment with CTDP31,345 dose-dependently inhibited cocaine self-administration in rats, an effect that lasted for at least 24 hrs after a single injection of 20 mg/kg of CTDP31,345; 3) this reduction in cocaine self-administration appeared to be due to CTDP31,345's substitution effects, because pretreatment with CTDP31,345 produced an enhancement of cocaine's effects on locomotion, electrical BSR and NAc DA; 4) such enhancing effects of CTDP31,345 on cocaine's actions are strikingly different from those of methadone on heroin's actions, in which methadone pretreatment produces a dose-dependent reduction in heroin self-administration, heroin-enhanced BSR and heroin-enhanced NAc DA; and finally 5) CTDP31,345 itself also maintained self-administration at lower rates than cocaine when tested at comparable doses in rats [121, 122].

The potential use of CTDP31,345 in the treatment of cocaine addiction remains to be determined. Although its cocaine-like rewarding effects and potential abuse liability may limit its use, the long-term inhibition of cocaine self-administration after a single dose of CTDP31,345 administration does support its potential utility. In addition, CTDP31,345-induced long-term increases in NAc DA may also be helpful in relieving drug craving and relapse to drug use by restoring reduced synaptic DA function in brain reward circuits [43, 45]. Clearly, more studies are required to determine whether CTDP31,345 or other slow-onset long-acting monoamine transporter inhibitors with different chemical structures will have similar or different pharmacological profiles in animal paradigms of drug addiction, as compared to methadone, a 'gold standard' in the treatment of opiate addiction.

4. GABA-BASED MEDICATION DISCOVERY

GABAergic hypothesis of drug reward: As noted above, an increase in mesolimbic DA transmission has been thought to underlie the drug reward produced by addictive drugs. However, how increased NAc DA mediates drug reward remains unclear. It is well documented that the neurotransmitter GABA plays an important role in the mesolimbic DA reward circuit [25, 123]. Anatomically, the majority of neurons in the striatum are medium-spiny GABAergic output neurons, which project predominantly to the dorsal globus pallidus (from the dorsal striatum) and the ventral pallidum (from the ventral striatum, i.e. the NAc) [124-126]. In addition, striatal GABAergic neurons also receive DA projections from the VTA and glutamatergic projections predominantly from the prefrontal cortex (PFC), and regulate striatal DA and glutamate release [28, 127]. Overall, DA produces an inhibitory effect on striatal medium-spiny GABAergic neurons [128-130], predominantly by activation of D_2-like DA receptors [131, 132]. Similarly, psychostimulants, such as cocaine or amphetamine, produce an inhibitory effect on VTA GABAergic neurons [133], striatal GABAergic neurons [131, 132, 134-136], and on GABA release in the ventral pallidum (VP) [137-139]. Based on this, the VTA-NAc-VP pathway, particularly the downstream NAc-VP GABAergic projection, has been proposed as a common final pathway underlying psychostimulant reward [13-14,17]. Thus, it has been hypothesized that any pharmacological strategy that increases GABAergic transmission by either elevating extracellular GABA levels or directly activating GABA receptors within brain reward circuits might directly counteract psychostimulant-induced inhibition of GABAergic neurons, thereby antagonizing psychostimulant abuse [123, 140, 141]. Based on this hypothesis, several GABAergic compounds, which are summarized in Table **3**, are being explored as candidate medications for the treatment of psychostimulant addiction.

4.1. Gamma-vinyl GABA (GVG): GVG is an irreversible GABA transaminase inhibitor [142]. GABA transaminase is the primary enzyme involved in GABA's metabolic breakdown, and therefore, and its inhibition elevates brain GABA levels. Since many anti-epilepsy and anticonvulsant medications are either direct or indirect GABA agonists, GVG (as an indirect agonist) was initially developed as an anticonvulsant, and has been used for that purpose in many countries for many years. About 10 years ago, Dewey and colleagues first proposed that GVG might be useful in the treatment of psychostimulant addiction by elevating brain GABA levels [140, 143]. So far, findings in their preclinical studies appear to be highly promising [12]. Systemic administration of GVG has been shown to inhibit: 1) cocaine-enhanced electrical BSR, but

[2]Froimowitz, unpublished data.
[3]Froimowitz and Forster, unpublished data.

Table 3. Pharmacological Actions of GABAergic Agents in Animal Models or Paradigms of Psychostimulant Addiction

	GVG	Gabapentin	Tiagabine	Topiramate	Baclofen
Pharmacological Actions	GABA transaminase inhibitor	GABAmimetic	GABA transporter inhibitor	Positive $GABA_A$ receptor modulator	$GABA_B$ receptor agonist
Self-Administration (SA)	↓ Cocaine SA (FR, PR)	No effect on cocaine SA	↓ SA of low dose cocaine		↓ Cocaine (amphetamine, METH) SA (FR, PR, 2nd-order)
Reinstatement of Drug-Seeking	↓ Relapse by cocaine	No effect on relapse by cocaine	No effect on relapse by cocaine		↓ Relapse by cocaine, by amphetamine
Conditioned Place Preference (CPP)	↓ CPP by cocaine or amphetamine				↓ CPP by METH
Enhanced Brain-Stimulation Reward (eBSR)	↓ eBSR by cocaine				↓ eBSR by cocaine
Psychostimulant-like Discriminative Stimulus Effects (DS)	No effect on DS by cocaine	No effect on DS by cocaine	No effect on DS by cocaine	No effect on DS by cocaine	No effect on DS by cocaine
Behavioral Sensitization (BS)	↓ BS by cocaine	Conflicting	No effect on cocaine BS		↓ BS by cocaine, by amphetamine
Abuse Liability	No SA by itself	Cases reported	No cocain-like DS by itself	No cocain-like DS by itself	No SA by itself
Natural Reward	↓ Food-taking ↓ Sucrose-seeking		↓ Food-taking		↓ Food-taking
Clinical Trials	Phase II	Phase I /II	Phase II	Phase II	Phase II

without significant effects on motor performance [144]; 2) cocaine self-administration under both FR5 and PR reinforcement [145, 146]; 3) cocaine-induced CPP [140]; 4) cocaine-induced behavioral sensitization [147]; and 5) cocaine-triggered reinstatement of drug-seeking behavior [146, 148]. In addition, at higher doses (~300 mg/kg), GVG also inhibits food-taking and sucrose-triggered reinstatement [145, 148, 149], but fails to inhibit the discriminative stimulus effects of cocaine [149].

Regarding the effects of GVG on NAc DA, previous studies by Dewey's group have shown that GVG significantly inhibits cocaine- or cocaine-associated cue-induced increases in NAc DA in rats [140, 150-152]. However, our recent studies demonstrate that GVG, when given systemically or locally into the NAc, dose-dependently elevates NAc extracellular GABA levels, but fails to alter either basal levels of, or cocaine-enhanced, NAc DA in drug naïve or cocaine-treated rats [148]. The same doses of GVG also fail to inhibit, but rather increase, NAc extracellular glutamate levels[4]. Clearly, these findings conflict with those from Dewey's group noted above. The reasons for this discrepancy are unclear. It does not appear to be related to GVG dose, GVG pretreatment time or animals' cocaine experience, but likely to be related to differences in rat strains (Long-Evans *vs* Sprague-Dawley) and/or brain regions of microdialysis sampling (medial NAc core/shell *vs* unspecified NAc subdomains) (see more discussion in [148]). Whatever the reasons for this discrepancy, our recent studies have further demonstrated that GVG-induced increases in NAc GABA are derived predominantly from non-neuronal (presumably glial) sources. This new finding provides a reasonable explanation for the ineffectiveness of GVG on NAc DA, i.e., that GVG-enhanced extrasynaptic GABA may not diffuse sufficiently into synaptic clefts to inhibit DA release. This is consistent with previous findings that local NAc perfusion of $GABA_A$ or $GABA_B$ receptor agonists, *but not GABA itself*, inhibits NAc DA and glutamate [127, 153, 154], and similarly inhibits cocaine or heroin self-administration and reinstatement of drug-seeking behaviors [154, 155]. GVG's ineffectiveness on NAc DA suggests that non-DA mechanisms may underlie GVG-induced inhibition of drug-seeking behavior.

We have proposed an alternative mechanistic hypothesis - that GVG-elevated extracellular GABA levels in GABAergic projection loci such as the VP or VTA, may underlie GVG's effects. That is, GVG-induced GABA elevations may directly counteract cocaine-induced reductions in GABA release, and therefore, may underlie the potential therapeutic effect of GVG on cocaine addiction [148]. This is consistent with our previous studies demonstrating that microinjection of GVG into the NAc failed to inhibit heroin self-administration, while microinjections of GVG into the VTA or VP significantly inhibited heroin self-administration [123].

Whatever the underlying mechanisms, the above-cited evidence strongly supports the potential use of GVG in the treatment of psychostimulant abuse. GVG is currently under double-blind placebo-controlled clinical trials for treatment of cocaine addiction. Preliminary open-label clinical trials demonstrated that GVG appears to manifest clinically-relevant anti-addiction, anti-craving, and anti-relapse properties in humans [156, 157]. The major concern for its use in humans, however, is the potential for visual field defects, which may limit its use.

4.2. Gabapentin: Gabapentin is structurally analogous to GABA but, unlike the latter, it crosses the blood–brain barrier and can be administered systemically [158]. Pharmacologi-

[4]Peng X-Q, Gardner EL, Xi Z-X. Abstract submitted to the 38th Annual Meeting of the Society for Neuroscience, Washington, DC, November 2008.

cally, gabapentin is a GABAmimetic drug that increases extracellular GABA levels, possibly by increasing the synthesis and nonvesicular release of GABA as well as by preventing GABA catabolism (reviewed in [159]). In addition, gabapentin also inhibits alpha2delta subunit-composed voltage-dependent Ca^{++} channels [160]. Early studies and small-scale, open-label outpatient trials suggested that gabapentin reduced cocaine craving and use [161-165]. However, this finding was later challenged by larger-scale, double-blind, placebo-controlled clinical trials demonstrating that gabapentin, at doses up to 2400-3200 mg/day for 6-12 weeks, had no effect on abstinence rates, craving or subjective effects of cocaine [166-169].

Recently, we assessed its efficacy in animal models of drug addiction. We found that gabapentin (25-200 mg/kg i.p.) failed to inhibit i.v. cocaine self-administration under FR2 reinforcement or cocaine-triggered reinstatement of cocaine-seeking behavior in rats [170]. Congruent with our findings, Filip *et al.* [146] recently reported that lower doses of gabapentin (10-30 mg/kg, i.p.) neither alter cocaine self-administration nor cocaine-induced reinstatement of drug-seeking behavior in rats. In addition, 1-30 mg/kg gabapentin was reported to have no effect on cocaine-induced hyperactivity or cocaine-induced behavioral sensitization [171, 172].

To study possible mechanisms underlying such ineffectiveness of gabapentin on cocaine's addictive behaviors, we further observed the effects of gabapentin on NAc extracellular GABA, DA and cocaine-enhanced NAc DA in rats. We found that gabapentin, at 100-200 mg/kg, produced a modest increase (maximally ~50 %) in extracellular NAc GABA levels, but failed to alter either basal or cocaine-enhanced NAc DA [170]. This is in striking contrast to our findings with GVG in which we observed a robust and dose-dependent increase (200-400% at 100-300 mg/kg) in NAc extracellular GABA and an inhibition of both cocaine self-administration and cocaine-triggered reinstatement [148]. These data suggest that gabapentin is a weak GABA enhancer and has limited potential in the treatment of psychostimulant addiction.

4.3. Tiagabine: Tiagabine is a selective type 1 GABA transporter (GAT1) inhibitor, approved as an antiepileptic medication that increases synaptic levels of GABA. There are four types of GABA transporter identified, GAT1 being the most abundant, with predominant localization on GABAergic neurons and glial cells [173, 174]. Given the effectiveness of GVG in preclinical animal models of drug addiction, it was proposed that tiagabine may also be effective in attenuating cocaine use in humans [175]. However, the results of clinical trials with tiagabine are conflicting. Two small-scale (45 and 76 subjects, respectively) placebo-controlled clinical trials indicated that tiagabine produced a moderate reduction (~30%) in self-reported and urine-measured cocaine use in methadone-treated cocaine addicts [168, 175]. In contrast to this finding, other studies demonstrated that the same doses of tiagabine neither altered the acute effects of oral cocaine [176], nor significantly lowered cocaine use in human cocaine addicts [177, 178].

Similar conflicting findings are also reported in preclinical animal studies. It was reported that tiagabine produced a dose-dependent reduction in self-administration maintained by a very low dose (0.032 mg/kg) of cocaine under a FR10 schedule of reinforcement in baboons [179]. In contrast, Filip *et al.* [146] reported that tiagabine significantly inhibited lever responding for cocaine (0.5 mg/kg/infusion) self-administration under FR5 reinforcement, but had no effect on either total cocaine intake during self-administration, cocaine-induced reinstatement of drug-seeking behavior, or cocaine's discriminative stimulus effects. The reasons for such conflicting findings are unclear. Possibly, tiagabine's binding properties could play a role. [^{3}H]Tiagabine has highest binding density in frontal cortex and parietal cortex, and lowest binding in NAc and putamen [180]. Overall, present data suggest that tiagabine may have limited potential for the treatment of psychostimulant addiction.

4.4. Topiramate: GABAergic neurotransmission can be increased by drugs that elevate endogenous GABA levels (such as GVG, gabapentin or tiagabine) or by positive modulators at $GABA_A$ or $GABA_B$ receptors. Topiramate is a positive modulator of $GABA_A$ receptors, licensed as an antiepileptic drug. In addition to its enhancement of $GABA_A$ receptor-mediated currents at non-benzodiazepine sites on the $GABA_A$ receptor, topiramate also has other pharmacological actions in the brain, including antagonism of AMPA/kainate glutamate receptors, inhibition of voltage-gated sodium and calcium channels and inhibition of carbonic anhydrase [181]. Based on this, topiramate was proposed to be able to inhibit cocaine-enhanced NAc DA and cocaine abuse by enhancing $GABA_A$-mediated inhibition and blocking excitatory glutamate activity [181, 182]. In a small preliminary clinical study (6 subjects), topiramate appeared to be effective at producing cessation of cocaine use, and alcohol consumption as well [183]. In another bigger double-blind, placebo-controlled clinical trial (40 subjects), topiramate significantly increased abstinance rates in patients with low cocaine withdrawal scores when compaired with placebo [184]. In contrast, a recent clinical report indicates that acute dosing with topiramate appears to enhance, rather than attenuate, the positive subjective effects of methamphetamine [185]. These data suggest that more large-scale clinical trials and preclinical mechanistic studies are required to determine whether or not topiramate is truly effective in antagonizing the addictive actions of psychostimulants.

4.5. Baclofen: Baclofen is a selective $GABA_B$ receptor agonist, licensed as an antispasmodic for patients with spinal cord injuries or multiple sclerosis. The efficacy of baclofen against cocaine use and relapse has been studied in both humans and animals extensively for many years, and appears promising for the treatment of cocaine addiction [186]. In rodents, pretreatment with baclofen dose-dependently attenuated cocaine-induced increases in NAc DA [187], cocaine-enhanced BSR [188], and cocaine self-administration under FR and PR reinforcement [189-191]. Baclofen also reduced cocaine-taking and cocaine-seeking behavior under second-order reinforcement in rats [192] and cocaine-triggered reinstatement of drug-seeking behavior [193, 194].

In an initial open-label clinical trial, baclofen (20 mg $\times$ 3) reduced self-reports of craving and cocaine use in 10 cocaine abusers [195]. In a subsequent 16-week double-blind study in 35 cocaine-dependent subjects, the same doses of baclofen reduced cocaine use and increased the number of cocaine-free urines [196], but did not significantly alter cocaine craving. In a recent placebo-controlled, double-blind study, baclofen (20 mg $\times$ 3/day, for 7 days) decreased self-administration of a low dose of smoked cocaine in 10 cocaine addicts, decreased cocaine craving in 7 opioid addicts, attenuated cocaine's

cardiovascular effects, but not cocaine's subjective effects ('high', 'stimulated') in both cocaine- and opioid-dependent subjects [197]. Another similar double-blind controlled study (7 subjects) demonstrated that a single dose of baclofen (10-30 mg/kg, p.o.) had no effect on either subject-rated or cardiovascular effects of intranasal cocaine [198]. Overall, baclofen seems to be well tolerated with no major side effects. The major limitation is its short-duration (3–4 hrs) of action, but slow-release preparations are likely to circumvent this limitation.

5. CANNABINOID-BASED MEDICATION DISCOVERY

Cannabinoid hypothesis of drug reward: Marijuana is the most widely used illicit drug in the United States and many other countries. As with other addictive drugs, cannabinoids produce significant rewarding and psychostimulating effects in both humans and experimental animals [199]. However, the underlying mechanisms are still unclear. The main psychoactive ingredient in marijuana is Δ^9-tetrahydrocannabinol (Δ^9-THC). Two major types of cannabinoid receptors, CB_1 and CB_2, have been cloned [200, 201]. CB_1 receptors are found primarily in the brain, whereas CB_2 receptors are located mainly in peripheral tissues associated with the immune system [202, 203].

As discussed above, a GABAergic mechanism may underlie the rewarding effects of addictive drugs. Here, we propose that a similar cannabinoid-induced inhibition of GABAergic neurons in the mesolimbic system may also underlie the actions of cannabinoids. This is supported by the following evidence: first, previous studies show that Δ^9-THC enhances NAc extracellular DA [204, 205], which may inhibit postsynaptic medium-spiny GABAergic neurons; and second, high densities of CB_1 receptors are found on medium-spiny GABAergic neurons and glutamatergic terminals in the striatum [203, 206]. Since CB_1 receptors are G_i-coupled, activation of CB_1 receptors located on GABAergic neurons produces an inhibitory effect on GABAergic neurons. Similarly, activation of CB_1 receptors located on glutamatergic terminals decreases glutamate release, thereby decreasing excitatory impact on striatal GABAergic neurons. Growing evidence demonstrates that cocaine, opioids, alcohol and DA significantly increase endocannabinoid release in the striatum [207-210], suggesting that such an increase in endocannabinoids release may contribute to the acute rewarding effects of psychostimulants by increasing endocannabinoid tone on CB_1 receptors located on both medium-spiny GABAergic neurons and glutamate terminals. This endocannabinoid hypothesis of drug reward may explain why deletion or pharmacological blockade of CB_1 receptors broadly affects almost all addictive drug actions in experimental animals [18, 211]. Based on this hypothesis, the selective CB_1 receptor antagonists summarized in Table **4** could be effective in attenuating the rewarding effects and relapse properties of drugs of abuse, including psychostimulants.

5.1. SR141716A: SR141716A [*N*-(piperidin-1-yl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-carboxamide] is the first developed selective CB_1 receptor antagonist [212], and has become a considerable focus for research on medication discovery for the treatment of drug abuse. It is well documented that SR141716A appears to be widely effective in attenuating self-administration of heroin, nicotine, or alcohol, and in attenuating reinstatement of drug-seeking behavior produced by these drugs [213-215]. However, the effects of SR141716A on cocaine's actions have been controversial [216]. The positive findings include: 1) SR141716A (0.3-3.0 mg/kg i.p.) significantly inhibited cocaine- or cocaine-associated environmental cue-, but not footshock stress-, induced reinstatement of drug-seeking behavior [217, 218]; 2) SR141716A (0.3-3.0 mg/kg) dose-dependently lowered the break-point for cocaine self-administration under PR reinforcement conditions in mice [219]; and 3) SR141716 significantly inhibited cocaine-induced phasic increase in NAc DA in rats as assessed by *in vivo* voltammetry [220]. In contrast to these positive findings, most other studies demonstrate that SR141716A, within the dose range of 0.3-10 mg/kg, has no significant effect on: 1) cocaine self-administration under FR or PR reinforcement conditions in mice, rats or nonhuman primates [139, 217, 221-224]; 2) cocaine-induced CPP [225]; 3) cocaine's discriminative stimulus effects [223]; 4) cocaine-enhanced BSR in rats [224]; 5) cocaine-induced behavioral sensitization [223, 225]; 6) cocaine-induced increases in NAc DA [139, 219]; and 7) cocaine-induced decreases in extracellular VP GABA levels [139]. These data suggest that SR141716A may have certain therapeutic potential in attenuating drug craving or relapse to drug-seeking behavior, but has limited potential in attenating cocaine's acute rewarding and neurochemical effects [211, 216].

5.2. AM251: AM251 [*N*-(piperidin-1-*yl*)-5-(4-iodophenyl)-l-(2,4-dichlorophenyl)-4-methyl-l-*H*-pyrazole-3-carboxamide] is a another CB_1 receptor antagonist. Compared with

Table 4. Pharmacological Actions of CB1 Receptor Antagonists in Animal Models or Paradigms of Psychostimulant Addiction

	SR141716	AM251
Pharmacological Actions	Prototypic CB1 receptor antagonist	Novel CB1 receptor antagonist
Self-Administration (SA)	Conflicting	↓ Cocaine SA (PR, not FR) ↓ METH SA (FR)
Reinstatement of Drug-Seeking (Relapse)	↓ Relapse by cocaine, cues, not stress	↓ Relapse by cocaine
Conditioned Place Preference (CPP)	No effect on cocaine CPP	
Enhanced Brain-Stimulation Reward (eBSR)	↓ eBSR by cocaine	↓ eBSR by cocaine
Behavioral Sensitization (BS)	Conflicting	↓ BS by cocaine
Natural Reward	↓ Food-taking	↓ Food-taking
Clinical Trials	Phase III for nicotine and alcohol, but not psychostimulant, dependence	No

SR141716A, AM 251 is roughly 2-fold more potent (K_i=7.49 *vs.* 11.5 nM) and more selective (1: 306 *vs.* 1: 143) than SR141716 for CB_1 over CB_2 receptors *in vitro* [226, 227]. The efficacy of AM251 on psychostimulant action has been assessed recently in preclinical animal models. In summary, it was reported that AM 251, within the dose range of 1-10 mg/kg i.p., dose-dependently inhibited: 1) methamphetamine (0.08 mg/kg/infusion) self-administration under FR3 reinforcement in rats [228]; 2) cocaine self-administration under PR, but not under FR2 reinforcement conditions in rats [224]; 3) cocaine-triggered reinstatement of drug-seeking behavior in rats [229]; 4) cocaine-enhanced electrical BSR in rats [224]; 5) cocaine- or amphetamine-induced behavioral sensitization in mice [230]; 6) cocaine-induced increases in NAc glutamate, but not in DA in rats [39]; and 7) cocaine-induced increases in phosphorylated extracellular signal-regulated kinase (p-ERK) [230]. In contrast to these positive findings, it was recently reported that, at lower doses (0.032-0.32 mg/kg i.v.), AM251 had no effect on methamphetamine-induced reinstatement of drug-seeking behavior in rats [231].

Together, these data suggest that AM251 appears to be more potent and more effective in attenuating cocaine's acute rewarding effects than SR141716. This is consistent with their *in vitro* binding properties noted above. In addition, the non-selective binding of SR141716A to other non-CB_1 receptor proteins may also contribute to its relative ineffectiveness in attenuating cocaine's rewarding efficacy (for more comprehensive review, see [211]).

Our most recent studies further demonstrate that a GABAergic mechanism within the NAc-VP GABAergic pathway appears to underlie AM251's anti-reward action [211]. This is largely based on our recent finding that systemic cocaine produced a significant and dose-dependent increase in extracellular DA in both the NAc and VP, but a dose-dependent reduction in extracellular GABA levels in the VP. Pretreatment with AM251, when administered systemically or locally into the VP, dose-dependently blocked cocaine-induced reductions in VP GABA levels, but had no effect on cocaine-induced increases in NAc or VP DA levels. In contrast to AM251, SR141716 significantly inhibited cocaine-induced reductions in VP GABA levels when administered locally, but not systemically [211]. In addition to this GABAergic mechanism, a glutamate-$mGluR_{2/3}$-dependent mechanism may also underlie the antagonism of AM251 or SR141716 on cocaine-triggered reinstatement of drug-seeking behavior [229]. Briefly, CB_1 receptor blockade-induced increases in NAc glutamate leads to an increase in glutamate tone on $mGluR_{2/3}$ autoreceptors on glutamatergic terminals, which subsequently inhibits cocaine-induced increases in NAc glutamate release and cocaine-induced reinstatement of drug-seeking behaviors [211, 229].

Taken together, these data support an important role for CB1 receptors in cocaine reward and relapse. AM251 or other more potent and more selective CB_1 receptor antagonists appear promising for the treatment of psychostimulant addiction. The effectiveness of AM251 in attenuating cocaine's rewarding effects also supports the endocannabinoid hypothesis of drug reward proposed above.

6. GLUTAMATE-BASED MEDICATION DISCOVERY

Glutamate hypothesis of drug reward: L-glutamate is the major excitatory neurotransmitter in the brain and acts through two heterogeneous families of glutamate receptors: ionotropic (iGluR) and metabotropic (mGluR). While iGluRs (i.e. NMDA, AMPA, kainate) are ligand-gated ion channels and responsible for fast excitatory neurotransmission, mGluRs ($mGluR_{1-8}$) are G-protein coupled receptors linked to intracellular second messenger pathways. The eight subtypes of mGluRs have been classified into three groups on the basis of sequence similarities and pharmacological properties. Group I ($mGluR_{1,5}$) receptors activate phospholipase C *via* $G_{\alpha q/11}$ proteins, whereas group II ($mGluR_{2,3}$) and group III ($mGluR_{4,6,7,8}$) receptors inhibit adenylate cyclase *via* $G_{\alpha i/o}$ proteins [232].

The role of NAc glutamate in mediating cocaine's rewarding effects is controversial. Growing evidence suggests that NAc glutamate transmission is negatively correlated to brain reward function and/or psychostimulant's rewarding effects. This view is supported by the following evidence: 1) repeated cocaine injections or cocaine self-administration produces long-term depression in basal glutamate transmission in the mouse NAc [233, 234]; 2) chronic cocaine self-administration produces a significant reduction in basal levels of extracellular glutamate in the rat NAc, an effect that persists for 5 days after the extinction of cocaine self-administration [235]; 3) repeated cocaine administration results in a decrease in glutamate immunoreactivity in presynaptic NAc terminals [236, 237]; 4) microinjections of NMDA receptor antagonists (phencyclidine, MK-801) produce an enhancement of electrical BSR in rats [238, 239]; further, NMDA receptor antagonists are self-administered locally into the NAc [240]; 5) systemic administration of MK-801 increases cocaine's rewarding efficacy, as assessed by an increase in break-point levels for cocaine self-administration under PR reinforcement conditions [241]; 6) activation of presynaptic $mGluR_{2/3}$ receptors, which inhibits glutamate release, enhances amphetamine reinforcement in amphetamine-sensitized rats [242], while $mGluR_{2/3}$ antagonists, which facilitate glutamate release, discrupt intra-NAc amphetamine-induced CPP [243]; 7) genetic deletion or pharmacological blockade of $mGluR_5$, which results in an increase in extracellular NAc glutamate, inhibits cocaine self-administration and cocaine-induced reinstatement of drug-seeking behavior [244] (see more discussion in section 6.2. below); and 8) electrical stimulation of PFC, which increases NAc glutamate release, or increased $GluR_1$ expression in the NAc, inhibits cocaine self-administration and cocaine-triggered reinstatement of drug-seeking behavior [245, 246]. These findings suggest that an increase in NAc glutamate transmission may attenuate, while a reduction in glutamate transmission may significantly contribute to, the rewarding effects produced by cocaine or amphetamine.

In contrast to these findings, other studies suggest an important role of *enhanced* glutamate transmission in mediating cocaine reward (for review, see [247]). The major evidence includes: 1) high doses of cocaine (30 mg/kg) or amphetamine (2 mg/kg) produce an increase in extracellular glutamate in the NAc in drug naïve rats [248, 249]; and 2) activation of NAc AMPA or NMDA receptors appears to enhance cocaine's rewarding effect as suggested by a compensatory reduction in cocaine self-administration behavior [250], while blockade of AMPA or NMDA receptors attenuate cocaine self-administration and cocaine- or amphetamine-induced CPP [250-253].

Glutamate hypothesis of relapse: It is well documented that drug craving and reinstatement (relapse) of cocaine-

seeking behavior are related to repeated cocaine-induced *reduction* in basal levels of glutamate transmission in the NAc during cocaine withdrawal or abstinence and to *enhanced* glutamate responses to acute cocaine priming (largely due to a reduction in basal levels of glutamate) [16, 127, 155, 233, 235, 254, 255]. In addition, such glutamate responses also can be seen in the presence of cocaine-associated environmental cues or footshock stress [256-258]. These data suggest that both a reduction in basal glutamate transmission and enhanced glutamate responding may constitute a neurobiological substrate of cocaine-, cocaine-associated cue-, or stress-triggered relapse. Such preclinical findings suggest a number of potential pharmacotherapeutic strategies (summarized in Table **5**): 1) normalization (increase) of reduced basal glutamate neurotransmission might be helpful in attenuating cocaine reward and relapse; and 2) blockade of enhanced glutamate responses to cocaine priming, cocaine-associated cues, or stress might attenuate reinstatement of drug-seeking behavior evoked by these relapse-triggers.

6.1. *N*-acetylcysteine: *N*-acetylcysteine is a cystine prodrug. Recently, it was reported that systemic administration of *N*-acetylcysteine or local perfusion of cystine itself into the NAc restored decreased NAc glutamate levels in chronic cocaine-treated rats by stimulating cystine-glutamate exchange (i.e. exchange of extracellular cystine for intracellular glutamate), and dose-dependently inhibited cocaine-triggered reinstatement of drug-seeking behavior [255, 259]. Although *N*-acetylcysteine did not inhibit cocaine self-administration or acute cocaine-induced hyperactivity, it inhibited escalation of drug intake and behavioral sensitization seen after repeated administration [259]. In addition, pretreatment with *N*-acetylcysteine inhibited cocaine-induced increases in NAc glutamate by a mechanism that increased glutamate tone on presynaptic $mGluR_{2/3}$ receptors [229, 255, 260, 261]. Also of interest is the fact that *N*-acetylcysteine is also a prodrug for the synthesis of the endogenous antioxidant glutathione, and that *N*-acetylcysteine pretreatment protected animals from high dose methamphetamine- or amphetamine-induced DA neurotoxicity and behavioral changes by lowering oxidative stress levels [262-265].

N-acetylcysteine is currently under Phase I trial for the treatment of cocaine addiction. So far, *N*-acetylcysteine appears to be safe and well tolerated as observed in 13 cocaine addicts [266]. An open-label clinical trial demonstrated that *N*-acetylcysteine, at 2400-3600 mg/day for 4 weeks, significantly reduced cocaine use in 16 of 23 human cocaine-addicted subjects [267]. Similarly, another double-blind, placebo-controlled trial demonstrated that *N*-acetylcysteine (600 mg/12 h × 4) significantly inhibited desire to use cocaine, interest in cocaine, or cue viewing time triggered by exposure to cocaine-related cues in 15 cocaine-addicted participants during a 3-day hospitalization study [266].

6.2. MPEP: MPEP [2-methyl-6-(phenylethynyl)-pyridine] is a selective group I $mGluR_5$ antagonist. The $mGluR_5$ receptor has become an important target in medication discovery for treatment of psychostimulant addiction, largely because of its relatively selective regional distribution in the NAc [268]. A large body of literature indicates that $mGluR_5$ plays an important role in behavioral responses to psychostimulants [269]. Systemic administration of MPEP significantly attenuated the rewarding effects of psychostimulants, as assessed by: 1) cocaine self-administration under FR or PR reinforcement in mice, rats and nonhuman primates [24, 270-276]; and 2) cocaine-, amphetamine- or MDMA-induced CPP in rats [277, 278]; MPEP also attenuated cocaine- or amphetamine-induced hyperactivity in rats or mice [279-281]. In addition, MPEP pretreatment inhibited reinstatement of drug-seeking behavior triggered by cocaine in rats and nonhuman primates [271, 272, 276] or by cocaine-associated cues in rats [282, 283], but not by footshock stress [272].

To further determine the site(s) of action of MPEP and the neurochemical mechanisms underlying the antagonism by

Table 5. Pharmacological Actions of Glutamate Agents in Animal Models or Paradigms of Psychostimulant Addiction

	N-Acetylcysteine	MPEP	LY379268	2-PMPA	AMN082
Pharmacological Actions	Cystine prodrug, glutathione prodrug	mGluR5 antagonist	mGluR2/3 agonist	NAALADase inhibitor	mGluR7 agonist
Self-Administration	No effect on cocaine SA	↓ Cocaine SA (FR, PR)	↓ Cocaine SA (FR)	↓ Cocaine SA (PR, notFR)	↓ Cocaine SA (FR, PR)
Reinstatement of Drug-Seeking	↓ Relapse by cocaine	↓ Relapse by cocaine, by cues, but not by stress	↓ Relapse by cocaine or cues	↓ Relapse by cocaine	↓ Relapse by cocaine
Conditioned Place Preference (CPP)		↓ CPP by cocaine, amphetamine or MDMA		↓ CPP by cocaine	
Enhanced Brain-Stimulation Reward (eBSR)		Conflicting		↓ eBSR by cocaine	↓ eBSR by cocaine
Psychostimulant-like Discriminative Stimulus Effects (DS)		↓ DS by cocaine			
Behavioral Sensitization (BS)	↓ BS by cocaine	↓ BS by cocaine	↓ BS by amphetamine	↓ BS by cocaine	
Natural Reward		↓ Food-taking	↓ Food-seeking	No effect on CPP for food	No effect on sucrose-taking
Clinical Trials	Phase I	No	No	No	No

MPEP of cocaine's actions described above, we microinjected MPEP into the NAc in conjunction with cocaine-triggered relapse. We found that intra-NAc MPEP (3-10 μg/side) significantly inhibited cocaine-triggered reinstatement of drug-seeking behavior[5]. These data suggest that the NAc is an important site underlying MPEP's anti-relapse action. Further, *in vivo* microdialysis studies demonstrated that MPEP itself selectively elevated NAc extracellular glutamate, but not DA levels. Further, pretreatment with MPEP selectively prevented cocaine-induced increases in NAc glutamate, but not in NAc DA [271]. Such increased NAc glutamate produced by MPEP is tetrodotoxin (TTX)-insensitive, suggesting non-vesicular glutamate origins. We believe that this increase in NAc glutamate by MPEP may play an important role in attenuating cocaine reward and relapse, likely by attenuating cocaine-induced reduction in VP GABA release, renormalizing reduced basal levels of glutamate transmission, and potentiating $mGluR_{2/3}$-mediated inhibition of cocaine-enhanced glutamate responding as discussed above. Taken together, these preclinical data suggest that the $mGluR_5$ antagonist MPEP could be promising in the treatment of psychostimulant addiction. So far, however, no clinical trials with MPEP have been undertaken.

6.3. LY379268: LY379268 [(-)-2-oxa-4-aminobicylco [3.1.0] hexane-4,6-dicarboxylic acid] is a selective and systemically effective group II receptor ($mGluR_{2/3}$) agonist [284]. Recently, $mGluR_{2/3}$ receptors have become attractive targets in medication development for the treatment of drug addiction because group II $mGluR_{2/3}$ receptors function as glutamate autoreceptors, and $mGluR_{2/3}$ activation inhibits glutamate release from neuronal and/or glial cells [285,286]. In addition, $mGluR_{2/3}$ activation inhibits the release of other striatal neurotransmitters, including DA [232,287]. Also, in comparison to other mGluRs, $mGluR_{2/3}$ are highly expressed in the NAc, hippocampus and PFC [268], suggesting that the $mGluR_{2/3}$ could be a target on which cocaine acts. Given that cocaine-induced increases in NAc DA and glutamate have been thought to play an important role in drug reward and relapse, it has been proposed that $mGluR_{2/3}$ agonists could be effective in the treatment of cocaine addiction [285,286,288].

With the recent development and widespread use of LY379268, its efficacy in animal models of drug addiction has been recently studied. It has been reported that: 1) systemic administration of LY379268 significantly inhibits both acute and sensitized locomotor behaviors induced by amphetamine [289,290]; 2) systemic administration of LY379268 inhibits cocaine self-administration and cocaine-associated cue-triggered reinstatement of drug-seeking behavior [291]; 3) systemic administration or microinjection of LY369268 into the NAc core significantly inhibits cocaine- or food-triggered reinstatement of reward-seeking behavior [292]; 4) systemic or local administration of LY379268 into the central amydala inhibits incubation of cocaine craving in rats [293]; and 5) systemic or intra-NAc administration of LY379268 inhibits heroin-associated contextual cue-triggered reinstatement of drug-seeking behavior [294,295]. Together, these data suggest that $mGluR_{2/3}$ agonists may be promising in the development of anti-cocaine medications.

6.4. 2-PMPA: 2-PMPA [2-(Phosphono-methyl)-pentanedioic acid] is a highly potent and selective inhibitor of the enzyme *N*-acetylated-α-linked acidic dipeptidase (NAALADase), which hydrolyzes *N*-acetylaspartate-glutamate (NAAG) to *N*-acetylaspartate (NAA) and glutamate [296]. NAAG is an endogenous $mGluR_3$ agonist, which negatively modulates the release of glutamate and other neurotransmitters [297]. At high concentrations, NAAG may also act as a mixed agonist/antagonist of NMDA receptors [298]. In addition to functioning as an $mGluR_3$ agonist, NAAG may also serve as a glutamate precursor, because it can be hydrolyzed by the enzyme NAALADase to NAA and glutamate. Immunohistochemical studies have shown that NAAG is located in neurons [299,300] and released in a Ca^{++}-dependent manner [301], while NAALADase and its mRNA are located primarily in astrocytes [302, 303]. This suggests that synaptically released NAAG is degraded by NAALADase predominantly located on astrocytic membranes. Thus, NAALADase appears to be a key enzyme regulating extracellular glutamate and neuronal glutamate availability [297]. Given the important role of NAc glutamate in drug reward and relapse, it has been hypothesized that a NAALADase inhibitor, such as 2-PMPA, may be a promising anti-cocaine medication - acting by inhibiting cocaine-induced increases in NAc DA and glutamate *via* $mGluR_3$ receptors, secondary to an increase in extracellular NAAG levels [304, 305].

Previous studies have shown that systemic administration of 2-PMPA significantly inhibits cocaine-induced CPP [306] and cocaine-induced behavioral sensitization [307]. Recently, we have shown that systemic administration of 2-PMPA, within a low dose window, significantly inhibited: 1) cocaine self-administration under a PR, but not FR2, reinforcement schedule; 2) cocaine-enhanced BSR; and 3) cocaine-triggered reinstatement of drug-seeking behavior [304, 305]. The same doses of 2-PMPA alone had no effect on BSR. These data suggest that inhibition of NAALADase by 2-PMPA produces an inhibitory effect on cocaine's rewarding effects and cocaine-triggered reinstatement of drug-seeking behavior.

To further determine the neurochemical mechanisms underlying these behavioral effects, we observed the effects of 2-PMPA on NAc DA, glutamate and GABA using *in vivo* brain microdialysis. We found that systemic administration of 2-PMPA (10-100 mg/kg, i.p.) dose-dependently decreased NAc extracellular DA, glutamate and GABA levels, an effect that was blocked by intra-NAc perfusion of the $mGluR_{2/3}$ antagonist LY341495 [305]. These data suggest mediation by activation of NAc $mGluR_3$ receptors secondary to an increase in NAAG levels. This is consistent with previous findings that $mGluR_{2/3}$ activation inhibits the release of DA, glutamate, GABA and many other neurotransmitters in the brain [232]. This nonselective inhibition of neurotransimitter release may explain the "dose-window" effectiveness of 2-PMPA in animal models of drug addiction noted above, and also suggests a potential limitation for the use of 2-PMPA or other $mGluR_{2/3}$ agonists in the treatment of addictive diseases. So far, no clinical trials with drugs from this receptor-active category have been undertaken.

6.5. AMN082: AMN082 [*N,N'*-Bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride] is a selective systemically effective $mGluR_7$ agonist [308]. The $mGluR_7$ receptor subtype is of particular interest, because: 1) mGluR7 is the most abundant subtype among group III mGluR receptors in reward-related brain regions such as striatum, hippocampus and olfactory tubercle [268]; 2) $mGluR_7$ is the most highly conserved mGluR

[5] Xi *et al.,* Abstract at the 35th Annual Meeting of the Society for Neuroscience, Washington, DC, November 12-16, 2005.

subtype across different mammalian species [309], suggesting that selective $mGluR_7$ ligands that are effective in laboratory animals are more likely to be effective in humans; and 3) microinjections of L-AP4, a non-selective brain-impermeable group III mGluR agonist, into the NAc or dorsal striatum inhibit NAc DA and glutamate [287, 310], and cocaine-induced increases in striatal DA and locomotion [311, 312]. These data may imply a potential role for $mGluR_7$ in the modulation of drug-taking and drug-seeking behaviors. However, the role of group III receptors in drug reward and relapse is comparatively unstudied because of lack of selective pharmacological tools.

With the recent availability of the systemically effective $mGluR_7$-selective agonist AMN082, we have assessed AMN082's actions in animal models of drug addiction. We found that systemic administration of AMN082 (1-20 mg/kg i.p.) dose-dependently inhibits: 1) cocaine self-administration behavior under both FR2 and PR reinforcement schedules; 2) cocaine-enhanced BSR; and 3) cocaine-triggered reinstatement of drug-seeking behavior. In contrast, the same doses of AMN082 had no effect on locomotion or sucrose self-administration behavior. AMN082 alone, at lower doses (1-10 mg/kg), did not alter BSR itself, while a higher dose (20 mg/kg) decreased BSR in an aversive-like manner [313].

To further determine the mechanisms underlying these effects, we observed the action of AMN082 alone or in combination with cocaine on NAc DA, glutamate and GABA using *in vivo* brain microdialysis. We found that AMN082 significantly lowered NAc extracellular GABA, increased extracellular glutamate, but had no effect on NAc DA levels [314]. Further, pretreatment with AMN082 did not inhibit cocaine-enhanced NAc DA [313], suggesting that a DA-independent mechanism underlies the observed behavioral effects. Consistent with the GABAergic hypothesis of drug reward discussed above, a decrease in NAc GABA and an increase in glutamate would increase NAc medium-spiny GABAergic neuronal activity, thereby counteracting cocaine-induced GABAergic inhibition and cocaine reward. In addition, AMN082-induced increases in NAc glutamate may also restore decreased basal levels of extracellular glutamate, and increase glutamate tone on presynaptic $mGluR_{2/3}$ receptors, thereby inhibiting cocaine priming-induced increases in NAc glutamate and cocaine-triggered reinstatement of drug-seeking behavior. Together, these preclinical experimental data suggest a potential utility for AMN082, a selective $mGluR_7$ agonist, in the treatment of cocaine or other psychostimulant addiction.

6.6. Modafinil: Modafinil is a stimulant drug used in clinical medicine to treat narcolepsy and idiopathic hypersomnia [315]. The neurochemical mechanisms underlying modafinil's actions are not fully understood. One of its most important actions appears to be to elevate extracellular levels of glutamate in such brain regions as striatum, thalamus, hippocampus, and hypothalamus [315, 316]. In addition, it may also inhibits GABA release [316], and elevate extracellular DA levels by inhibiting DA reuptake and/or potentiating DA release in the striatum [317, 318]. Consistent with these actions, modafinil has been shown to have weak cocaine-like discriminative stimulus and rewarding effects in both rats and nonhuman primates [319, 320], and weak stimulant-like subjective effects in humans [321, 322]. This being the case, modafinil has been suggested as a 'substitution treatment' for cocaine addiction, similar to methadone for the treatment of opioid addiction. Recent clinical trials have shown that modafinil significantly relieves cocaine's withdrawal symptoms, including hypersomnia, lethargy, dysphoric mood, cognitive impairment, and increased appetite [323]. It also significantly blunts the euphorigenic effects of cocaine, reduces daily cocaine use, and prolongs abstinence in human cocaine addicts [324-326]. Modafinil itself does not appear to produce euphoria or evoke cocaine craving in humans [316, 327], suggesting that it has low abuse potential [320, 328]. Overall, these findings support the above-noted glutamate hypothesis that a drug that increases extracellular glutamate levels may produce a reduction in cocaine reward and intake, likely by 'normalization' of reduced extracellular glutamate and/or 'restoration' of glutamate tone on presynaptic mGluR2/3 receptors that attenuates the ability of cocaine to further increase glutamate release [261]. Additional studies are needed to study the efficacy of modafinil in attenuating cocaine self-administration and preventing relapse to cocaine use in both humans and experimental animals.

7. OPIOID-BASED MEDICATION DISCOVERY

Kappa opioid receptor–DA hypothesis: It is well documented that opioid μ and κ receptors differentially modulate DA release in the mesolimbic DA system. In general, opioid μ receptor agonists stimulate, while κ receptor agonists inhibit DA release [19, 329]. Based on this, κ receptor agonists have been considered as functional psychostimulant antagonists that may have possible utility as treatments for psychostimulant addiction. Dynorphin A (Dyn A) is an endogenous κ receptor agonist. Dyn A has been shown to significantly decrease basal levels of extracellular NAc DA, and also to block cocaine-induced increases in NAc DA, cocaine-induced CPP, and cocaine-induced hyperactivity [19]. Since Dyn A is a peptide that cannot penetrate the blood-brain barrier after systemic administration, it has no potential for clinical use. However, since the early 1980s, a series of nonpeptide κ receptor selective agonists have been developed, including the benzomorphans (cyclazocine, bremazocine), arylacetamides (U50, 488, U59,693, spiradoline), epoxymorphinans (nalfurafine), and several natural products from plants or herbs (ibogaine, salvinorin A) [329, 330]. The actions of a number of κ receptor agonists (Table **6**) in animal models of psychostimulant abuse are reviewed below.

7.1. U50,488: U50,488 is a prototypic κ receptor selective agonist. The first suggestions that κ agonists might be useful as functional cocaine antagonists were based on the actions of U50,488 in animal models of drug addiction. Maisonneuve *et al.* [331] first showed that pretreatment with U50,488 attenuated cocaine-induced increases in extracellular NAc DA, an effect that was reversed by the κ opioid antagonist nor-binaltorphimine (nor-BNI). Later work showed that acute U50,488 produced a dose-related decrease in cocaine self-administration in rats [332, 333]. Perhaps even more importantly, chronic administration of U50,488 dose-dependently inhibited cocaine self-administration in nonhuman primates [334]. However, at doses that inhibited cocaine self-administration, U50488 also produced emesis, sedation, and decreased food-maintained responding. In the drug discriminative paradigm, U50,488 was found to attenuate low-dose (3.0 mg/kg), but not high-dose (10.0 mg/kg), cocaine-induced discriminative stimulus effects [335]. However, U50,488 itself also produced weak cocaine-like discriminative stimulus ef-

Table 6. Pharmacological Actions of Kappa Opioid Receptor Agonists in Animal Models or Paradigms of Psychostimulant Addiction

	U50488	U69593	Nalfurafine
Pharmacological Actions	Kappa receptor agonist	Kappa receptor agonist	Kappa receptor agonist
Self-Administration (SA)	↓ Cocaine SA (FR)	↓ Cocaine SA (FR)	
Reinstatement of Drug-Seeking (Relapse)		↓ Relapse by cocaine or amphetamine	
Conditioned Place Preference (CPP)	↓ CPP by cocaine	↓ CPP by cocaine, amphetamine	↓ CPP by cocaine
Psychostimulant-like Discriminative Stimulus Effects (DS)	↓ DS by cocaine	↓ DS by cocaine, amphetamine	↓ DS by cocaine
Behavioral Sensitization (BS)	↓ BS by cocaine	↓ BS by cocaine, amphetamine	
Abuse Liability	cocaine-like DS by itself; Rewarding or aversive by itself		No cocaine-like DS effects; No rewarding effects by itself
Natural Reward	Conflicting	↓ Food-taking	
Clinical Trials	No	No	No

fects [336] and potentiated the reinforcing effects of cocaine in nonhuman primates [337]. These data suggest that U50,488 may have therapeutic potential but also may have significant side-effects by itself.

7.2. U69,593: U69,593 is another prototypic κ receptor agonist (an analog of U50,488) [329]. Various studies have shown that U69,593 modulates the neurochemical and behavioral effects of cocaine. Treatment with U69,593 was reported to attenuate cocaine's discriminative stimulus properties, its conditioned reinforcing effects, its self-administration, and reinstatement of extinguished drug-taking behavior in rats [338-340]. In addition, U69,593 attenuates the psychomotor stimulant effects of amphetamine and cocaine and modulates neurotoxic effects of methamphetamine [341-343]. Furthermore, U69,593 attenuates the discriminative stimulus effects of amphetamine in squirrel monkeys [344], albeit with large interindividual differences.

7.3. Nalfurafine (TRK-820): Nalfurafine is a novel potent and selective κ receptor agonist [345, 346]. The antinociceptive effects produced by nalfurafine are approximately 350-fold greater that that of U50,488 [347, 348]. Behavioral studies have shown that nalfurafine significantly attenuated the discriminative and rewarding effects of cocaine in rats, an effect that was blocked by nor-BNI [349]. Nalfurafine, at low doses, did not produce CPP or conditioned place aversion. However, at high doses, it significantly induced place aversion [349]. Nalfurafine produced neither cocaine-like discriminative stimulus effects in rats [350], nor psychotomimetic effects or significant tolerance in healthy human volunteers [351]. These findings suggest that nalfurafine may have potential for the treatment of psychostimulant addiction without severe side-effects such as dysphoria and psychotomimesis.

In addition to these 3 compounds, the pharmacological efficacy of several other selective κ receptor agonists or mixed κ agonist/μ antagonist agents has also been reported [19,329,330]. Overall, both selective and nonselective κ agonists have been shown to attenuate stimulant self-administration in a variety of animal models. While highly selective κ agonists attenuate psychostimulant self-administration in nonhuman primates, they are associated with behavioral side effects such as sedation, dysphoria and emesis. Mixed-action κ agonists appear to be more effective in attenuating cocaine's actions and intake with a lower incidence of undesirable effects [352].

8. SEROTONIN-BASED MEDICATION DISCOVERY

5-HT-DA Interaction hypothesis: Serotonin (5-HT) neurons originate in the raphe nuclei in the midbrain and project to numerous regions throughout the brain, interacting with many other neurotransmitter systems [353]. The actions of 5-HT are mediated through at least 14 subtypes of 5-HT receptors, which are grouped into seven families according to their structural and functional characteristics [353]. In general, an increase in 5-HT levels produces an inhibitory effect on cocaine's rewarding actions [15]. This effect is mediated indirectly by actions on 5-HT receptors located within the mesolimbic DA system [15, 354]. Of the 14 5-HT receptors, the 5-HT_{2A} and 5-HT_{2C} receptors are the two most important modulators of DA output. Briefly, 5-HT_{2C} receptors tonically inhibit, while 5-HT_{2A} receptors potentiate mesolimbic DA output [15, 353, 354]. Thus, 5-HT_{2A} receptor *antagonists* and 5-HT_{2C} receptor *agonists* have been proposed as possibly effective in alternating the neurochemical and behavioral effects of psychostimulants. Preclinical studies appear to support this suggestion - 5-HT_{2A} receptor *antagonists* and 5-HT_{2C} receptor *agonists* appear to reduce cocaine intake and craving and/or relapse [15, 354]. Although selective 5-HT_{2A} receptor antagonists or 5-HT_{2C} agonists are presently unavailable for use in human cocaine abusers, a number of selective 5-HT_2 ligands are currently under development at preclinical levels. Two representive 5-HT_2 ligands are reviewed below (Table **7**).

8.1. M100907: M100907 is a potent and selective 5-HT_{2A} receptor antagonist [355]. *In vitro*, M100907 binds with subnanomolar affinity to 5-HT_{2A} receptors, with at least 100-fold lower affinity for other receptors [356]). It has been reported that M100907 does not alter basal DA neuron function [357]. However, pretreatment with M100907 markedly diminished the effects of amphetamine on the firing rate of VTA DA neurons, and attenuated MDMA-induced DA release [358, 359]. In behavioral studies, M100907 attenuated cocaine- or amphetamine-induced hyperactivity [360-362], cocaine-induced CPP [354], and cocaine- or cocaine cue-induced reinstatement of

Table 7. Pharmacological Actions of Serotonine (5-HT_{2A}, 5-HT_{2C}) Agents in Animal Models or Paradigms of Psychostimulant Addiction

	M100907	Ro 60-0175
Pharmacological Actions	5-HT_{2A} antagonist	5-HT_{2C} agonist
Self-Administration (SA)	No effect on cocaine SA	↓ Cocaine SA (FR, PR)
Reinstatement of Drug-Seeking (Relapse)	↓ Relapse by cocaine or cues	↓ Relapse by cocaine or cues
Conditioned Place Preference (CPP)	↓ CPP by cocaine	
Psychostimulant-like Discriminative Stimulus Effects (DS)	↓ DS by cocaine	↑ DS by cocaine
Behavioral Sensitization (BS)	↓ BS by cocaine or amphetamine	↓ Cocaine-induced hyperactivity
Abuse Liability	cocaine-like DS by itself	cocaine-like DS by itself
Natural Reward		↓ food-taking
Clinical Trials	No	No

extinguished drug-seeking behavior [354, 363]. However, M100907 was also reported to alter neither cocaine self-administration [363], nor amphetamine-enhanced BSR [360]. It also did not alter amphetamine's discriminative stimulus properties [363]. These data suggest that the selective 5-HT_{2A} receptor antagonist M100907 may lack efficacy for reducing cocaine or amphetamine intake, but may be effective at reducing relapse to drug use and enhancing abstinence. Currently, it is under Phase II/III trials for the treatment of depression and/or sleep disorders, but not for psychostimulant addiction [354].

8.2. Ro 60-0175: Ro 60-0175 is a non-selective 5-HT_{2C} receptor agonist with similar high affinity for human 5-HT_{2C} (pK_i=9.0) and 5-HT_{2B} receptors (pK_i=9.3) [364,365]. *In vivo* microdialysis studies demonstrate that systemic administration of Ro 60-0175 (1 mg/kg, i.p.) did not alter cocaine, but attenuated haloperidol (a D2-like antagonist)-induced increases in extracellular DA in the NAc [366]. However, intra-VTA injection of Ro 60-0175 dose-dependently attenuated cocaine-induced increases in NAc DA [367]. Behavioral studies indicate that systemic administration of Ro 60-0175 (0.1-3 mg/kg, i.p. or s.c.) dose-dependently attenuated cocaine-induced hyperactivity, intravenous cocaine self-administration and cocaine- or cocaine-associated cue-induced reinstatement of drug-seeking behavior [363, 368, 369]. Also, intra-VTA injection of Ro 60-0175 produced a dose-dependent inhibition of cocaine-induced hyperactivity and of intravenous cocaine self-administration under both FR5 and PR reinforcement conditions [370]. Importantly, this antagonism of cocain's effects by Ro 60-0175, after systemic administration or microinjection, in all these animal models was completely blocked by SB-242084, a highly selective 5-HT_{2C} receptor antagonist [371]. These data suggest that the antagonism by Ro 60-0175 of cocaine's actions is mediated by activation of VTA 5-HT_{2C} receptors. In addition, Ro 60-0175, at the doses that inhibit cocaine self-administration, also inhibited food-maintained behavior, an effect that was also blocked by SB-242084 [363, 368, 370]. Taken together, these findings support a potential use of Ro 60-0175 in the treatment of cocaine or other psychostimulant addiction, although with possible adverse effects on natural reward-driven behavior.

In addition to M100907 and Ro 60-0175, several other selective or nonselective 5-HT_{2A} antagonists (SR 46349B, risperidone) or 5-HT_{2C} agonists (*m*-chlorophenylpiperazine, MK 212) have been proposed as treatments for psychostimulant addiction [354, 372]. Taken together such work suggests that 5-HT_{2A} antagonists and/or 5-HT_{2C} agonists may be effective in reducing craving and enhancing abstinence in treatment-seeking psychostimulant addicts, while 5-HT_{2C} agonists may also be effective for reducing cocaine use. Currently, no selective ligands are available for use in human cocaine abusers. In addition to compounds that target 5-HT_{2A} and 5-HT_{2C} receptors, several compounds that target other 5-HT receptor subtypes (5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-HT_3) have been also reported to affect animal drug-taking and drug-seeking behavior [15]. Given that the findings are controversial or inconclusive, we do not discuss them in this review article.

9. CONCLUSION

In this review article, we reviewed the role of NAc DA, GABA, endocannabinoids, glutamate, opioids, and 5-HT in drug reward and relapse. We also evaluated the pharmacological actions of 27 pharmacological agents that target these brain substrates and mechanisms in multiple animal models of drug addiction. Briefly, the VTA-NAc-VP pathway and, in particular, functional inhibition of NAc-VP GABAergic projection neurons appears to play a critical role in mediating psychostimulant reward and relapse. The same pathway may also mediate endocannabinoid reward by activating CB_1 receptors located on both GABAergic and glutamatergic neurons and/or terminals that results in an inhibition of medium-spiny GABAergic neurons. This GABAergic hypothesis may also explain why NMDA receptor antagonists have rewarding effects. Further, decreased NAc glutamate transmission during cocaine self-administration or early withdrawal/abst-inence appears to play a critical role in drug craving and relapse to drug use. Decreased glutamate tone on $mGluR_{2/3}$ autoreceptors located on presynaptic glutamate terminals may also provide an explanation for the increased glutamate response upon re-exposure to cocaine or cocaine-associated environmental cues. Thus, pharmacological strategies that either block NAc DA receptors or increase GABAergic transmission in brain reward circuits could antagonize a given drug's rewarding effects ("antagonist" treatment), while restoration of reduced basal glutamate or DA transmission could be helpful in relieving drug craving or relapse to drug use ("agonist" treatment).

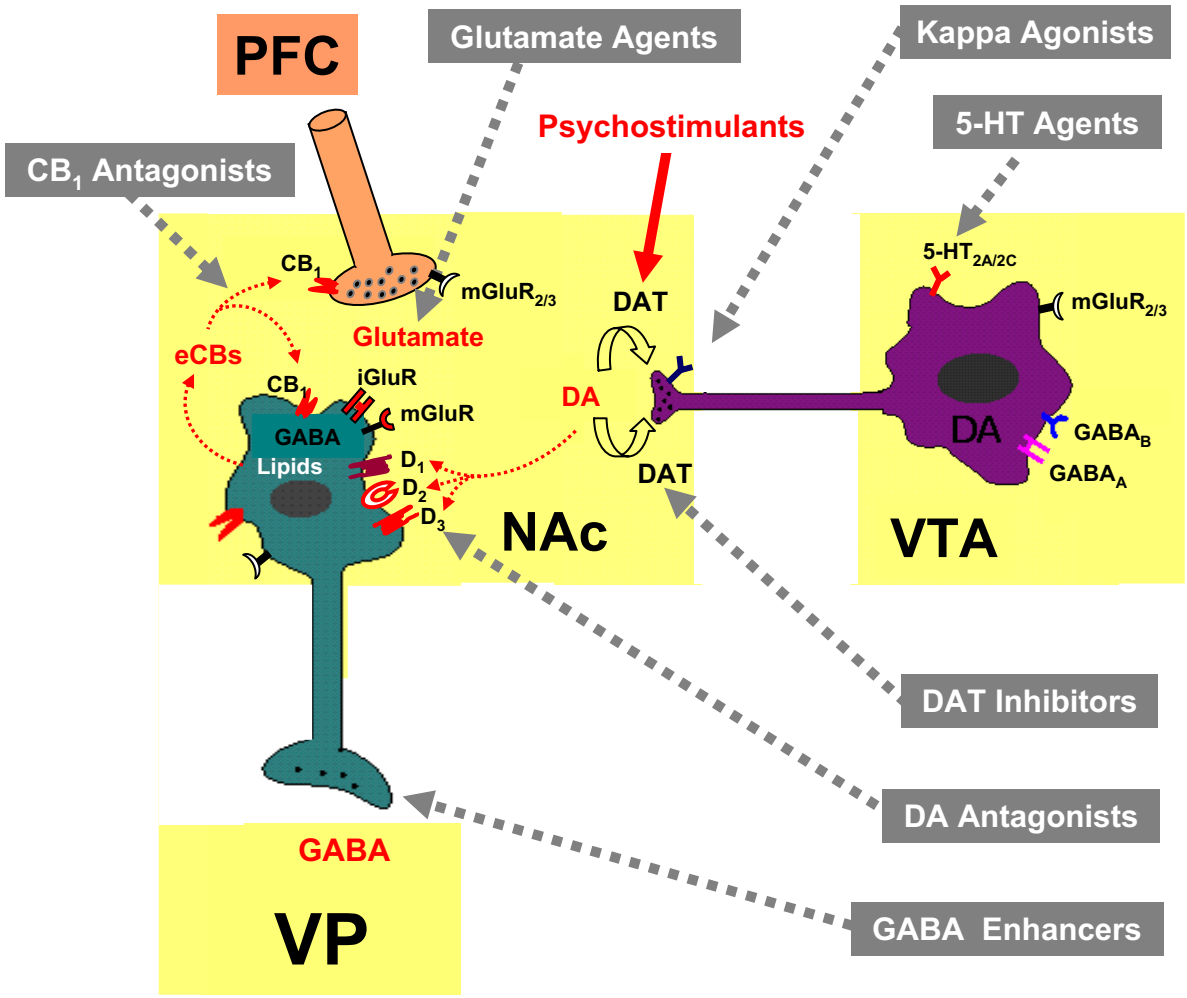

Fig. (1). Schematic diagram of the VTA-NAc-VP reward pathway, illustrating the actions of psychostimulants (including cocaine, amphetamine, methamphetamine) on extracellular DA, endocannabinoids (eCBs), glutamate and GABA in both the NAc and VP, and the sites of action of 6 classes of mechanism-based pharmacological agents in development for the treatment of psychostimulant addiction, as reviewed in the present article. The mesolimbic DA system originates in the midbrain ventral tegmental area (VTA) and projects predominantly to the forebrain nucleus accumbens (NAc). DA afferents from the VTA and glutamatergic afferents originating predominantly from the prefrontal cortex (PFC) synapse on NAc medium-spiny GABAergic neurons, which predominantly project to the ventral pallidum (VP). In general, activation of ionotropic glutamate receptors (iGluRs) activates, while activation of DA (D_2-like) receptors inhibits NAc medium-spiny GABAergic neurons. Functional inhibition of the NAc-VP GABAergic pathway is believed to play a critical role in drug reward and addiction. Psychostimulants elevate extracellular NAc DA by blocking and/or reversing DA transporters (DAT) on NAc DA axon terminals, which stimulates the release of eCBs from medium-spiny GABAergic neurons, leading to a reduction in release of NAc glutamate and VP GABA. Based on this hypothesis and these underlying neural substrates of addiction, it is proposed that: (1) blockade of DA receptors, in particular D_3 receptors, may directly block psychostimulant-enhanced NAc DA transmission and psychostimulant-induced reward and relapse; (2) slow-onset long-acting DAT or monoamine transporter inhibitors may substitute for psychostimulants by blocking DA or monoamine transport, but with pharmacokinetic properties that militate against addiction; (3) GABAmimetic compounds (at least that subset with therapeutic potential for psychostimulant addiction) may act at GABAergic terminals within the (a) VP (shown) or (b) VTA on GABAergic afferents synapsing upon DA neurons (not shown); (4) cannabinoid CB_1 receptor antagonists may modulate NAc-VP GABAergic neuronal function by acting on CB_1 receptors located on both NAc GABAergic neurons and glutamatergic terminals; (5) compounds acting on mGluRs may alter psychostimulant action by modulating release of presynaptic glutamate and/or the neuronal activity of post-synaptic NAc GABAergic neurons; (6) kappa opioid receptor agonists may attenuate psychostimulant actions by inhibiting DA release in the NAc; and (7) compounds acting on $5\text{-}HT_{2A}$ and/or $5HT_{2C}$ receptors may attenuate psychostimulant action by modulating DA neuron activity and DA release in the NAc. More details are discussed in the text of this review.

Based upon these mechanistic hypotheses, we summarize DA-based medication discovery strategies predominantly from our research group at the U.S. National Institute on Drug Abuse. We found that a non-selective DA receptor antagonist (*l*-THP), D_3-selective or D_3-preferring receptor antagonists (SB-277011A, NGB 2904, S33138), or slow-onset long-acting DA or monoamine transporter inhibitors (GBR 12909, RTI-336, CTDP31,345) appear to be promising approaches for the development of anti-psychostimulant medications. Next, we summarized recent studies with various GABAmimetic drugs,

and found that the GABA enhancer GVG and $GABA_B$ receptor agonist baclofen appear to be promising for the treatment of psychostimulant addiction. Then, we reviewed recent research progress on the potential use of selective CB_1 receptor antagonists for the treatment of psychostimulant dependence. We found that the novel CB_1 receptor antagonist AM251 appears to be more promising than the prototypic CB_1 receptor antagonist SR141716 for the treatment of drug addiction. For glutamate-based medication discovery, we reviewed recent progress on the $mGluR_{2/3}$ agonists LY379268 and 2-PMPA, the $mGluR_5$ antagonist MPEP, and the $mGluR_7$ agonist AMN082 in preclinical models. Finally, we briefly reviewed current studies of opioid- and serotonin-based pharmacological strategies for the treatment of psychostimulant abuse. Although it is difficult to predict from where promising new compounds for the treatment of addictive disease may arise, we believe that the probability is high that potentially useful compounds may arise from mechanistic considerations of these 6 neurotransmitter systems and from hypothesis-driven medication development strategies based upon such mechanistic considerations. If any of the discussed compounds reach human trials and demonstrate anti-reward, anti-craving, and/or anti-relapse efficacy, the beneficial impact on addiction medicine will be considerable.

Key Learning Objectives:

1. Psychostimulant abuse represents a significant global public health problem. Although a number of preliminary 'clinic'-based pharmacotherapies have been reported, none has yet been proven to be effective for use in humans.
2. Given that a better understanding of psychostimulant actions in the brain may better guide development of effective treatment medications, in this review, we first discuss the role of brain dopamine, GABA, endocannabinoids, glutamate, opioids and serotonin in psychostimulant addiction, and then evaluate the pharmacological efficacy, in animal models of drug addition, of various novel pharmacological agents that target these neurotransmitter systems.
3. Such "mechanism"-based medication development strategies may significantly promote medication discovery for effective treatment of psychostimulant addiction in humans.

Future Research Directions:

1. For the DA receptor antagonist strategy, more highly selective D3 receptor antagonists and more D_3-preferring mixed D_3/D_2 receptor antagonists should be developed and pharmacologically evaluated. This is based on recognition that highly selective D3 receptor antagonists have proven highly promising in preclinical animal models of addiction and blockade of both D_3 and D_2 receptors may produce an additive therapeutic effect, with fewer unwanted side-effects (which seem to be produced predominantly by blockade of D_2 receptors).
2. For the DA agonist substitution strategy, any compound that "competitively" inhibits psychostimulant binding to DAT or monoamine transporters should be pharmacologically evaluated. This is based on evidence that the therapeutic effects of methadone on heroin addiction appear to be mediated by functional antagonism of heroin's actions, not a simple "agonist substitution" effect as previously thought.
3. For the GABA-based medication strategy, development of GVG-like GABA transaminase inhibitors with $GABA_C$ receptor antagonist properties may represent a new research direction in medication development for the treatment of psychostimulant addiction. This is based on recognition that the visual field defects reported with long-term GVG use in humans are probably mediated by *activation* of $GABA_C$ receptors located in retina secondary to the increase in extracellular GABA levels.
4. For the cannabinoid-based medication strategy, development of more potent and selective neutral CB1 receptor antagonists may be more promising than the existing CB1 receptor antagonists SR141716A and AM251, which have significant inverse agonist properties.
5. For the glutamate-based medication strategy, any compound that modestly elevates extracellular NAc glutamate, but with fewer unwanted side-effects, should be tested in animal models related to drug craving and relapse. In addition, more studies are required to clarify the functional role of brain glutamate in drug reward and relapse.
6. For the opioid-based medication strategy, mixed kappa-preferring opioid receptor agonists with partial mu receptor agonist properties may be more promising in attenuating psychostimulant addiction and also lowering the unwanted side-effects such as dysphoria and emesis produced by activation of kappa opioid receptors.
7. For the serotonin-based medication strategy, development of more effective and systemically active $5\text{-}HT_{2C}$ receptor agonists may represent another medication development direction.

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