11

Medication Development for the Treatment of Cocaine Addiction – Progress at Preclinical and Clinical Levels

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1. Introduction

Cocaine addiction continues to be an important public health problem in the United States and other countries. Acute cocaine produces potent rewarding and psychostimulant effects primarily by blocking dopamine (DA) transporters (DAT) in the brain's reward system – the mesocorticolimbic DA system. However, repeated use of cocaine leads to addiction, persistent craving and a high risk of relapse. To date, there are no proven pharmacotherapies for cocaine addiction. Recent progress in the neurobiology of drug dependence in preclinical animal models has lead to the discovery of various novel compounds that appear to be promising for the treatment of drug addiction. Some have been tested in controlled clinical trials and have produced encouraging results in reducing cocaine use and in increasing abstinence from relapse. In this review article, I will focus on those medication strategies that are well-studied in experimental animals and are currently under clinical trials for the treatment of addiction or for other diseases. These strategies include DAT-based agonist therapy, DA receptor-based antagonist therapy, glutamate-based therapy, GABA-based therapy and endocannabinoid-based therapy. For each treatment, I will first review the rationale and the underlying neurochemical mechanisms of the therapy, and then summarize the major findings of the drugs in each category at both preclinical and clinical levels.

2. Dopamine transporter-based agonist therapies

Rationale: The mesocorticolimbic DA system is thought to be critically involved in drug reward and addiction (Wise, 2005; Sulzer, 2011). This system originates from the DA neurons in the ventral tegmental area (VTA) in the midbrain and projects predominantly to the nucleus accumbens (NAc) and prefrontal cortex (PFC) in the forebrain (Figure 1). Almost all addictive drugs, such as cocaine, heroin, nicotine and alcohol, have been shown to increase extracellular DA in the NAc via different mechanisms (Wise, 2005; Sulzer, 2011). For example, cocaine elevates extracellular DA by blockade of DAT, while heroin increases extracellular DA by inhibition of GABA release in the VTA that disinhibits (activates) DA

neurons. Such an increase in NAc DA has been thought to underlie the euphoria associated with drug abuse. Based on this DA hypothesis, much attention in medication development for treatment of addiction has been focused on manipulation of DA transmission in the brain reward circuitry. One strategy is to target DAT (agonist therapy), and another is to target brain DA receptors (antagonist therapy) (Figure 2).

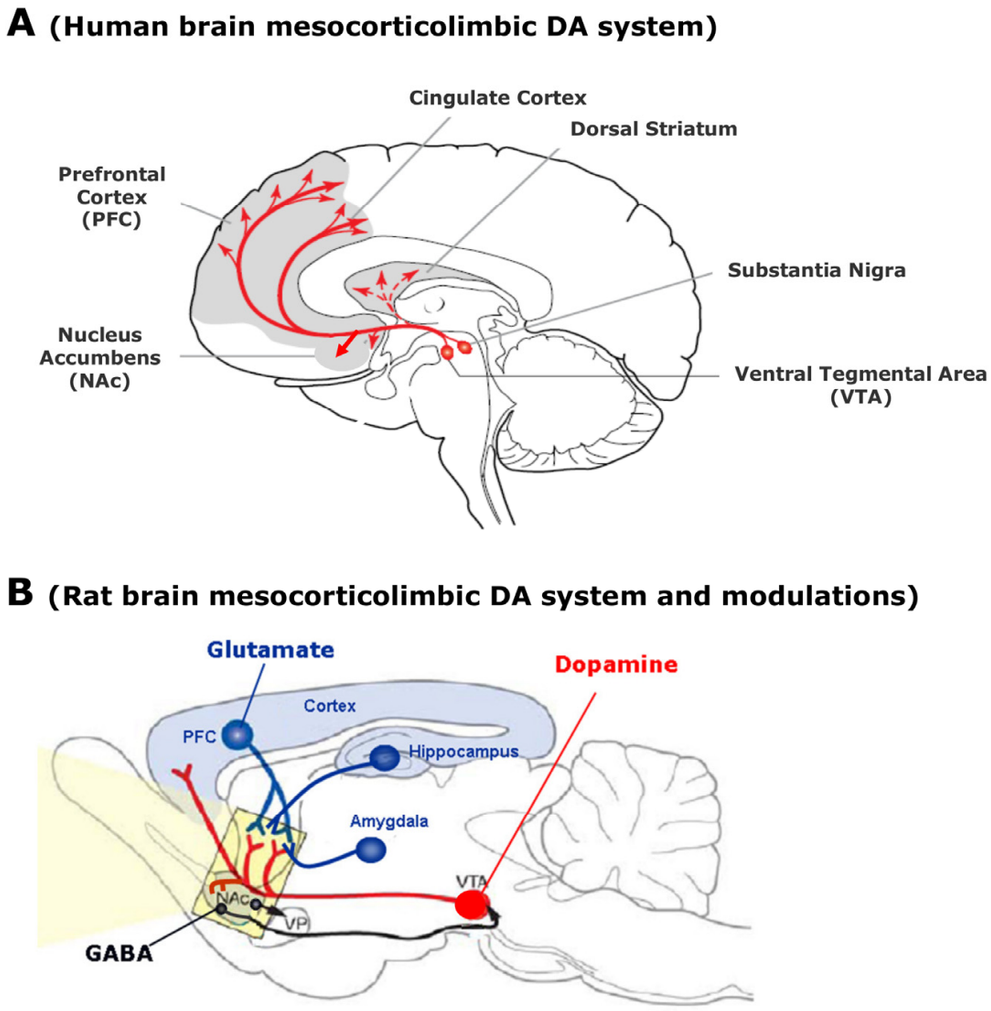

Fig. 1. Schematic diagrams, illustrating the mesocorticolimbic DA reward system in human (A) and rat (B) brains. The mesocorticolimbic DA system originates in the midbrain ventral tegmental area (VTA) and projects predominantly to the nucleus accumbens (NAc) and prefrontal cortex (PFC). Dopaminergic afferents from the VTA and glutamatergic afferents from the PFC, hippocampus and amygdala synapse on NAc medium-spiny (GABAergic) neurons (MSN), which project to the VTA and the ventral pallidum (VP).

Agonist or substitution therapies have been successful in the treatment of opioid (Mattick et al., 2009) and nicotine dependence (Xi et al., 2009; Xi, 2010). As such, drugs that block the DAT, but have lower addictive potential than cocaine, would have potential as 'cocaine-like' agonist therapies for the treatment of cocaine addiction. Indeed, this strategy has been at the

forefront of medication development for the treatment of cocaine addiction for more than a decade (Rothman and Baumann, 2006; Howell and Kimmel, 2008). To date, many DAT inhibitors have been developed, and several of them have been tested in human clinical trials (Newman and Kulkarni, 2002; Runyon and Carroll, 2006; Rothman et al., 2006, 2008).

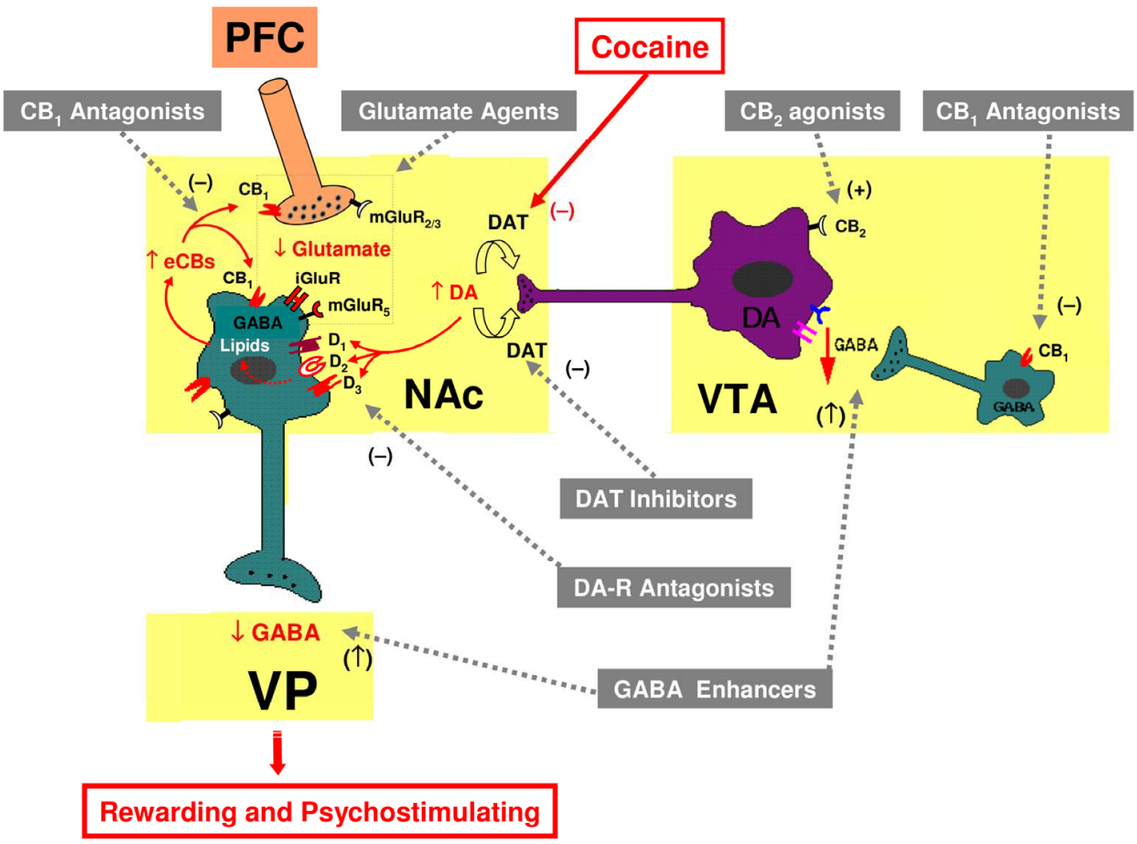

Fig. 2. Schematic diagram of the VTA-NAc-VP reward pathway, illustrating the actions of acute cocaine on extracellular DA, endocannabinoids (eCBs), glutamate and GABA in the NAc and VP, and the sites of action of various mechanism-based pharmacological agents in the brain reward system. Cocaine elevates extracellular DA in the NAc by blocking DAT on presynaptic DA terminals. DA activates postsynaptic DA receptors, in particular D2 and D3 receptors, producing an overall inhibitory effect on NAc medium-spiny (GABAergic) neurons (MSN). In addition, activation of D2 receptors may also increase eCB release from MSNs, which subsequently activates cannabinoid CB1 receptors located on presynaptic glutamatergic terminals and GABAergic MSNs themselves, causing a reduction in glutamate release and in MSN excitability. Thus, increases in NAc DA and eCBs and a reduction in NAc glutamate release lead to a reduction in MSN excitability and GABA release in the VTA (not shown) and VP. Decreased GABA release in the VTA causes an increase in DA neuron activity (via a disinhibition mechanism) and DA release in the NAc. Based upon these neurochemical hypotheses, various pharmacological therapies have been proposed and tested in animal models of drug addiction to interfere with cocaine's action. More details are discussed in the text of this review.

However, none have proven to be successful due to significant abuse liability by those compounds themselves and/or unwanted side-effects. Given the recent finding that rewarding and psychostimulant effects of the drugs are positively correlated with the speed of onset and offset of action on brain DA (Volkow et al., 1995; Kimmel et al., 2007; Xi and Gardner, 2008), it has been proposed that DAT inhibitors (Figure 2), in particular those with a slower-onset longer-acting profile than cocaine, would have lower addictive potential by themselves. In the following sections, we will review several DAT inhibitors with such a slow-onset long-action profile.

2.1 GBR-12909

Preclinical studies: GBR-12909 (Vanoxerine), a phenyl-substituted piperazine derivative, is a relatively slow-onset long-acting DAT inhibitor compared to cocaine (Howell and Wilcox, 2001). To date, it is the most extensively studied DAT inhibitor proposed to be beneficial in the treatment of cocaine addiction (Rothman et al., 2008). GBR-12909 binds at the DAT site with high affinity, and selectively inhibits DA re-uptake. GBR-12909 can also compete with psychostimulants at the DAT site, thus blocking cocaine- or amphetamine-induced increases in extracellular DA. Compared to the same doses of cocaine, GBR-12909-induced increases in striatal DA and locomotion are relatively slow-onset and long-lasting (Baumann et al., 1991, 1994; Kelley and Lang, 1989). 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 (Glowa et al., 1995). Repeated treatment with low doses of GBR-12909 sustains the selective suppression of cocaine self-administration *versus* food self-administration (Glowa et al., 1995). Further, a single injection of a slow-release formulation of GBR-12909 produced a prolonged (up to one month) suppression of cocaine self-administration in nonhuman primates (Glowa et al., 1996). These findings support GBR-12909 as a potential candidate for the treatment of cocaine addiction (Rothman et al., 2008).

Clinical trials: GBR-12909 was investigated in clinical trials at NIDA and University of Texas from 2003 to 2008 (Table 1). However, the appearance of cardiovascular side-effects has prevented its further development as an anti-cocaine medicine at NIDA, NIH (Vocci and Elkashef, 2005).

2.2 RTI-336

Preclinical studies: RTI-336 is a novel DAT inhibitor of the 3-phenyltropane class and has a slower-onset (30 min *vs.* < 10 min) longer-acting (4 hrs *vs.* 1-2 hrs) profile than cocaine (Carroll et al., 2006; Kimmel et al., 2007). It has >1000- and >400-fold selectivity for DAT over serotonin transporter (SERT) and norepinepherine transporter (NET), respectively (Carroll et al., 2006). Pretreatment with RTI-336 produced a dose-dependent reduction in cocaine self-administration in both rats and nonhuman primates (Haile et al., 2005; Howell et al., 2007). 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 inhibitors fluoxetine or citalopram produced more robust reductions in cocaine self-administration in non-human primates than RTI-336 alone (Howell et al., 2007), suggesting that blockade of both DAT and SERT may be more effective

in attenuating cocaine's reinforcing effects than selective blockade of DAT alone (Rothman et al., 2007). In addition, at the doses that effectively suppressed cocaine self-administration, RTI-336 also inhibited food-taking behavior (Howell et al., 2007). This differs from GBR-12909, which selectively inhibits cocaine self-administration but not food-taking behavior. RTI-336, like many other DAT inhibitors, reliably maintained self-administration behavior in all non-human primates tested (Howell et al., 2007) and produced locomotor stimulating effects in mice and rats, suggesting abuse potential by itself. However, compared to cocaine, RTI-336 maintained lower rates of responding and lower progressive-ratio (PR) break-points in the self-administration paradigm. It also produced weaker locomotion hyperactivity and drug discriminative stimulus effects, and showed very low sensitization in locomotion (Carroll et al., 2006; Czoty et al., 2010). These data suggest that RTI-336 may have lower abuse potential than cocaine.

Clinical trials: RTI-336 has been investigated in Phase I clinical trials at RTI International (NC, USA) and NIDA (MD, USA) since 2008 (Table 1). It was a double-blind, placebo-controlled Phase I study to evaluate the safety, tolerability, and pharmacokinetics of RTI-336 in healthy, male subjects. The study has been completed, but not yet reported.

Compound	Company	Pharmacology	Indication	Status	Reference
GBR-12909	Antia Lab., China; Others	DAT inhibitor	Safety and PK profiles; Cocaine addiction	Phase I, terminated at NIDA in 2008	http://clinicaltrials.gov
RTI-336	RTI, NC, USA	DAT inhibitor	Safety, tolerability & PK profiles	Phase I,	http://clinicaltrials.gov
Methylphenidate	Shire US, Dublin, Ireland	DAT inhibitor	Substance Abuse (cocaine, methamphetamine)	Phase II	http://clinicaltrials.gov
Modafinil	Cephalon, PA, USA	DAT inhibitor; Glutamate enhancer; GABA inhibitor	Drug Addiction (cocaine, methamphetamine Schizophrenia	Phase II Phase IV	http://clinicaltrials.gov
Disulfiram	LKT Lab., MN, USA	Aldehyde dehydrogenase inhibitor; Dopamine-β-hydroxylase inhibitor	Substance Abuse (cocaine, heroin or methamphetamine) Others	Phase III	http://clinicaltrials.gov

Table 1. DAT- or DA-related drug candidates in clinical trials

2.3 CTDP-31,345

Based upon the above finding that a combination of DAT and SERT inhibitors appears to be more potent and effective than DAT inhibitor alone in attenuation of cocaine self-administration (Howell et al., 2007), we studied slow-onset long-acting monamine transporter

(MAT) inhibitors that have higher affinity for both DAT and SERT over to NET. In addition, our interest in non-selective MAT inhibitors as potential anti-cocaine medications originally stems from the fact that cocaine is also a non-selective MAT inhibitor. Thus, it was hypothesized that a 'cocaine-like' MAT inhibitor with slow-onset and long-acting profiles would be able to substitute for cocaine for the treatment of cocaine dependence (Peng et al., 2010c). CTDP-31,345 is such a MAT inhibitor with slow-onset (30-60 min) long-acting (at least 6 hrs) (Peng et al., 2010c) and with higher selectivity for DAT and SERT over NET (K_i = 18, 23 and 81 for DAT, SERT and NET, respectively) (Froimowitz et al., 2000). The "CTDP" terminology derives from the "Cocaine Treatment Discovery Program" of the NIDA Extramural Program. Structurally, it is a *trans*-aminotetralin derivative (Peng et al., 2010c). It is a prodrug, which is metabolized (*N*-demethylated) to CTDP-31,346, a slow-onset long-acting MAT inhibitor. Pretreatment with a single dose of CTDP-31,345 produced a dose-dependent long-term (24-48 h) reduction in cocaine self-administration in rats (Peng et al., 2010c). CTDP-31,345 itself appears to have lower abuse liability than cocaine because it produces weaker brain-stimulation reward and maintains a lower rate of self-administration than cocaine (Peng et al., 2010c). In addition, systemic administration of CTDP-31,345 produces moderate, but long-lasting, increases in NAc DA, which may translate to decreases in drug craving and relapse by restoring reduced synaptic DA in brain reward circuits (Volkow et al., 1999). CTDP-31,345 is not currently in clinical trials.

2.4 Methylphenidate

Preclinical studies: Methylphenidate is a FDA-approved DAT inhibitor for the treatment of attention deficit hyperactivity disorder (ADHD). It binds to presynaptic DAT and NET, but not to SERT, blocking DA and NE re-uptake and increasing synaptic DA and NE (Leonard et al., 2004). Methylphenidate is self-administered in rodents, and pretreatment with methylphenidate significantly shifts the cocaine self-administration dose-response curve to the left (Hiranita et al., 2009, 2011), suggesting that methylphenidate has cocaine-like abuse potential and produces additive effects in combination with cocaine.

Clinical trials: ADHD has high comorbidity with cocaine-dependent patients as much as 30% in some studies (Schubiner et al., 2000). Because of this, its therapeutic effects for the treatment of cocaine addiction in this population have been recently evaluated in clinical trials (Table 1). Placebo-controlled studies produced mixed results with one study reporting no effect (Schubiner et al., 2002) while three studies demonstrating a significant reduction in both cocaine use and the positive subjective effects of cocaine compared to placebo (Winhusen et al., 2006; Collins et al., 2006; Levin et al., 2007). Because the half-life of methylphenidate is short (2-3 hrs in humans), the drug has been made available in sustained-release formulations in addition to the traditional immediate-release formulation. The sustained-release methylphenidate displayed much lower abuse potential than immediate-release, and appears to be more effective than immediate-release in decreasing cocaine use and the positive subjective effects (Arria and Wish, 2006; White et al., 2006).

2.5 CTDP-32,476

Based on the aforementioned findings of sustained-release methylphenidate in clinical trials, we have recently developed a series of methylphenidate analogs with slow-onset long-acting profiles as medication candidates for the treatment of cocaine addiction. CTDP-32,476 is a

representative compound in this drug category. Structurally, CTDP-32,476 is a metabolically stable methylphenidate analog, in which the metabolically unstable ester moiety of methylphenidate is removed from methylphenidate's structure (Froimowitz et al. 2007). *In vitro* binding assays suggest that CTDP-32,476 is a selective DAT inhibitor with ~50-fold and ~350-fold selectivity for DAT over NET and SERT (K_i= 16, 5900 and 840 nM for DAT, SERT and NET, respectively) (Froimowitz et al., 2007). Functional reuptake assays reveal that CTDP-32,476 has IC_{50} values of 8.6, 490 and 120 nM for inhibition of DA, 5-HT and NE reuptake, respectively. In addition, it also displays approximately 30-fold higher affinity for the DAT than cocaine (K_i: 16 *vs.* 500 nM; IC_{50}: 8.6 *vs.* 244 nM) (Froimowitz et al., 2007). Systemic administration of CTDP-32,476 produced a slow-onset (20-60 min) long-term (6-12 hrs) increase in locomotion and extracellular DA in the NAc (Xi et al., 2009). Pretreatment with CTDP-32,476 significantly and dose-dependently inhibited intravenous cocaine self-administration under both FR and PR reinforcement, shifted the cocaine dose-response self-administration curves downward and to the right, and attenuated cocaine-induced increases in locomotion and extracellular DA in the NAc (Xi et al., 2011a). These data suggest that pretreatment with CTDP-32,476 produced functional antagonism of cocaine's action, likely by attenuating cocaine's binding to DAT. CTDP-32,476 itself appears to have much lower addictive potential than cocaine. Drug naïve rats selectively self-administer cocaine, but not CTDP-32,476. In rats trained to self-administer cocaine, CTDP-32,476 maintained significantly lower rates of self-administration and lower PR break-points than cocaine. Taken together, these data suggest that CTDP-32,476 appears to be an excellent agonist therapy for cocaine dependence. CTDP-32,476 has not been tested in human clinical trials.

2.6 Modafinil

Preclinical studies: Modafinil is a wake-promoting drug used in the clinic for the treatment of narcolepsy and idiopathic hypersomnia (Wise et al., 2007). However, the neurochemical mechanisms underlying modafinil's action are not fully understood. It is reported that modafinil increases extracellular levels of glutamate in numerous brain regions including striatum, thalamus, hippocampus, and hypothalamus (Ballon and Feifel, 2006; Wise et al., 2007). In addition, it also inhibits brain GABA release (Ballon and Feifel, 2006). Recent studies suggest that modafinil is a DAT inhibitor in humans and primates (Madras et al., 2006; Volkow et al., 2009). This is further supported by the findings that mice lacking DAT or DA (D1 and D2) receptors do not respond to the wake-promoting effects of modafinil (Qu et al., 2008; Wisor et al., 2001). *In vivo* microdialysis studies demonstrated that modafinil increases extracellular DA (Wisor et al., 2001; Ferraro et al., 1997; Murillo-Rodríguez et al., 2007). Neuroimaging studies in both non-human primates and healthy human subjects demonstrated significant occupancy of DAT (and also NET) by intravenously-administered modafinil (Madras et al., 2006; Volkow et al., 2009). Consistent with these findings, modafinil has been shown to have weak cocaine-like discriminative and reinforcing effects in both rodents and non-human primates (Gold and Balster., 1996; Deroche-Gamonet et al., 2002), and weak stimulant-like subjective effects in humans (Kruszewski, 2006; O'Brien et al., 2006). Based on these recent findings, modafinil is categorized as a DAT-based 'agonist therapy' for cocaine dependence.

Clinical studies: Dackis et al (2003) first reported that modafinil's stimulant-like activity may diminish the symptoms of cocaine withdrawal, including hypersomnia, lethargy, dysphoric

mood, cognitive impairment, and increased appetite, thereby reducing the desire to use cocaine. The first randomized, double-blind clinical trial involved 62 cocaine-dependent outpatients who received either a single dose of modafinil or placebo daily for 8 weeks (Dackis et al., 2005). Patients treated with modafinil had significantly less cocaine use than patients treated with placebo (Hart et al., 2008). No significant adverse effects were noted. The therapeutic effects of modafinil in cocaine users have been supported by a recently completed multi-site, placebo-controlled clinical trial involving 210 cocaine-dependent outpatients (Anderson et al., 2009). Currently, more than 10 additional clinical trials are under way to further evaluate the efficacy of modafinil treatment for cocaine addiction (Table 1).

2.7 Disulfiram

Preclinical studies: Although disulfiram is not a DAT inhibitor, I list it under this treatment category because it elevates extracellular DA by inhibiting DA metabolism, producing effects similar to DAT inhibitors. In 1937, disulfiram was first reported as a potential treatment for alcoholism by Williams, a plant physician in a chemical company. Unexpectedly, Williams observed that after exposure to disulfram, his laboratory assistants could not drink alcohol in any form because alcohol produced a series of unwanted effects such as flushing, sweating, headaches, nausea, tachycardia, palpitations, arterial hypotension and hyperventilation (Williams, 1937). Since then, disulfiram has been used in the treatment of alcoholism for more than half a century (Suh et al., 2006; Barth and Malcolm, 2010). Disulfiram is an inhibitor of aldehyde dehydrogenase, the enzyme that transforms acetaldehyde into acetate during alcohol metabolism (Weinshenker, 2010). When a person drinks alcohol while taking disulfiram, the resulting acetylaldehyde accumulation causes an aversive reaction as described above, which discourages further drinking. In addition, disulfiram also inhibits dopamine-β-hydroxylase (DBH) (Weinshenker, 2010), the enzyme that transforms DA into norepinephrine. Such DBH inhibition would increase brain DA levels while decreasing brain NE release. This effect could be therapeutic for cocaine dependence since an increase in brain DA may be helpful in attenuating withdrawal syndromes and craving (Volkow et al., 1999), while a decrease in NE may be helpful in attenuating relapse to drug use (Smith and Aston-Jones, 2008; Weinshenker, 2010). In experimental animals, disulfram stimulates DA release and potentiates cocaine-induced increases in extracellular DA in the prefrontal cortex (Devoto et al., 2011). It also facilitates the development and expression of locomotor sensitization to cocaine in rats (Haile et al., 2003). However, in animal models of relapse, pretreatment with disulfram attenuates cocaine-induced reinstatement of drug-seeking behaviour (Schroeder et al., 2010).

Clinical trials: The initial impetus for the use of disulfiram to treat cocaine dependence was the high rate of comorbidity between cocaine abuse and alcohol abuse (Gossop and Carroll, 2006). Thus, it was hypothesized that a reduction in alcohol use would lead to secondary reduction in cocaine use. Additionally, abstinence from alcohol would prevent formation of cocaethylene, a metabolite formed when alcohol and cocaine are present together. Cocaethylene has pharmacological actions similar to cocaine and increases subjective euphoria and heart rate (Hart et al., 2000). Several short-term clinical trials in outpatients using both cocaine and alcohol showed that disulfiram, along with cognitive behavioural therapy (CBT), significantly reduced cocaine and alcohol use (Carroll et al., 1998; Higgins et

al., 1993; Grassi et al., 2007). In one study, the reduction in cocaine use was still present one year after treatment (Carroll et al., 2000). An 11-week, double-blind, placebo-controlled trial evaluated the efficacy of disulfiram, naltrexone and their combined treatment in 208 patients with concurrent cocaine and alcohol dependence. Patients taking disulfiram alone or in combination with naltrexone were more likely to achieve combined abstinence from cocaine and alcohol than placebo-treated patients (Pettinati et al., 2008). In several randomized, placebo-controlled trials, disulfiram seemed to directly reduce cocaine use rather than reducing it indirectly by reducing concurrent alcohol use (George et al., 2000; Petrakis et al., 2000; Carroll et al., 2004). In addition, dilsufiram appears to be effective in attenuating cocaine use in comorbid cocaine- and opioid-dependent individuals (Oliveto et al., 2011). As a caveat, disulfiram is reported to inhibit cocaine metabolism, and therefore increases cocaine plasma levels in humans (Baker et al., 2006). Because of this, it should be used cautiously in comorbid cocaine and alcohol patients with severe cardiovascular diseases (Malcolm et al., 2008).

3. Dopamine receptor-based antagonist therapies

Rationale: Cocaine's action is largely mediated by elevation of extracellular DA that activates postsynaptic DA receptors. Thus, blockade of DA receptors is a plausible therapeutic approach for cocaine addiction (Figure 2). There are five DA receptor subtypes identified in the brain that are classified as D1-like (D1, D5) and D2-like (D2, D3, D4) based on their pharmacological profile (Beaulieu and Gainetdinov, 2011). Although both D1 and D2 receptor subtypes have been shown to play predominant roles in mediating actions of DA, clinical trials with selective D1 or D2 receptor antagonists for the treatment of cocaine addiction have failed due to ineffectiveness and/or unwanted side-effects such as sedation and extra pyramidal locomotor syndromes (see review by Platt et al., 2002; Gorelick et al., 2004). In response, efforts have increased to develop relatively low selective D1/2 receptor antagonists or D3 receptor-based antagonist therapies for cocaine dependence.

3.1 *Levo*-tetrahydropalmatine (*l*-THP)

Preclinical studies: Tetrahydropalmatine (THP) is a tetrahydroprotoberberine (THPB) isoquinoline alkaloid and a primary active constituent of the herbal plant species *Stephania rotunda Lour* and *Corydalis ambigua* (Yanhusuo) (Jin et al., 1987). The levo-isomer of THP (*l*-THP) has been shown to contribute to many of the therapeutic effects of these herbs such as sedative, neuroleptic and analgesic effects (Chu et al., 2008; Jin, 1987). Purified or synthetic *l*-THP has been approved in China as a traditional sedative-analgesic agent for the treatment of chronic pain and anxious insomnia for more than 40 years. Pharmacologically, *l*-THP is a non-selective DA receptor antagonist with roughly 3-fold selectivity for D1 *versus* D2 receptor and 10-fold selectivity for D1 *versus* D3 receptor (K_i = 124, 388, or 1420 nM for D1, D2, or D3 receptors, respectively) (Wang and Mantsch, 2012). In addition, it has moderate binding affinity to alpha (α_1, α_{2A}) adrenergic and 5-HT_{1A} (K_i = 340 nM) receptors. Because cocaine is a non-selective MAT inhibitor, which increases brain DA, NE and 5-HT levels, it was hypothesized that blockade of multiple DA, adrenergic and 5-TH_{1A} receptors by *l*-THP would functionally antagonize cocaine's action (Mantsch et al., 2007; Xi et al., 2007). In support of this hypothesis, *l*-THP was found to significantly inhibit intravenous cocaine self-administration under FR and PR reinforcement schedules (Mantsch et al., 2007, 2010; Xi et

al., 2007), cocaine-induced conditioned place preference (CPP) (Luo et al., 2003), cocaine-enhanced electrical brain-stimulation reward (Xi et al., 2007), and cocaine-, cue- or stress-induced reinstatement of drug-seeking behaviour in rats (Mantsch et al., 2007, 2010; Figueroa-Guzman et al., 2011). These anti-cocaine effects are unlikely due to *l*-THP-induced sedation or locomotor impairment, since the effective doses that decrease cocaine's effects are much lower (3-10 fold) than those that produce locomotion inhibition (Xi et al., 2007). These data suggest that *l*-THP may have therapeutic potential for treatment of cocaine addiction in humans.

Clinical studies: A pilot study examined the efficacy of *l*-THP in reducing craving and relapse in 120 heroin addicts (Yang et al., 2008). In this randomized, double-blind, placebo-controlled study, patients received 4 weeks of *l*-THP treatment and three months follow-up after *l*-THP treatment. The results showed that *l*-THP significantly lowered opiate withdrawal symptoms and craving and increased abstinence rate. Another study examined the therapeutic effect of *l*-THP combined with methadone for heroin detoxification (Hu et al., 2006), and found that *l*-THP, combined with methadone, significantly elevated detoxification rate, lowered total amount of methadone and decreased time for the detoxification. *L*-THP is being investigated in human clinical trial for the treatment of cocaine addiction in University of Maryland, Baltimore (Table 2).

Compound	Company	Pharm. Action	Indication	Status	Reference
L-THP	Best & Wide, Nanning, China	D1/D2/D3 Antagonist	Drug abuse (heroin, cocaine)	Phase I, Phase II	Yang et al., 2008; Wang & Mantsch, 2012
BP-897	Bioproject, Paris, France	D3 Partial Agonist	Safety Study	Phase II	Garcia-Ladona & Cox, 2003
Cariprazine	Gideon Richter, Budapest, Hungary	D3-Partial Agonist	Bipolar disorder; Schizophrenia	Phase III	http://clinicaltrials.gov
ABT-925	Abbott, IL, USA	D3 Antagonist	Schizophrenia	Phase II	http://clinicaltrials.gov
ABT-614	Abbott, IL, USA	D3 Antagonist	PK properties D3R binding by PET	Phase I	http://clinicaltrials.gov
GSK598809	GSK, Uxbridge, UK	D3 Antagonist	Substance abuse (nicotine); Food reward	Phase II	http://clinicaltrials.gov
GSK618334	GSK, Uxbridge, UK	D3 Antagonist	Substance abuse (alcoholism)	Phase I	http://clinicaltrials.gov
S33138	Institut de Recherches Servier, Croissy sur Seine, France	D3-Preferring Antagonist	D3R binging by PET; Safety	Phase I	Thomasson-Perret et al., 2008; Millan et al., 2008

Table 2. DA receptor-based drug candidates in clinical trials

3.2 BP-897

Preclinical studies: BP-897 is the first developed D3-selective partial agonist (Pilla et al., 1999) or antagonist (Wicke and Garcia-Ladona, 2001). A series of studies have assessed the efficacy of BP-897 in animal models of drug addiction (see reviews by Garcia-Ladona and Cox, 2003; Le Foll et al., 2005; Heidbreder et al., 2005). BP-897 produces a dose-dependent decrease in cocaine self-administration under second-order reinforcement, cocaine-induced CPP, cocaine's discriminative stimulus properties, and cocaine- or cue-induced reinstatement of cocaine-seeking behaviour. These data support the potential use of BP-897 in the treatment of cocaine addiction, particularly in relapse to drug-seeking behavior.

Clinical trials: BP-897 entered Phase II clinical studies for the treatment of drug addiction in the early 2000s. However, the detailed results about its safety, pharmacokinetics and therapeutic efficay have not yet been reported.

3.3 Cariprazine

Preclinical studies: Cariprazine (RGH-188) is a novel D3 receptor partial agonist with 10-fold selectivity for D3 over D2 (Gründer, 2010; Kiss et al., 2010). It is also a weak 5-HT_{1A} and 5-HT_{5C} partial agonist. Although limited preclinical data are available, the 'concept-proven' finding with BP-897 suggests that cariprazine might be similarly effective in attenuation of cocaine's actions.

Clinical studies: Cariprazine is currently in Phase III clinical trials for the treatment of schizophrenia and bipolar disorder (Table 2). Data from Phase II trials in patients with schizophrenia and bipolar mania indicate that the drug has antipsychotic and antimanic properties that are superior to placebo. The efficacy of cariprazine for treatment of cocaine addiction has not been evaluated.

3.4 SB-277011A

Preclinical studies: SB-277011A is the most well-characterized D3 receptor antagonist in preclinical animal models of drug addiction to date (Heidebreder et al., 2005; Heidbreder and Newman, 2010). SB-277011A has high affinity for human D3 receptor, and the selectivity for human and rat D3 over D2 receptor is 120 and 80, respectively (Reavill et al., 2000). In experimental animals, SB-277011A significantly and dose-dependently attenuates cocaine-enhanced brain-stimulation reward (Vorel et al., 2002; Spiller et al., 2008), cocaine-induced CPP (Vorel et al., 2002), cocaine self-administration under PR or FR10 (but not FR1 or FR2) reinforcement (Xi et al., 2005), and reinstatement of drug-seeking behavior caused by cocaine priming, cue or footshock stress (Vorel et al., 2002; Xi et al., 2004b; Gilbert et al., 2005). In addition, systemic administration or intracranial microinjections into the NAc or basolateral amygdala significantly and dose-dependently inhibited contextual cue-induced incubation of cocaine craving in rats (Xi et al., 2012). These data suggest that SB-277011A is a promising candidate in medication development for treatment of cocaine addiction.

Clinical trials: Further development of SB-277011A as a medication for treatment of cocaine addiction has been halted by GlaxoSmithKline Pharmaceuticals, due to unexpected poor bioavailability (~2%) and a short half-life (<20 min) in primates (Austin et al., 2001; Remington and Kapue, 2001). Therefore, much effort has been made to develop other D3-

selective antagonists with higher bioavailability and more promising pharmacotherapeutic profiles (Newman et al., 2005).

3.5 GSK598809 and GSK618334

Preclinical studies: Based on the results with SB-277011A, GSK is currently developing other D3 receptor antagonists, such as GSK618334 and GSK598809, for the treatment of substance abuse and addiction. GSK598809 is a novel, potent and selective DA D_3 receptor antagonist (Searle et al., 2010). Functional assays showed that GSK598809 has >100-fold selectivity for D_3 receptors over D_2, histamine H_1, muscarinic M_1, M_2, M_3, M_4, serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors (te Beek et al., 2012). CPP experiments in animal models indicated that GSK598809 significantly reduced nicotine- and cocaine-seeking behaviour in a dose-dependent manner (te Beek et al., 2012). In addition, GSK598809 significantly prevented relapse to nicotine-seeking behaviour, although no effect was observed on reducing alcohol consumption in rats.

Clinical studies: GSK618334 is currently under Phase I and Phase II clinical trials (Table 2). A recent PET imaging study suggests that GSK598809 significantly and dose-dependently inhibits [^{11}C]PHNO binding in D3-rich brain regions such as the ventral striatum, globus pallidus and substantia nigra (Searle et al., 2010). In healthy volunteers, single doses of GSK598809 were generally well tolerated. Plasma concentration of GSK598809 increased rapidly after oral administration (T_{max} 2-3 hrs) and subsequently decreased in an apparent bi-exponential manner (terminal half-life of roughly 20 hrs). The CNS effects of GSK598809 alone were limited to elevation of serum prolactin and a small decrease in adaptive tracking performance (te Beek et al., 2012). GSK598809, at a dose (175 mg) that associated >90% D2/3 receptor occupancy, appeared to have no overall effect on attention bias to food-related cues (as measured behaviorally) (Nathan et al., 2011), on subjective hunger or craving ratings and on brain response to food images (as measured by fMRI) in overweight and obese binge eating individuals (Dodds et al., 2012). These findings are consistent with previous findings in experimental animals demonstrating that SB-277011A or NGB-2904 have no significant effects on food-induced CPP and food-taking behavior (Vorel et al., 2002; Ross et al., 2007; Thanos et al., 2008). Contrary to the promising finding in experimental animals, a recent clinical trial with GSK598809 for the treatment of alcoholism demonstrated that it produces an additive, not an expected inhibitory, effect on alcohol intake (te Beek et al., 2012). GSK598809 is currently under Phase II clinic trial for treatment of nicotine dependence (http://clinicaltrials.gov/). The effects of GSK598809 on cocaine dependence have not yet been evaluated.

3.6 ABT-925

ABT-925, also known as A-437203 or BSF-201640, is a selective D3 receptor antagonist developed by Abbott Laboratories. It has an approximately 100-fold selectivity for D3 versus D2 receptors (Geneste et al., 2006). Although the preclinical data for this compound are currently unavailable, proof-of-concept for D3 receptor antagonists in treatment of schizophrenia and drug abuse has been well-estabolished. In Phase I and Phase II clinical trials (Table 2), ABT-925 was safe and generally well tolerated up to the highest dose levels tested (600 mg single dose, 500 mg once daily for 7 days) (Day et al., 2010; Graff-Guerrero et al., 2010; Redden et al., 2011). However, a recent double-blind, placebo-controlled study for

the treatment of acute schizophrenia suggest that ABT-925, at 50-150 mg per day, did not produce statistically significant therapeutic effects compared to placebo (Redden et al., 2011).

3.7 NGB-2904

NGB-2904 is another highly selective D3 receptor antagonist with >150-fold or 800-fold selectivity for primate or rat D3 over D2 receptors and 5000-fold selectivity for D3 over D1, D4, and D5 receptors (Yuan et al., 1998). Based upon its high selectivity for DA D3 receptors, we have recently evaluated the pharmacological effects in animal models of drug addiction. We found that systemic administration of NGB-2904 dose-dependently inhibits cocaine self-administration under PR (but not FR2) reinforcement (Xi et al., 2006b), cocaine-enhanced electrical brain reward function (Xi et al., 2006b; Spiller et al., 2008), and cocaine- and cocaine cue-induced reinstatement of cocaine-seeking behavior (Gilbert et al., 2005; Xi et al., 2006b). NGB-2904 alone neither produces dysphorigenic effects in brain-stimulation reward nor substitutes for cocaine in self-administration, suggesting that NGB-2904 itself has no abuse potential (Xi and Gardner, 2007). NGB-2904 is not currently under clinical trials, and detailed data regarding bioavailability and pharmacokinetic properties are presently unavailable.

3.8 YQA-14

YQA-14 is a novel D3 receptor antagonist developed recently (Song et al., 2012). Structurally, YQA-14 is a NGB-2904 analog. *In vivo* pharmacokinetic assays suggest that YQA-14 has improved oral bioavailability (>40%) and a longer half-life (>6 h in humans) compared to SB-277011A (~20 min in primates). In experimental animals, YQA-14 dose-dependently inhibits cocaine self-administration under both FR2 and PR reinforcement schedules, cocaine-induced CPP, cocaine-enhanced brain-stimulation reward, and cocaine- or cue-induced reinstatement of drug-seeking behavior (Song et al., 2012). Strikingly, at the doses that inhibit cocaine's actions, YQA-14 failed to alter oral sucrose self-administration and locomotor activity. YQA-14 is neither self-administered in drug-naïve rats nor substitutes for cocaine in maintenance of self-administration in rats previously trained for cocaine self-administration, suggesting that YQA-14 itself has no abuse liability. Deletion of DA D3 receptors in D3-knockout mice almost completely abolished the inhibitory effect by YQA-14 of cocaine self-administration, suggesting an effect mediated by blocking DA D3 receptors *in vivo* (Song et al., 2012). YQA-14 is currently not under clinical trials.

3.9 S33138

Preclinical studies: S33138 is a preferential D3 *versus* D2 receptor (~25-fold selectivity) antagonist (Millan et al., 2008). It was hypothesized that blockade of D3 plus partial blockade of D2 receptors may produce additive anti-cocaine therapeutic effects, but have fewer unwanted side-effects such as sedation and extrapyramidal locomotor impairment due to partial blockade of D2 receptors (Peng et al., 2009). In experimental animals, we found that S33138 produced biphasic effects – low doses increase, while high doses inhibit, cocaine self-administration under FR2 reinforcement. We interpret this increase in cocaine self-administration as a compensatory response to a reduction in cocaine's rewarding efficacy at low doses. In addition, S33138 also dose-dependently inhibits cocaine-enhanced brain-

stimulation reward and cocaine-induced reinstatement of drug-seeking behavior (Peng et al., 2009). S33138, at low-to-moderate doses, has no effect on brain reward function by itself, while at high doses, produces an aversive-like effect as assessed by electrical brain-stimulation reward experiments, suggesting a D2 receptor-mediated effect at high doses. Further high doses of S33138 also inhibit oral sucrose self-administration, suggesting possible unwanted effects on nature reward at high doses.

Clinical trials: S33138 is currently under clinical trials as an anti-psychotic agent for the treatment of schizophrenia and other psychiatric diseases (Millan and Brocco, 2008; Thomasson-Perret et al., 2008). The efficacy of S33138 for treatment of cocaine addiction has not been evaluated in human clinical trials.

4. Glutamate-based medication strategies

Rationale: L-glutamate is the major excitatory neurotransmitter in the brain and acts through two heterogeneous families of glutamate receptors: ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors. While iGluRs (i.e. NMDA, AMPA and kainite) 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_q 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 (see review by Cartmell and Schoepp, 2000).

Although the role of glutamate in mediating cocaine's rewarding effects remains unclear (see review by Xi and Gardner, 2008), growing evidence suggests that glutamate is critically involved in relapse to drug-seeking behavior (Figure 3) (Kalivas, 2009; Bowers et al., 2010). In brief, chronic cocaine produces a reduction in basal levels of extracellular glutamate or glutamate transmission in the NAc during cocaine withdrawal, while cocaine priming or re-exposure to cocaine-associated cues stimulate glutamate release in both the VTA and NAc. These findings suggest that both a reduction in basal glutamate transmission and enhanced glutamate responding to cocaine or cocaine-associated cues may constitute a neurobiological substrate of relapse to drug-seeking behavior (Kalivas, 2009). Based on this hypothesis, a number of pharmacotherapeutic strategies have been proposed. These include, first, normalization (increase) of reduced basal glutamate neurotransmission during abstinence, and second, antagonism of enhanced glutamate responses to cocaine or cocaine-associated cues (Figure 3).

4.1 *N*-acetylcysteine

Preclinical studies: N-acetylcysteine (NAC) is a cystine prodrug. It is approved for the treatment of pulmonary complications of cystic fibrosis and paracetamol (acetaminophen) overdose. By providing a source of extracellular cysteine, which is converted to cystine, NAC can exchange extracellular cystine for intracellular glutamate. This restores (renormalizes) decreased basal levels of extracellular glutamate (Baker et al., 2003). The increased extracellular glutamate may subsequently attenuate cocaine-induced increases in glutamate release by activation of presynaptic mGluR2/3 receptors, and therefore inhibits

cocaine- or cocaine cue-induced reinstatement of drug-seeking behaviour (Figure 3). NAC did not decrease cocaine self-administration or acute cocaine-induced hyperactivity, while it decreased repeated cocaine-induced escalation of drug intake and behavioural sensitization (Madayag et al., 2007). In addition, repeated NAC treatments also attenuated cocaine-induced increases in drug seeking in rats (Baker et al., 2003; Amen et al., 2010). Interestingly, NAC is also a prodrug for the synthesis of the endogenous antioxidant glutathione, and that NAC pretreatment protects animals from high dose methamphetamine- or amphetamine-induced DA neurotoxicity and behavioural changes by lowering oxidative stress levels (Fukami et al., 2004; Achat-Mendes et al., 2007).

Clinical trials: NAC is currently under clinical trials (Table 3). In double-blind, placebo-controlled clinic trials, NAC was well tolerated and produced a significant reduction in cocaine-related withdrawal symptoms and/or cravings triggered by exposure to cocaine-related cues or by an experimenter-delivered intravenous injection of cocaine (LaRowe et al., 2006, 2007; Amen et al., 2010). A 4-week open-label clinical trial demonstrated that NAC significantly reduced cocaine use in 16 of 23 human cocaine-dependent subjects (Mardikian et al., 2007). More clinical trials are currently underway (http://clinicaltrials.gov/).

Compound	Company	Pharm. Action	Indication	Status	Reference
N-acetylcysteine (NAC)	TwinLab, NY, USA; Others	Cystine prodrug	Substance abuse (cocaine, nicotine, methamphetamine)	Phase II	http://clinicaltrials.gov
AZD8529	AntraZeneca, London, UK	mGluR2/3 PAM	Schizophrenia	Phase II	http://clinicaltrials.gov
ADX71149	Janssen, USA	mGluR2 PAM	Schizophrenia; Anxiety	Phase II	http://www.addexpharma.com/pipline/
LY214023	Eli Lilly, USA	mGluR2/3 PAM	PK study	Phase I	http://clinicaltrials.gov
LY404039	Eli Lilly, USA	mGluR2/3 PAM	Schizophrenia	Phase II	Patil et al., 2007
LY354740	Eli Lilly, USA	mGluR2 PAM	Schizophrenia; Anxiety	Phase II	Dunayevich et al., 2008
JNJ-40411813	Johnson & Johnson, USA	mGluR2 PAM	Schizophrenia	Phase II	http://clinicaltrials.gov
GPI-5633	Guiford, USA	mGluR3 PAM	Safety & PK profile	Phase I	Van der Post et al., 2005
Fenobam	Enzo Life Sci. USA; Others	mGluR5 NAM	Anxiety; Fragile X syndrome	Phase II	http://clinicaltrials.gov
ADX10059	Addex Switzerland	mGluR5 NAM	Gastro-oesophageal reflux	Phase II	http://clinicaltrials.gov
STX107	Seaside, USA	mGluR5 NAM	Fragile X Syndrome	Phase II	http://clinicaltrials.gov

Table 3. Glutamate-based drug candidates in clinical trials

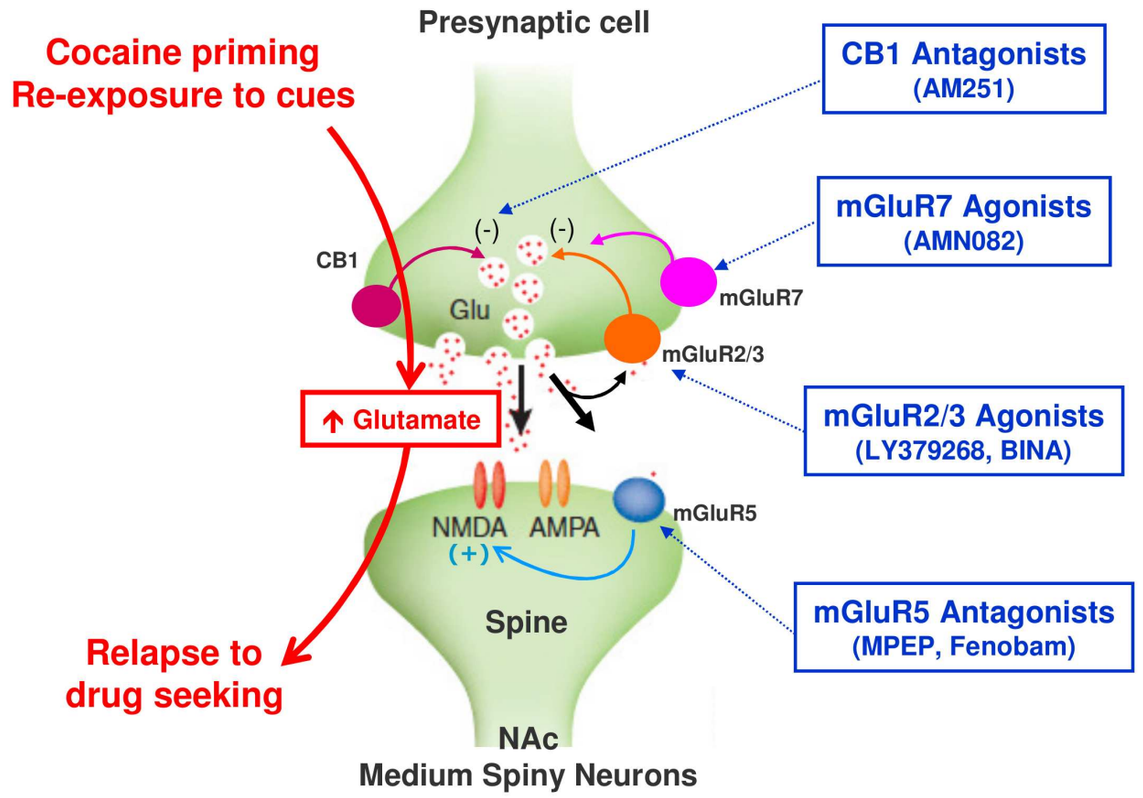

Fig. 3. Schematic diagram of glutamatergic synaptic transmission in the NAc, illustrating that cocaine priming or re-exposuse to cocaine-associated cues evokes an increase in glutamate release and relapse to drug-seeking behaviour in rats. Various compounds that target CB1 and mGluRs may attenuate cocaine- or cue-induced increase in glutamate release or in postsynaptic glutamate receptor signalling, and therefore, inhibit relapse to drug-seeking behaviour.

4.2 MPEP

Preclinical studies: MPEP is a selective $mGluR_5$ negative allosteric modulator (NAM) or antagonist (Gasparini et al., 1999). The first study to examine the role of mGluR5 in drug addiction reported that deletion of mGluR5 subtype abolishes cocaine self-administration in mice, while systemic administration of MPEP significantly inhibited cocaine self-administration in mice (Chiamulera et al., 2001). Since then, a large number of studies suggest that systemic administration of MPEP or its analog MTEP (a more selective mGluR5 NAM) (Lea and Faden, 2006) significantly and dose-dependently inhibits cocaine self-administration in rats (Xi et al., 2004a, 2004c; Tessari et al., 2004; Paterson and Markou, 2005; Kenny et al., 2005; Lee et al., 2005), cocaine-induced CPP (McGeehan and Olive, 2003; Herzig and Schmidt, 2004), cocaine-induced hyperactivity (McGeehan et al., 2004), and cocaine-, cue- or stress-induced reinstatement of cocaine-seeking behaviour (Xi et al., 2004a, 2004c; Lee et al., 2005; Backstrom and Hyytia, 2006; Kumaresan et al., 2009; Martin-Fardon and Weiss, 2011; Wang et al., 2012). These data strongly suggest that mGluR5 antagonists may be promising in the treatment of cocaine addiction.

Clinical trials: MPEP and MTEP have not been tested in clinical trials. Relatively poor selectivity of MPEP for mGluR5 over other targets (NET, NR2B-containing NMDA receptor, monoamine oxidase A and mGluR4) may have prevented its use in human clinical trials.

4.3 Fenobam

Preclinical studies: Fenobam (McN-3377) was originally developed as a nonbenzodiazepine anxiolytic in the 1980s with an unknown molecular target until 2005 when it was reported that fenobam is a selective mGluR5 NAM or antagonist (Porter et al., 2005). Fenobam was reported to have improved mGluR5 selectivity compared to MPEP, as assessed by the use of mGluR5-KO mice, and rapidly penetrate brain-blood barrier to concentrate in the brain (Montana et al., 2009). Systemic administration of fenobam dose-dependently elevates stimulation threshold for brain-stimulation reward in rats, suggesting a reduction in brain reward function (Cleva et al., 2012). In addition, our pilot experimental data also suggest that oral administration of fenobam significantly inhibits cocaine self-administration and cocaine- or cue-, induced cocaine-seeking behaviour.

Clinical trials: Fenobam was investigated in Phase II clinical trials in the 1980s for the treatment of anxiety and depression (Table 3). Earlier single- or double-blind, placebo-controlled clinical trials demonstrated that fenobam was effective in attenuating severe anxiety with good safety profiles (Pecknold et al., 1982; Pecknold et al., 1980; Lapierre and Oyewumi, 1982). However, in another report, it was reported to be inactive and have psychostimulant effects by itself (Friedmann et al., 1980). At the time, fenobam was discontinued from further development as an anxiolytic. In 2006, it was granted orphan drug designation by the FDA for clinical trials in the treatment of Fragile X syndrome, an inherited mental retardation disorder. The efficacy of fenobam in the treatment of cocaine addiction has not yet been evaluated.

4.4 ADX10059

ADX10059 is another novel mGluR5-selective NAM or antagonist with an IC_{50} of 17.1 nM at human mGluR5, showing good selectivity for mGluR5 over > 65 other receptors, transporters, ion channels and enzymes (Marin and Goadsby, 2010). Although limited preclinical data are available, it has been under Phase I and Phase II clinical trials for the treatment of gastro-oesophageal reflux disease (Zerbib et al., 2010, 2011) and migraine (Marin and Goadsby, 2010) (Table 3). To date, ADX10059 has been studied in at least 10 clinical trials. However, Addex Pharmaceuticals announced the discontinuation of development of ADX10059 in December 2009 due to liver enzyme changes. The efficacy of ADX10059 in the treatment of cocaine addiction has not been evaluated.

4.5 LY379268

Preclinical studies: LY379268 is a systemically effective $mGluR_{2/3}$ orthosteric (competitive) agonist (Marek, 2004). The $mGluR_{2/3}$ receptors have become attractive targets in medication development for the treatment of drug addiction because $mGluR_{2/3}$ receptors function as glutamate autoreceptors, modulating presynaptic glutamate release (Xi et al., 2002a) (Figure 3). In addition, $mGluR_{2/3}$ modulates DA and other neurotransmitter release in the NAc. Since cocaine-induced increases in NAc DA and glutamate are critically involved in drug

reward and relapse, it was proposed that $mGluR_{2/3}$ agonists might be useful for the treatment of cocaine addiction (Xi et al., 2002a). Systemic administration of LY379268 inhibits cocaine self-administration and cocaine cue-induced reinstatement of drug-seeking behaviour (Baptista et al., 2004; Peters and Kalivas, 2006). Microinjections of LY369268 into the NAc or central amygdala also inhibit cocaine- or food-triggered reinstatement of reward-seeking behaviour (Peters and Kalivas, 2006) or incubation of cocaine craving in rats (Lu et al., 2007). These data suggest that LY369268 may be useful for the treatment of cocaine addiction.

Clinical studies: LY379268 is not currently under clinical trials. This may be related to its intrinsic competitive agonist properties that may produce unwanted side-effects by itself and/or reduce efficacy due to competitive binding inhibition by excessive glutamate release under pathological conditions. In contrast to LY379268, several other mGluR2/3 positive allosteric modulators (PAMs) are being investigated in Phase I and Phase II clinical trials for the treatment of schizophreria and anxiety (Mezler et al., 2010; Patil., et al., 2007). These compounds include AZD8529, LY404039, LY354740, and LY2140023 (Table 3). The potential effects of these mGluR2/3 agonists in treatment of cocaine addiction have not been evaluated.

4.6 BINA

Preclinical studies: Biphenylindanone A (BINA) is a selective mGluR2 PAM or agonist (Johnson et al., 2003; Galici et al., 2006). Recent studies suggest that the pharmacological effects of LY379268 (a competitive mGluR2/3 orthosteric agonist) in animal models relevant to neuropsychiatric diseases could be mediated predominantly by activation of mGluR2, not mGluR3 receptor (Woolley et al., 2008), suggesting that mGluR2-selective agonists may produce similar therapeutic effects but have fewer unwanted effects than LY379268. Recently, Markou and her colleagues have compared the pharmacotherapeutic effects of BINA and LY379268 in animal models of drug addiction. They found that BINA selectively inhibits cocaine self-administration and cue-induced reinstatement of cocaine-seeking behaviour without affecting behaviours motivated by food reinforcement, while LY379268 nonselectively inhibits both cocaine- and food-taking and –seeking behaviour (Jin et al., 2010). These data suggest that selective mGluR2 PAMs (BINA) might have better therapeutic potential than dual mGluR2/3 agonists (LY379268) for the treatment of cocaine addiction.

Clinical trials: BINA is currently not under clinical trials. However, other mGluR2 PAMs such as AZD71149, LY354740 and JNJ-40411813 are currently under clinical trials for safety and *in vivo* binding property in healthy volunteers (Table 3).

4.7 2-PMPA and GPI-5693

Preclinical studies: 2-PMPA and GPI-5693 (also called 2-MPPA) are inhibitors of NAALADase (*N*-acetylated-α-linked acidic dipeptidase, also called glutamate carboxypeptidase II, GCPII), an enzyme that hydrolyzes *N*-acetylaspartate-glutamate (NAAG) to *N*-acetylaspartate (NAA) and glutamate (Neal et al., 2000, 2011). NAAG is an endogenous $mGluR_3$ agonist, which negatively modulates the release of glutamate and other neurotransmitters (Neale et al., 2000, 2011). Given the important role of NAc glutamate in relapse to drug seeking as stated above, it was hypothesized that inhibition of NAALADase

by 2-PMPA and GPI-5693 would increase extracellular NAAG and decrease extracellular glutamate levels (due to decreased glutamate release from NAAG degradation), while the increase in NAAG would further inhibit glutamate release from neuronal terminals and/or glial cells by activating mGluR3 receptors (Xi et al., 2002a, 2010b). In addition, NAAG also inhibits DA release by activating mGluR3 receptors located on DA terminals in the NAc (Xi et al., 2010b). Thus, the endogenous NAALADase-NAAG-mGluR3 signal system may constitute a novel important target in medication development for the treatment of cocaine addiction. Earlier studies have shown that systemic administration of 2-PMPA inhibits cocaine-induced CPP (Slusher et al., 2001) and cocaine-induced behavioural sensitization (Shippenberg et al., 2000). Recently, we reported that systemic administration of 2-PMPA or GPI-5693 inhibited cocaine self-administration, cocaine-enhanced brain-stimulation reward, and cocaine-triggered reinstatement of drug-seeking behaviour (Xi et al., 2010a, 2010b; Peng et al., 2010b). This action was blocked by pretreatment with LY341495, a selective mGluR2/3 antagonist. In addition, 2-PMPA dose-dependently attenuated cocaine-induced increases in extracellular DA and glutamate in the NAc (Xi et al., 2010a; 2010b). Taken together, these data suggest that inhibition of NAALADase by 2-PMPA or GPI-5693 produces an inhibitory effect on cocaine-taking and cocaine-seeking behaviour

Clinical trials: GPI-5693 was investigated in a Phase I clinical trial for its safety, pharmacokinetics and efficacy for treatment of neuropathic pain (Table 3) (van der Post et al., 2005). It was reported to be safe and tolerable in healthy subjects.

4.8 AMN082

AMN082 is a novel systemically active mGluR7 PAM or agonist (Mitsukawa et al., 2005). The $mGluR_7$ receptor subtype has attracted much attention in medication development for treatment of addiction for several reasons (Li et al., 2012). First, mGluR7 is the most abundant subtype of the group III mGluR subtypes in reward-related brain regions such as striatum, hippocampus and olfactory tubercles (Ferraguti and Shigemoto, 2006). Second, activation of group III mGluRs (including mGluR7) by L-AP4 inhibits DA and glutamate release in the NAc (Hu et al., 1999; Xi et al., 2003b). Third, it is the most conserved mGluR subtype across different mammalian species (Makoff et al., 1996), suggesting that selective $mGluR_7$ ligands that are effective in experimental animals are more likely to be effective in humans. And fourth, the development of AMN082 has allowed us to explore the role of mGluR7 in drug reward and addiction.

Based on the above, we and others have recently reported that systemic administration of AMN082 inhibits cocaine self-administration behaviour under both FR2 and PR reinforcement, cocaine-enhanced brain reward function, and cocaine-induced reinstatement of drug-seeking behaviour. In addition, AMN082 also decreases, while the selective mGluR7 antagonist MMPIP increases, alcohol intake and preference (Salling et al., 2008; Bahi et al., 2011). Importantly, the same doses of AMN082 neither alters locomotion or sucrose self-administration (Li et al., 2010; Bahi et al., 2011; but see Salling et al., 2008) nor alters brain reward function (Li et al., 2008), suggesting that AMN082 produces therapeutic anti-cocaine effects without significant unwanted effects such as sedation, dysphoria or natural reward depression. Further mechanistic studies suggest that a NAc-VP GABAergic mechanism underlies its antagonism of cocaine reward (Li et al., 2008, 2009), while a glutamate-mGluR2/3 mechanism underlies its antagonism of relapse to drug-seeking behaviour (Li et

al., 2008, 2010, 2012). Together, these preclinical data suggest a potential utility of AMN082 in the treatment of cocaine addiction. AMN082 has not yet been tested in clinical trials.

5. GABA-based medication strategies

Rationale: It is well known that the mesolimbic DA system is critically involved in drug reward and addiction. However, it remains unclear how increased NAc DA underlies these actions. Anatomically, the majority of neurons in the striatum are medium-spiny GABAergic output neurons, which receive DA projections from the VTA and glutamatergic projections predominantly from the prefrontal cortex, and project to the dorsal globus pallidus (from the dorsal striatum) and the ventral pallidum (VP) and VTA (from the ventral striatum, i.e. the NAc) (Bennett and Bolam, 1994; Groenewegen et al., 1996). Overall, DA produces a net inhibitory effect on striatal medium-spiny GABAergic neurons (Nicola and Malenka, 1997; Umemiya and Raymond, 1997), predominantly by activation of D2-like DA receptors (Centonze et al., 2002). Similarly, cocaine also produces an overall inhibitory effect on VTA GABAergic neurons (Cameron and Williams, 1994), striatal GABAergic neurons (Uchimura and North, 1990; White et al., 1993; Centonze et al., 2002; Schramm-Sapyta et al., 2006), and GABA release in the VP (Tang et al., 2005; Li et al., 2010). Based on this, the NAc-VP/VTA GABAergic projection constitutes common final pathway underlying drug reward and addiction (Figure 2). Thus, it has been hypothesized that a pharmacological strategy that enhances GABAergic transmission in the VTA and/or the VP would produce an inhibitory effect on cocaine- or DA-induced reductions in GABA release, therefore antagonizing cocaine's rewarding effects. Based on this, several GABAergic compounds have been studied extensively in experimental animals.

5.1 Gamma-vinyl GABA

Preclinical studies: Gamma-vinyl GABA (GVG) (also called vigabatrin) is an irreversible GABA transaminase inhibitor. GABA transaminase is an enzyme that breaks down GABA, causing an increase in brain GABA after GVG administration (Peng et al., 2010a). In the 1990s, Dewey and colleagues first proposed that GVG might be useful for the treatment of drug addiction (Dewey et al., 1998). Since then, many preclinical studies appear to support this hypothesis (Xi and Gardner, 2008). Systemic administration of GVG inhibits cocaine self-administration, cocaine-enhanced brain-stimulation reward, cocaine-induced CPP and behavioural sensitization (see review by Xi and Gardner, 2008). Similarly, it also dose-dependently inhibits cocaine-induced reinstatement of drug-seeking behaviour (Peng et al., 2008). All these data support the use of GVG in the treatment of cocaine addiction.

Clinical trials: GVG is currently under clinical trials for treatment of cocaine addiction (Table 4). In three open-labeled studies, GVG was well-tolerated and produced a significant increase in cocaine abstinence rate (Brodie et al., 2003, 2005; Fechtner et al., 2006). In a more recent randomized, double-blind, placeto-controled trial, short-term GVG treatment significantly increased abstinence rate compared to placebo (Brodie et al., 2009). However, in another clinical trial for the treatment of methamphetamine dependence, GVG was not effective (De La Garza et al., 2009). GVG is not marketed in the USA because of concerns over ophthalmological side-effects, but none were observed during these short-term studies (Fechtner et al., 2006). More studies are underway to confirm its efficacy for cocaine dependence (http://clinicaltrials.gov).

Compound	Company	Pharm. Action	Indication	Status	Reference
GVG	Aventis, Quebec, Canada	GABA transaminase inhibitor	Substance abuse (cocaine, methamphetamine)	Phase II	http://clinicaltrials.gov
Topiramate	Meliapharm, Montreal, Canada VIVUS, CA, USA	$GABA_A$ PAM	Substance abuse (cocaine)	Phase II	http://clinicaltrials.gov
Tiagabine	Cephalon, PA, USA	GABA transporter inhibitor	Substance abuse (cocaine); Anxiety Schizophrenia	Phase II Phase III	http://clinicaltrials.gov
Baclofen	Remedy Repack, PA, USA	$GABA_B$ receptor agonist	Substance abuse (cocaine, nicotine, alcohol)	Phase II	http://clinicaltrials.gov
Gabapentin	Meliapharm, Montreal, Canada	GABA enhancer, Alpha2delta-Ca^{++} channel blocker	Substance abuse (cocaine, nicotine, alcohol)	Phase II	http://clinicaltrials.gov

Table 4. GABA receptor-based drug candidates in clinical trials

5.2 Tiagabine

Preclinical studies: Tiagabine is a selective type 1 GABA transporter (GAT1) inhibitor, which increases extracellular GABA levels (Eriksson et al., 1999). It has been approved as an antiepileptic medication (Schousboe et al., 2011). Preclinical studies suggest that tiagabine inhibited intravenous cocaine self-administration in rats (Filip et al., 2007) or baboons (Weerts et al., 2005), but had no significant effect on cocaine-induced reinstatement of drug-seeking behaviour (Filip et al., 2007; Weerts et al., 2007). Our experimental data suggest that tiagabine, at much higher doses (10-20 mg/kg) than those used in the above-cited studies, selectively inhibited cocaine self-administration, but had no effect on cocaine-induced reinstatement of drug-seeking behaviour in rats (Yang et al., 2012).

Clinical trials: The results of clinical trials with tiagabine are mixed. Two small-scale (45 and 76 subjects, respectively) placebo-controlled clinical trials indicated that tiagabine produced a moderate reduction (~30%) in cocaine use in methadone-treated cocaine addicts (González et al., 2003, 2007), while other studies demonstrated that the same doses of tiagabine neither altered the acute effects of cocaine (Lile et al., 2004), nor lowered cocaine use in cocaine addicts (Winhusen et al., 2005; 2007).

5.3 Topiramate

Preclinical studies: Topiramate is a positive modulator of $GABA_A$ receptors (acting at non-benzodiazepine sites) and a licensed antiepileptic drug (Czuczwar and Patsalos, 2001). In addition, topiramate has other pharmacological actions, including antagonism of AMPA/kainate glutamate receptors, inhibition of voltage-gated sodium and calcium channels and inhibition of carbonic anhydrase (Johnson, 2005). In animal studies, topiramate was reported to inhibit cocaine self-administration and attenuate NAc DA response to cocaine or cocaine-associated cues (Johnson, 2005).

Clinical studies: In a double-blind, placebo-controlled clinical trial (40 subjects), topiramate significantly increased abstinence rates compared to placebo (Kampman et al., 2004). A recent 12-week, open-label pilot study showed a significant reduction in craving intensity and duration in 25% of the sample group (Reis et al., 2008). Evidence for a beneficial role of topiramate in the treatment of cocaine dependence is promising but is limited by small sample sizes (Cubells, 2006; Minozzi et al., 2008). More studies are currently underway (Table 4).

5.4 Baclofen

Preclinical studies: Baclofen is a selective $GABA_B$ receptor agonist, licensed as an antispasmodic for patients with spinal cord injuries or multiple sclerosis. In rodents, pretreatment with baclofen dose-dependently attenuates cocaine self-administration under FR and PR reinforcement (Roberts et al., 1996; Brebner et al., 2000), cocaine-enhanced brain-stimulation reward (Slattery et al., 2005), and cocaine-induced increases in NAc DA (Fadda et al., 2003). It also inhibited cocaine- or cue-induced cocaine-taking and cocaine-seeking behaviour (Di Ciano and Everitt, 2003; Campbell et al., 1999; Weerts et al., 2007).

Clinical trials: In an initial open-label clinical trial, baclofen reduced self-reports of craving and cocaine use in 10 cocaine abusers (Ling et al., 1998). In a subsequent 16-week double-blind study in 35 cocaine-dependent subjects, baclofen reduced cocaine use and increased the number of cocaine-free urines (Shoptaw et al., 2003), but did not alter cocaine craving. In a recent placebo-controlled, double-blind study, baclofen lowered cocaine intake, decreased cocaine craving, and attenuated cocaine's cardiovascular effects in both cocaine- and opioid-dependent subjects (Haney et al., 2006). However, a more recent large scale (160 cocaine addicts), double-blind, placebo-controlled clinical trial demonstrated that baclofen was not effective in attenuating cocaine use (Kahn et al., 2009). Thus, more studies are required to determine its efficacy in relapse prevention.

5.5 Gabapentin

Preclinical studies: Gabapentin is structurally analogous to GABA but, unlike the latter, it crosses the blood–brain barrier and can be administered systemically. Pharmacologically, 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 (Taylor et al., 1998). In addition, gabapentin also inhibits alpha2delta subunit-composed voltage-dependent Ca^{++} channels (Gee et al., 1996). Early studies suggest that gabapentin (1-30 mg/kg, i.p.) significantly inhibited cocaine-induced hyperactivity and locomotor sensitization (Filip et al., 2006; but see Itzhak and Martin, 2000). However, other

studies demonstrate that gabapentin, at a broad dose range (10-200 mg/kg i.p.), neither inhibited cocaine self-administration nor altered cocaine-induced reinstatement of drug-seeking behaviour in rats (Filip et al., 2007; Peng et al., 2008b). *In vivo* microdialysis studies demonstrate that gabapentin, at 100-200 mg/kg, produced a significant increase (~50 %) in extracellular GABA in the NAc, but failed to alter either basal or cocaine-enhanced NAc DA (Peng et al., 2008b). These data suggest that gabapentin is a weak GABA enhancer and may have limited potential in the treatment of cocaine addiction.

Clinical trials: Early clinical studies and small-scale, open-label outpatient trials demonstrated that gabapentin reduced cocaine craving and use (Raby and Coomaraswamy, 2004; Myrick et al., 2001; Hart et al., 2004, 2005). However, this finding was not repeated 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 rate, craving or subjective effects of cocaine (Bisaga et al., 2006; Berger et al., 2005; González et al., 2007; Hart et al., 2007). More clinical trials are currently under way to evaluate the effects of gabapentin or gabapentin combined with the antidepressant sertraline on cocaine or other addictive drug dependence (Table 4).

6. Cannabinoid-based medication strategies

Rationale: Marijuana is the most widely used illicit drug in the United States. Δ^9-tetrahydrocannabinol (Δ^9-THC) is the major psychoactive ingredient in marijuana. Two major types of cannabinoid receptors, CB_1 and CB_2, have been cloned. Since CB_1 receptors are found in both brain and peripheral tissues, whereas CB_2 receptors are found predominantly in peripheral immune system, it is generally belived that the psychoactive effects of Δ^9-THC or marijuana are mediated by activation of brain CB1, not CB2, receptors (Tanda and Goldberg, 2003). However, growing evidence suggests that functional CB_2 receptors are also found in the brain (Van Sickle et al., 2005; Gong et al., 2006; Xi et al., 2011), suggesting that brain CB_2 receptors may be also involved in marijuana's actions.

As stated above, the mesolimbic DA and the downstream NAc-VP GABAergic transmission have been thought to underlie cocaine reward and addiction. Growing evidence suggests that similar mechanisms may also underlie the action produced by Δ^9-THC or marijuana. It was reported that Δ^9-THC elevates extracellular DA in the NAc (Chen et al., 1990; Tanda et al., 1997). This action could be mediated by a GABAergic mechanism, i.e., Δ^9-THC may initially activate CB1 receptors located on VTA GABAergic interneurons and produce a decrease in GABA release, which subsequently disinhibits (or activates) VTA DA neurons (Figure 2) (Fernandez-Ruiz et al., 2010). In addition, CB_1 receptors are also highly expressed on presynaptic glutamatergic terminals in the NAc (Lupica et al., 2004). Thus, activation of CB1 receptors located on glutamatergic terminals decreases glutamate inputs onto medium-spiny GABAergic neurons in the NAc and decrease GABA release in their projection areas – the VP and VTA. Further, CB1 receptors are also expressed on striatal GABAergic neurons, and activation of the CB1 receptors produces a direct inhibitory effect on medium-spiny GABAergic neurons and decreases GABA release in the VP and the VTA (Maldonado et al., 2011). Lastly, cocaine or DA has been shown to increase endocannabinoid release in the striatum (Giuffrida et al., 1999; Centonze et al., 2004; Caille et al., 2007), which subsequently increases endocannabinoid binding to CB1 receptors located on presynaptic glutamatergic terminals and postsynaptic GABAergic neurons (Figure 2). Taken together, activation of

CB1 receptors located on both GABAergic and glutamatergic neurons causes an increase in NAc DA and a decrease in GABA release in both the VTA and VP. This decrease in NAc-VP GABAergic transmission constitutes a final common pathway underlying drug reward and addiction. Accordingly, blockade of CB_1 receptors in both the VTA and NAc would attenuate the actions of cocaine on NAc DA and VP GABA release, and therefore attenuate cocaine reward and addiction.

6.1 SR141716A

Preclinical studies: SR141716A (also called rimonabant) is the first developed CB_1 receptor antagonist (also an inverse agonist) (Rinaldi-Carmona et al., 1994). SR141716A was reported to inhibit cocaine self-administration under PR reinforcement (Soria et al., 2005; Xi et al., 2008), decrease cocaine-enhanced NAc DA (Cheer et al., 2007; Soria et al., 2005), and inhibit cocaine- and cue-induced reinstatement of drug-seeking behaviour (De Vries et al., 2001), while other studies suggest that it has no effect on cocaine self-administration under low FR reinforcement, cocaine-induced CPP, or cocaine-induced behavioural sensitization (Arnold, 2005). These data suggest that SR141716A may have therapeutic effects in attenuating relapse to drug-seeking behaviour, but is limited in terms of attenuating cocaine's acute rewarding effects (Beardsley and Thomas, 2005; Xi and Gardner, 2008).

Clinical trials: SR141716A was the first CB1 receptor antagonist to be approved for clinical trials for the treatment of obesity and cigarette smoking. However, there are some safety concerns with rimonabant – increased risk of anxiety, depression, and suicide tendency, which had led it to being withdrawn from the market in Europe and North America in 2008. Since then, many pharmaceutical companies (Sanofi-Aventis, Merck, Pfizer, Solvay) have announced that they will stop further clinical research on this class of drug.

6.2 AM251

Preclinical studies: AM251 is a more potent and selective CB_1 receptor antagonist than SR141716A (Krishnamurthy et al., 2004). In animal models of drug addiction, AM251 appears to be more potent and effective than SR141716A in attenuating cocaine's action (Xi et al., 2006, 2008). For example, AM251 significantly and dose-dependently inhibited cocaine self-administration (under PR, but not FR reinforcement) (Xi et al., 2008), cocaine-enhanced brain-stimulation reward (Xi et al., 2008), and cocaine-induced behavioural sensitization (Corbille et al., 2007), as well as cocaine-triggered reinstatement of drug-seeking behaviour (Xi et al., 2006). Further, a glutamate-mGluR2/3 mechanism has been shown to underlie the antagonism of reinstatement of drug seeking (Xi et al., 2006). That is, blockade of CB1 receptors by AM251 elevates extracellular glutamate in the NAc, which subsequently increased glutamate binding to presynaptic mGluR2/3 receptors, inhibiting cocaine-induced increases in glutamate release and relapse to drug-seeking behaviour (Xi et al., 2006) (Figure 3). These findings suggest that AM251 may be more potent and effective than SR141716A for treatment of cocaine addiction.

Clinical trials: Since the above mentioned side-effects of SR141716A have been linked to its inverse agonist property, it is generally believed that AM251, a CB1 receptor antagonist with similar inverse agonist property might have the same unwanted side-effects. It is not under clinical trials.

6.3 JWH133

Preclinical studies: In addition to CB1 receptors, recent breakthrough findings suggest that brain CB_2 receptors are also involved in drug reward and addiction (Onaivi et al., 2008; Xi et al., 2011; Aracil-Fernández, et al., 2012). JWH133 and GW405833 are highly selective CB2 receptor agonists. We have recently reported that systemic, intranasal or intra-NAc administration of JWH133 or GW405833 significantly and dose-dependently inhibits cocaine self-administration, cocaine-induced increases in locomotion and extracellular DA in wild-type and CB1-KO mice, but not in CB2-KO mice. Similarly, overexpression of CB2 receptors in mouse brain decreases intravenous cocaine self-administration and cocaine-induced locomotor sensitization (Aracil-Fernández, et al., 2012). These data suggest that CB2 receptor agonists may have therapeutic potential for the treatment of cocaine addiction (Figure 2) (Xi et al., 2011).

Clinical trials: JWH133 and GW405833 are currently not under clinical trials. However, many other selective CB2 receptor agonists, such as cannabinor, GW842166, GRC-10693, LY-2828360, ABT-521, and KHK-6188, are currently under Phase I and Phase II clinical trials for the treatment of pain or other diseases (Table 5). In addition, several dual CB1/CB2

Compound	Company	Pharm. Action	Indication	Status	Reference
Cannabinor	Pharmos, NJ, USA	CB2 agonist	Pain	Phase II	http://www.pharmoscorp.com/development/cannabinor.html
GW842166	GSK, London, UK	CB2 agonist	Pain	Phase II	http://clinicaltrials.gov
GRC 10693	Glenmark, Munbai, India	CB2 agonist	Pain	Phase I	http://www.evaluatepharma.com/Universal/View.aspx?type=Story&id=183092
LY-2828360	Eli Lilly, USA	CB2 agonist	Pain	Phase II	http://clinicaltrials.gov
ABT-521	Abbott, USA	CB2 agonist	Pain	Phase I	http://www.pharmalive.com/special_reports/sample.cfm?reportID=283
KHK-6188	Kyowa Hakka Kirin, Japan	CB2 agonist	Pain	Phase I	http://clinicaltrials.gov
Nabilone (Cesamet): Δ^9-THC analog	NEMA Research, USA	CB1/CB2 agonist	Cannabis addiction; Pain	Phase III Phase IV	http://clinicaltrials.gov
Marinol (Dronabinol): Δ^9-THC	UNIMED, USA	CB1/CB2 agonist	Substance abuse (opioid, marijuana, alcohol), PTSD	Phase II Phase IV	http://clinicaltrials.gov
Sativex: Δ^9-THC + Cannabidiol	GW, London, UK	CB1/CB2 agonist	Cannabis abuse, Pain	Phase II	http://clinicaltrials.gov

Table 5. Cannabinoid-based drug candidates in clinical trials

receptor agonists such as Nabilone (a Δ^9-THC analog), Marinol (Δ^9-THC), Sativex (a mixture of THC and cannabidiol) have been approved for the treatment of pain and chemotherapy-induced nausea and vomiting (Table 5). Based upon the recent findings that activation of CB2 receptors in primary afferents and spinal cord produces analgesic effects (Anand et al., 2009; Beltramo, 2009), and that activation of CB2 receptors in the brainstem inhibits morphine-6-glucuronide–induced emesis (vomiting) (Van Sickle et al., 2005), it is likely that the therapeutic effects of these dual CB1/CB2 receptor agonists may at least in part be mediated by activation of brain CB2 receptors.

7. Conclusion

In this review article, I first briefly reviewed the neurochemical mechanisms underlying cocaine reward and addiction, and then provided the rationale for development of various pharmacological therapies for the treatment of cocaine addiction. Lastly, I summarized the major findings of multiple pharmacological agents in each drug catagory in animal models of drug addiction and the current status in clinical trials for the treatment of drug addiction and/or other neuropsychiatric diseases. In summary, the VTA-NAc-VP pathway, including the mesolimbic DA and the NAc-VP GABAergic transimission, appears to play a critical role in mediating cocaine's rewarding effects (Figure 2), while a NAc glutamate-mGluR2/3 mechanism plays an important role in controlling relapse to drug-seeking behaviour (Figure 3). Accordingly, various pharmacological agents have been proposed and tested in animal models of drug addiction to interfere with the pharmacological actions produced by cocaine. Among those compounds discussed above, the DAT inhibitors (modafinil, RTI-335, CTDP31,345, CTDP-32,476), the DA receptor antagonists (*l*-THP, S33138, GSK598809, YQA-14) and the glutamatergic ligands (NAC, MPEP, LY369268, 2-PMPA) appear to be promising in preclinical animal models of drug addiction. In addition, several compounds (such as modafinil, disulfram, topiramate) were initially found to be effective in humans with unknown mechanisms, while subsequent preclinical studies helped to uncover the mechanisms of the actions. Although many compounds are currently or at some point were, under clinical trials, most of them have been used to evaluate their safety and efficacy for other neuropsychiatric diseases such schizophrenia, anxiety, obesity or smoking, rather than for cocaine addiction. Clearly, more translational studies from preclinical research to human clinical trials are required to promote the medication discovery for the treatment of cocaine dependence.

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