Dopaminergic agents for the treatment of cocaine abuse

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Cocaine is a major drug of abuse whose devastating effects have captured the attention of health officials and policy makers. Based upon the alarming health and crime-related costs associated with the use of this powerful reinforcing drug, immediate therapies are needed for the treatment of cocaine addiction. In this review, some of the small-molecule-based approaches that have been pursued in the search for such medications are highlighted. Because the pharmacological actions of cocaine stem largely from its ability to block the dopamine transporter, many intervention strategies have focused on the dopaminergic pathway.

Cocaine, a plant alkaloid from the leaves of *Erythroxylon coca*, has long been recognized as a potent CNS stimulant and is one of the most addictive substances known[1]. Individuals who are addicted to cocaine can lose their ability to function both at work and in interpersonal relations. As a result of the introduction of purer forms of cocaine, such as crack, the use of this drug has led to one of the most serious health problems in the US and, to a lesser extent, in western Europe. In the US alone, an estimated five million people use cocaine each year[2]. Because of the high incidence of cocaine dependence and the large profits arising through the cocaine distribution network, it is estimated that drug-associated crime costs $50 billion per year. It is clear that immediate strategies are needed for the treatment of individuals who have become addicted to this powerfully reinforcing drug. Behavioral observations have identified a window of approximately the first ten weeks of abstinence in which the susceptibility to relapse is the greatest[3]. The development of therapeutic agents that will assist addicted individuals during this critical initial withdrawal stage is imperative for the success of outpatient detoxification programs.

Dopamine hypothesis

Cocaine elicits a multitude of behavioral and psychological effects that depend on the dose and route of administration. On a pharmacological level, cocaine is a nonselective drug interacting at a variety of pharmacologically distinct sites. It binds with high affinity to the transporter sites for the neurotransmitters dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA), thereby inhibiting the reuptake of these amines into the presynaptic neurons. Cocaine also binds with moderate affinity to sodium channels and with a still lower affinity to the opioid, muscarinic, cholinergic and σ-receptors, as well as to calcium channels[4]. Among this multitude of pharmacological actions, the behavioral effects of cocaine in man have been linked most strongly with its ability to inhibit DA reuptake[5]. Such effects include euphoria, reduced fatigue, psychomotor stimulation and improved mental clarity. These rewarding effects finally lead to abuse and addiction, which is characterized by psychological and physical withdrawal, as well as craving (the desire to re-experience effects of cocaine that becomes reflected in repetitive drug-seeking behavior). This action of cocaine on DA reuptake is further supported by its correlation with self-administration in mice and rats[6], and its ability to reduce the threshold for brain-stimulation reward, which is

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indicative of increased reward[7–10]. Moreover, cocaine is well known to increase DA levels in mesolimbic and mesocortical dopaminergic terminal regions of the brain[11]. Chronic cocaine use has been reported to alter limbic extracellular DA levels in a biphasic fashion; initially there is a dramatic increase in extracellular levels followed by a decrease to below basal values after several days of repeated administration[12]. Microdialysis experiments in rats suggest that continued self-administration of cocaine is triggered by this fall in DA levels below the baseline[13], suggesting that the ability of cocaine to alter the regulation of extracellular DA plays a critical role in the addictive properties of this drug. The postulated decrease in basal DA levels following cessation of cocaine use results in tolerance to further challenges with cocaine and withdrawal symptoms such as restlessness, irritability, anxiety, depression and dysphoria. To alleviate the resulting dysphoria, addicts use cocaine at a higher frequency and dose.

The mesolimbic DA pathway is also widely believed to play a prominent role in the reinforcing properties of a number of other drugs of abuse including amphetamine. Much additional support for this hypothesis has been reported over the last decade[14,15]. It should be noted, however, that several compounds that strongly inhibit the reuptake of DA, such as mazindol, do not display significant abuse liability in humans or in animal models of addiction[16], probably because of a different pharmacokinetic profile. With cocaine, for example, its rapid onset of action (peak plasma concentrations in 30 min) and its relatively short half-life (15–60 min, depending on the route of administration) might be responsible, in part, for its addictive potential[17]. It is notable that some success has been achieved in the use of slow-onset sustained-action agonists for the treatment of addiction, including oral methadone for opiate abuse and nicotine patches for tobacco addiction. Based on these and other studies, a 'rate hypothesis' for addiction has been proposed. This hypothesis predicts that the abuse liability of a compound depends on the strength of its positive psychological response and is proportional to the rate-of-onset of these effects[18].

A number of more recent studies have implicated the involvement of other neurotransmitter systems in the reinforcing (addictive) properties of cocaine, in particular the serotonergic system[19–22]. Studies have shown that agents that potentiate serotonergic activity, such as tryptophan (a 5-HT precursor)[23] and fluoxetine (a 5-HT-selective reuptake inhibitor)[24], reduce the self-administration of cocaine in rodents. Furthermore, the use of knockout mice has revealed a cocaine-conditioned place preference (CPP) even in mice lacking the DA receptor[20]. While this result can be confounded by developmental compensations, it suggests the possibility that other mechanisms are involved in the reinforcement caused by cocaine administration. The involvement of opioid receptors in the motivational facilitation of cocaine addiction has also been postulated[25].

Although additional studies are required for a full understanding of the complex neurobiology of cocaine addiction, the pressing need for immediate therapies has spawned a wide number of programs aimed at the discovery of possible cocaine medications. Pharmacological agents are needed to address three distinct problems associated with cocaine abuse. Drugs are needed that can block the acute reinforcing effects of cocaine, alleviate withdrawal, and treat the long-term effects of cocaine abuse, i.e. craving. It is likely that different pharmacotherapies are needed for each of these indications. There are established animal models for the acute effects of cocaine as well as cocaine reward, whereas those for cocaine craving are still in development[26,27]. On the basis of available experimental evidence, DA is the major neurotransmitter involved in the reinforcing properties of cocaine, and the current literature is replete with studies that specifically target this system in the search for potential treatments. Drawing on the current literature, this review will focus on the development of therapeutic agents for the treatment of cocaine withdrawal that act directly on the DA reward pathways, with an emphasis on those agents acting at the DA receptor.

Points for intervention

The DA pathway is shown schematically in Fig. 1. This mesolimbic pathway consists of dopaminergic neurons in the ventral tegmental area and their projections to forebrain structures including the nucleus accumbens (NAc). DA is synthesized *in vivo* from tyrosine by tyrosine hydroxylase to L-DOPA, followed by decarboxylation to afford DA. DA is packaged into vesicles which, upon stimulation of the neuron, are released into the synaptic cleft. DA then binds to specific G protein-linked receptors on postsynaptic neurons resulting in impulse transmission. Presynaptic DA autoreceptors on the terminal can modify neurotransmission by inhibition of either DA synthesis or release, or both. In addition, somatic autoreceptors can modify the firing rate of dopaminergic neurons by altering the conductance of calcium and/or potassium channels. The primary mechanism for removal of DA is through its reuptake by specific dopamine transporters (DATs) located synaptically and extrasynaptically.

The DA pathway allows for several points of intervention in the dopaminergic transmission:

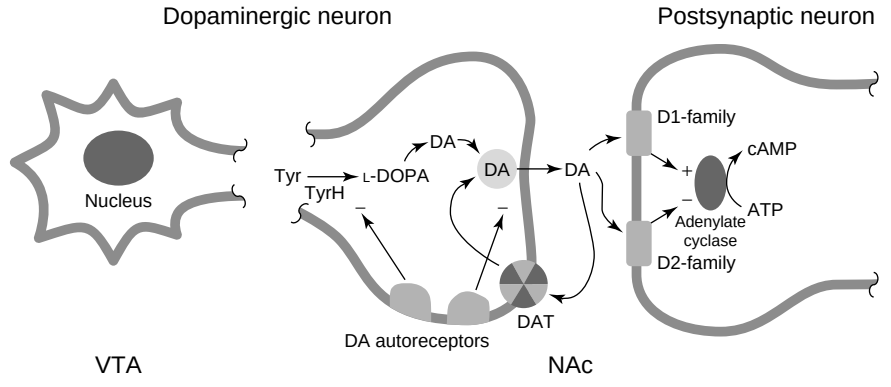


Figure 1. *The dopamine (DA) pathway. This mesolimbic pathway consists of dopaminergic neurons in the ventral tegmental area (VTA) and their projections to forebrain structures, including the nucleus accumbens (NAc). Abbreviations: DAT, dopamine transporter; TYR, tyrosine; TyrH, tyrosine hydroxylase.*

- Specific DA receptor agonists or antagonists allow intervention at the postsynaptic neuron.
- DA autoreceptor agonists or antagonists allow for intervention either by regulating firing rate at the cell-body level or by altering DA synthesis or release at the level of the nerve terminal. Because there are few ligands that are selective for DA autoreceptors, a discussion of this possible point of intervention will, out of necessity, involve the postsynaptic intervention point above.
- Inhibitors of the DA receptor, such as cocaine, potentiate dopaminergic transmission through an increase in the extracellular DA levels. Compounds that antagonize cocaine's actions at the DA receptor can therefore inhibit the increase in extracellular DA levels.

A number of other strategies have been developed that modify the DA pathway indirectly, and some of the more promising strategies will be highlighted.

Antagonist or agonist?

Therapeutic benefits might be derived from approaches making use of drugs that act as either antagonists or agonists of cocaine's effects. Treatments using cocaine antagonists would be expected to result in a decrease in the euphoric effects of cocaine and, as such, might help to maintain abstinence. In addition, antagonists might afford potential treatments for the acute effects of cocaine (e.g. overdose cases), whereas highly selective cocaine antagonists would be expected to have little or no abuse potential. A serious disadvantage of this form of treatment is that these agents are unlikely to decrease cocaine craving and might actually increase the dysphoria associated with cocaine abstinence. A possible implication of this strategy is that addicts who relapse during treatment programs reinforced by cocaine antagonists might resort to using increased doses of cocaine to overcome this antagonism. On the one hand, this could result in serious problems arising from the other physiological effects of cocaine, such as cardiotoxicity. On the other hand, therapeutic agents that bind to the DA receptor and inhibit DA transport completely (cocaine agonists) or incompletely (partial agonists) might alleviate cocaine craving, while the mood-elevating effects of such drugs might result in increased compliance in treatment programs. However, these full or partial agonists might be prone to abuse depending on the extent of their reinforcing properties. This would necessitate the careful control of the pharmacological and pharmacokinetic profile of such a cocaine agonist to maximize the suppression of craving while minimizing the reinforcing properties.

Potential therapeutic agents

Dopamine receptor ligands

The use of DA receptor ligands for the treatment of cocaine abuse has been recently reviewed[28] and will therefore only be covered in an introductory fashion. DA receptors are divided into two general classes, the D1-family of receptors (D1, D5), which are positively coupled to adenylate cyclase, and the D2-family of receptors (D2, D3 and D4), which are negatively coupled to the adenylate cyclase. The mechanism for the complex interaction between the D1- and D2-families of receptors is not fully understood, and has been the topic of several recent symposia[29,30]. In general, both families of DA receptors have been suggested to contribute to the reinforcing properties of cocaine[31], with D1- and D2-receptor agonists having opposing effects on the modulation of cocaine-seeking behavior in animal models[32]. Here we will focus on specific agonists and antagonists at the DA receptors that have been explored as potential treatments for cocaine abuse.

D1-family receptor ligands

To date, few studies are available on the effect of D1-family receptor agonists or antagonists on cocaine abuse. Recent studies have suggested that the D1-receptor density

in the NAc of Rhesus monkeys is decreased by chronic self-administration of cocaine[33]. This suggests that the D1 receptor is crucial for cocaine-induced plasticity. The reinforcing properties of D1-receptor agonists are somewhat controversial. For example, Weed and Woolverton have demonstrated that the low-efficacy agonists SKF38393 and SKF77434 are not self-administered by monkeys, whereas the high-efficacy agonists SKF81297 and SKF82958 readily substitute for cocaine[34]. On the other hand, SKF77434 has been reported to function as a positive reinforcer in rats, although this might have been due to the D2-receptor activity of this compound[35]. More recently, SKF82958 has been shown to prevent the cocaine-induced relapse into drug-seeking behavior in rats[22]. On the basis of tissue distribution, the D5 receptor has been proposed to be an autoreceptor, and is a potential target for therapeutic intervention in cocaine abuse[36]. These potential functional differences in the D1-receptor family, together with the limited knowledge of the selectivities of the individual D1-receptor ligands, make it difficult to predict the therapeutic value of agents targeting the D1-family of receptors.

D2-family receptor ligands

A wide variety of D2-family receptor agonists are used in the treatment of schizophrenia. As a consequence of this clinical history, bromocriptine (Fig. 2), a D2-receptor agonist with significant D1-receptor activity, has been tested clinically for the treatment of cocaine abuse with mixed results. In early double-blind clinical trials, bromocriptine was poorly tolerated, resulting in high dropout rates[37]. A more recent double-blind trial suggests that bromocriptine is well tolerated and the results are promising[38]; however, the small sample size of this study, as well as questions regarding patient selection, limit the conclusions that can be drawn[39]. Other larger studies have reported that bromocriptine produces no alterations in subjective effects after cocaine administration[40].

In general, D2-receptor agonists demonstrate poor selectivity between the members of this receptor family. Nevertheless, most are reinforcing and trigger self-administration in humans and animals. However, SC-XI-75, a putatively selective D2-receptor agonist, did not substitute for cocaine in self-administration studies with monkeys[28]. In the same studies, quinpirole, a drug that exhibits some selectivity as a D3-receptor agonist, partially substituted for cocaine, whereas another somewhat selective D3-receptor agonist, 7-OH-DPAT, substituted for cocaine fully. However, analyses of these results are complicated by variations in the selectivity reported for these compounds. The D3 receptor exhibits a unique distribution in the brain, and its pharmacological properties have led to its classification as a DA autoreceptor. Its autoreceptor function is further supported by the observation that the relatively selective D3-receptor antagonists (+)-AJ76 and (+)-UH232 exhibit mild stimulant properties. Such ligands have been put forward as potential cocaine agonists for treatment programs[41]. Pramipexole, quinelorane, and PD128,907 are agonists exhibiting a 10- to 50-fold selectivity for the D3 receptor over the D2 receptor and have been reported to decrease the self-administration of cocaine in rats, whereas the D2-receptor agonist bromocriptine has no effect[42].

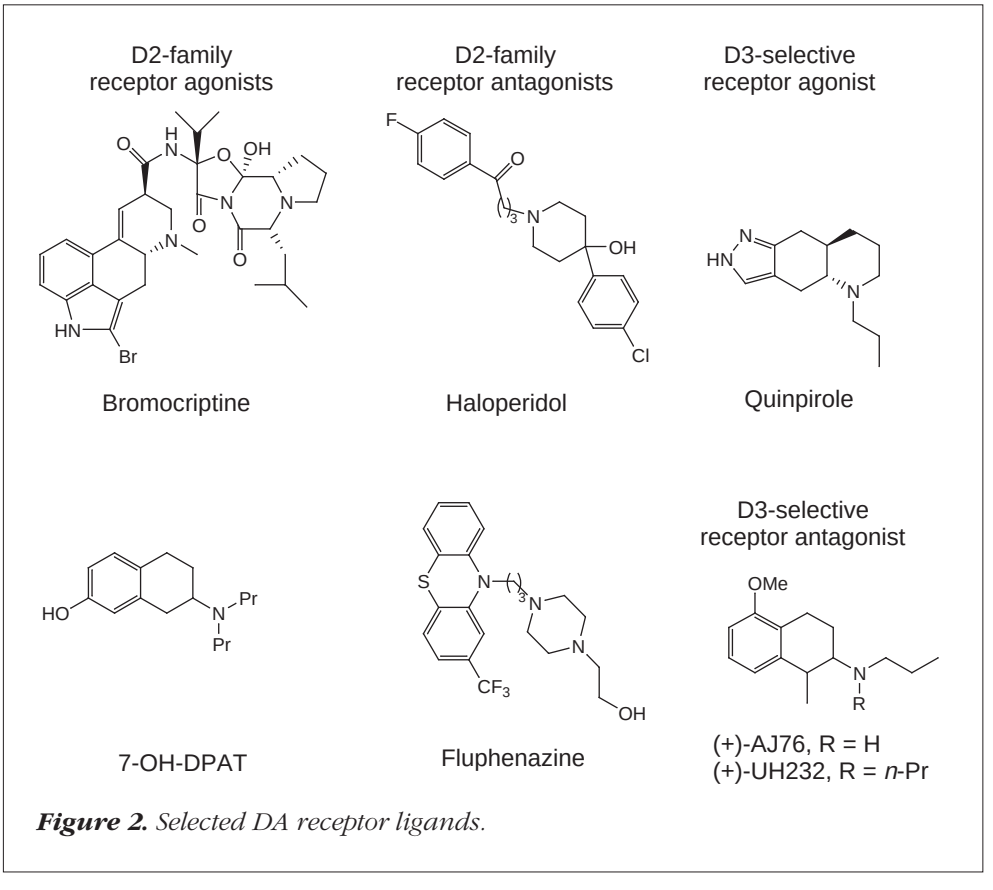


Figure 2. *Selected DA receptor ligands.*

In humans, pretreatment with haloperidol, a D2-receptor antagonist, showed a decrease in the subjective rewarding effects of cocaine, but exhibited little effect on the cocaine 'rush'[43]. Further animal studies have shown that chronic haloperidol treatment enhances CPP, whereas acute treatment blocks CPP (Ref. 44). This effect might be because of the super-sensitivity of the receptor and an enhanced locomotor response to cocaine resulting from chronic treatment[45]. In another study, cocaine-abusing, schizophrenic patients taking therapeutic doses of haloperidol or fluphenazine reported no decrease in the subjective effects of cocaine[46]. Antagonists of D2 receptors exacerbate cocaine withdrawal symptoms, such as dysphoria[47] and thus, although they might not be helpful in the treatment of cocaine abuse, they might have potential as therapeutic agents for drug abuse. Agonists of the D2 receptors may have potential for the development of therapeutic agents for drug abuse. The synthesis of compounds that exhibit higher selectivities for the various receptor families and subtypes is needed to facilitate this goal.

DAT ligands

The inhibition of the reuptake of DA by cocaine and related analogs has been reported to be competitive[48], noncompetitive[49] and uncompetitive[50]. Furthermore, cocaine may bind to a site on the transporter complex different from the substrate site, as suggested by the observation that DA reuptake inhibitors bind to different putative transmembrane-spanning helices in the cloned receptor[51], this being supported by recent kinetic studies[48]. Hence, it should be possible to design therapeutic agents that bind to the cocaine recognition site and either fail to inhibit (cocaine antagonists) or only weakly inhibit (cocaine partial agonists) DA transport. It is worth noting that, although cocaine antagonists have received significant attention in the current literature, the use of such analogs in the treatment of cocaine abuse would probably be limited to those cases involving acute overdose. However, the identification of partial agonists makes it possible to effect the partial generalization of the cocaine response. Such therapeutic agents might be capable of partially mimicking the cocaine response without exhibiting cocaine's full reinforcing properties.

Mazindol

Mazindol (Fig. 3) is a DA and NA reuptake inhibitor that is used clinically for the treatment of obesity and has revealed little, if any, abuse liability[52]. Despite the DA receptor activity of mazindol, it has been reported to be dysphoric in humans[53], whereas pretreatment with mazindol has been reported to decrease the cocaine response in monkeys[54]. In clinical trials, mazindol was not found to alter the subjective effects of cocaine[55], which might be because of the limited occupation of the DA receptor by mazindol. Thus, a recent single photon emission computed tomography (SPECT) investigation performed on cocaine addicts revealed that, at physiological tolerable doses, less than 25% of the DA receptor sites were occupied, and that higher doses of the drug might be required to antagonize the effects of cocaine[56].

Bupropion

Bupropion (Fig. 3) is a nonspecific inhibitor of monoamine reuptake with significant opioid receptor activity, which is currently prescribed as an antidepressant. In clinical studies, bupropion failed to produce cocaine-like subjective effects in humans[57]. In an initial small open-label pilot study, bupropion was reported to show good efficacy for supporting abstinence in methadone-maintained patients[58]; however, in a subsequent large multi-center trial, bupropion revealed little clinical efficacy[59].

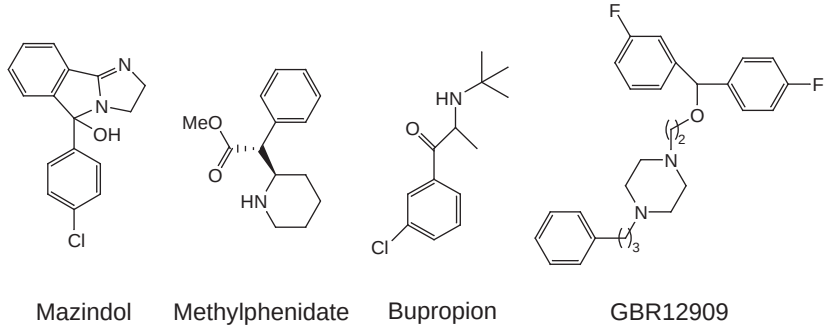


Figure 3. *Selected DAT ligands.*

Methylphenidate

Methylphenidate (Fig. 3) exhibits a high affinity at the DAT and this drug is used as a stimulant in the treatment of attention-deficit hyperactivity disorder in children and for the treatment of narcolepsy and depression in adults. A recent clinical study using methylphenidate showed no efficacy for the treatment of cocaine dependence[60]. Despite the failure of the parent compound, additional studies are being performed on methylphenidate analogs with a view towards developing

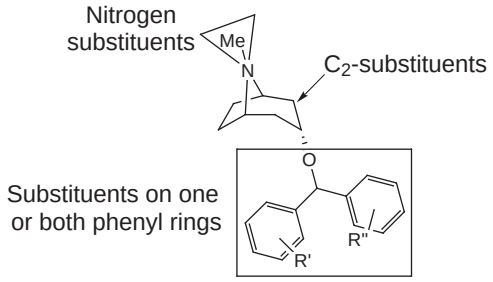


Figure 4. *Structure–activity relationship of benztropine.*

partial agonists or antagonists. These structure–activity relationship studies have focused on the substitution pattern in the aromatic ring. The meta-bromo and -chloro derivatives were found to exhibit the highest affinity for the DAT, with up to a fivefold lower potency for inhibition of reuptake. This suggests that it is possible to design analogs of methylphenidate with partial agonist or antagonist activity[61].

GBR analogs

Broad ranges of alkylphenylpiperazine derivatives connected to a benzhydryl moiety are known as GBR derivatives (Fig. 3). These compounds are potent DAT ligands and have been studied in Europe as a treatment for depression. A number of structure–activity relationship studies have been reported for the GBR series and some of these will be summarized. The piperazine moiety can be replaced by other diamines[62] or by a piperidine ring, with little or no loss in activity[63]. Other studies have focused on modifications in the (diphenylmethoxy)ethyl and phenylpropyl portions of the molecule, and these studies have shown that a broad range of modifications is possible without a loss in binding affinity. 4,4′-difluoro-substitution or no substitution in the diphenylmethoxy part affords compounds with the highest affinity. Bioisosteric replacement of the benzene rings by a thiophene ring is possible. Shorter alkyl chains can replace the propyl spacer, or this spacer can be made more rigid by the introduction of a double-bond. Replacement of the phenyl ring in the phenylpropyl chain by simple and fused heteroaromatic rings results in a number of compounds with high affinity for the DAT and improved selectivity over the 5-HT transporter (5-HTT; Ref. 64).

Most behavioral studies have focused on GBR12909 (IC_{50} 14 nM against [^{3}H]WIN35428)[65,66]. The acute reinforcing effects of GBR12909 in rats are comparable with those of cocaine, as measured by brain-stimulation reward[66] and this compound exhibits a pharmacological and pharmacokinetic profile, rendering it a promising candidate as a therapeutic agent in the treatment of cocaine abuse. Rather than the stimulant effects that would be expected based on its DAT activity, GBR12909 was shown to produce sedation in humans[67]. GBR12909 is a very lipophilic, slowly dissociating DAT ligand with a slow onset and long duration of action. *In vivo*, it exhibits a lower efficacy as a motor stimulant in rats than cocaine[68]. Furthermore, microdialysis experiments suggest that GBR12909 attenuates extracellular DA levels elevated by cocaine in rat striatum and NAc (Refs 69,70). In contrast, another study has reported that GBR12909 fails to antagonize the cocaine-induced elevation in DA levels in striatal slices[71]. However, a GBR12909 analog has recently been shown to selectively decrease cocaine-seeking behavior[72].

Benztropine

Benztropine is an anticholinergic DAT inhibitor, equipotent to cocaine, which is used clinically for the treatment of movement disorders that accompany Parkinson's disease. Structurally, benztropine possesses a tropane ring, as found in cocaine, and a diphenylmethane ether group, as found in the GBR series. It is distinct from cocaine in its lack of a substituent at the 2-position of the tropane ring. Drug design strategies have focused mainly on the substitution pattern in the aromatic moiety (R′, R″) and the replacement of the *N*-methyl group by other substituents (Fig. 4). All of the 4′- and 4′,4″-halogen-substituted compounds exhibit a higher affinity for the DAT compared with the parent compound, the general trend being F > Cl > Br, whereas increases in steric bulk or stronger electron-withdrawing or donating groups decrease DAT affinity. Meta-substitution does not have a dramatic impact on affinity of these compounds for the DAT, but selectivity for the DAT over the muscarinic M_1 receptor is decreased[73].

Substitution of the *N*-methyl group by other groups results in decreased muscarinic activity. The best compound in this series is the *N*-*n*-butylphenyl analog, which exhibits a lack of cocaine-like discriminative stimulus effects[74]. Substitutions leading to a nonbasic nitrogen are not tolerated, and substitution of the nitrogen by oxygen leads to a drastic decrease in binding affinity at the DAT. The introduction of a 2-carbomethoxy group into these benztropines results in a new class of compounds. Astonishingly, only the *S*-(+) derivative exhibits significant DAT affinity (the *R*-isomer is the most active in the cocaine series) and the most potent representative is the

4′,4″-difluoro-compound[75]. In preclinical studies aimed at gauging its possible use in the treatment of cocaine abuse, 4′,4″-difluorobenztropine has shown some promise in the attenuation of cocaine effects in animal studies[76]. In comparison with cocaine analogs, benztropine and some of its derivatives were not as efficacious as locomotor stimulants[77].

Cocaine analogs

Because cocaine is the drug that is being abused, it has served as an important starting material for the synthesis of analogs with properties that can be tailored selectively. A wide range of analogs have been synthesized to date, and excellent reviews of the structure–activity relationships of cocaine have been published[78,79]. Three sites of interaction of tropane analogs with the DAT have been proposed by Carroll *et al.*[78] These sites encompass the 3β-benzoyl ester group, the 2β-carbomethoxy substituent and the tropane nitrogen (Fig. 5). It should be noted that the *R* configuration of the tropane ring is generally assumed to be the most active one, being up to 1000-fold more active than the *S*-enantiomer[78]. In several recent reports a much smaller difference in activity of only 1.5–1.8-fold has been noted for the *R*- and *S*-enantiomers of structurally related tropanes[80,81]. These results suggest that the preference of the DAT for the *R*-tropane is not absolute and might depend on the substitution pattern.

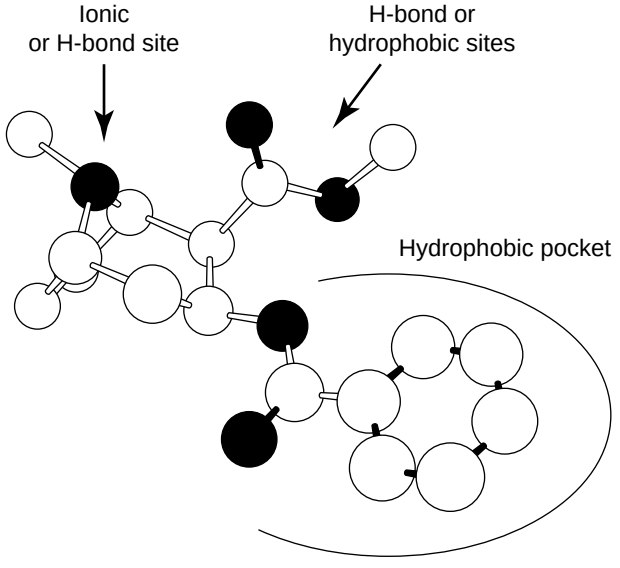


Figure 5. *Putative model for cocaine binding at its recognition site.*

Substitution at the 3-position of the tropane has been studied extensively and binding of the tropane analogs to the DAT is highly sensitive to changes at this site. The ester linkage at the 3β-position is not required, and can be removed readily by the direct linkage of the phenyl group to the tropane ring to afford compounds referred to as the WIN series (Fig. 6)[82]. These compounds exhibit a significantly enhanced (2–200-fold) activity. The hydrophobic pocket of the DA receptor is sufficiently large to allow for the introduction of a variety of small substituents, with particular attention being paid to the introduction of substituents into the *p*-position of the phenyl ring. The presence of these small substituents generally increases binding affinity as follows: 3,4-Cl_2 > 4-I > 4-Cl > 4-Me > 4-F > H (Ref. 83).

Davies *et al.* have reported the introduction of a 2-naphthyl at the 3β-position, which results in one of the most potent tropane analogs known to date[84]. The introduction of ethyl, ethenyl, isopropyl or isopropenyl in the *p*-position of the phenyl ring results in compounds displaying an increased affinity for the 5-HTT. A selectivity of up to 150-fold for the 5-HTT over the DAT has been reported[85]. A related study has disclosed that a *p*-ethyl-*m*-iodophenyl nortropane derivative possesses nearly 500-fold selectivity for the 5-HTT over the DAT (Ref. 86). Recently, a number of WIN compounds with a 3α-configuration of the phenyl ring have been reported[87,88]. In general these compounds exhibit a small decrease in activity at the DAT in comparison with the corresponding 3β-analogs. The selectivity of the 3α-compounds for the DAT over the 5-HTT is, however, increased, and based upon comparison of K_is rather than IC_{50} values, the selectivity can reach as much as 70-fold.

Extensive studies have been reported by Kozikowski *et al.*[89] and Carroll *et al.*[90] for modifications at the tropane 2-position. The DAT allows a wide range of substituents in the 2β-position with little or no loss in activity, including the introduction of sterically bulky groups[91,92]. Kozikowski's group has demonstrated that the transporter does not require a carbonyl group at this position and a variety of 2β-alkyl or alkenyl groups can be introduced, resulting in ligands that retain potencies in the nanomolar range at the DAT (Ref. 89). Such analogs in the WIN series are stable to endogenous esterases and exhibit increased biological half-lives. Despite the tolerance of the DAT for a wide variety of changes at the 2β-position, inversion to the 2α-configuration generally results in a decrease in activity[78].

Substitution at the tropane nitrogen has been studied in less detail and is much less understood. Early studies showed that, in general, there is a decrease in activity with increasing size of the nitrogen substituent, and that a basic

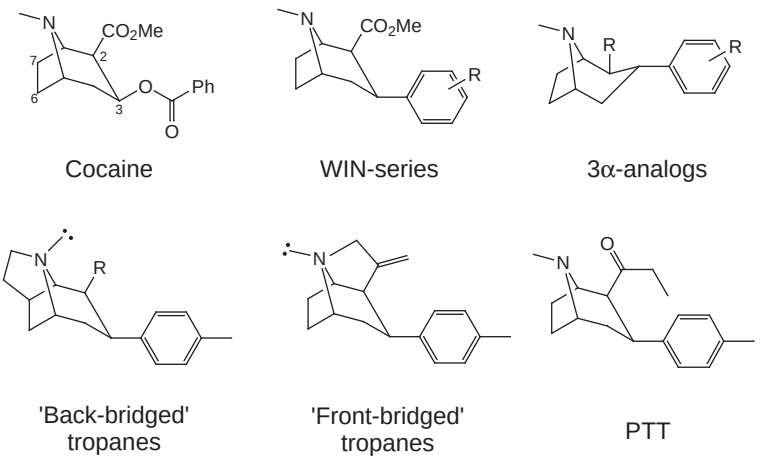


Figure 6. *Selected cocaine analogs.*

3′ amine is required for high activity at the DAT (Ref. 78). More recent studies have shown that these structure–activity relationships do not fully explain the interactions at this position. Several potent tropane analogs have been reported that contain bulky substituents tethered to the tropane nitrogen through an alkyl spacer, including the technetium complex, technepine[93]. This suggests that the DAT can accommodate large substituents near the tropane nitrogen. The directionality of the tropane nitrogen lone pair has been shown to be of consequence in the binding of these ligands to the monoamine transporters[94]. In general, those analogs in which the nitrogen lone pair is constrained over the 3-carbon bridge of the tropane ('back-bridged'; Fig. 6) are selective for the DAT over the 5-HTT, whereas those with the nitrogen lone pair directed over the 2-carbon bridge ('front-bridged'; Fig. 6) are selective for the 5-HTT. Several additional studies have shown that a basic nitrogen is not required for binding to the DAT and a series of *N*-sulfonamide (Ref. 95) and *N*-nitroso (Ref. 96) derivatives retain significant binding potency. More recently, a series of 8-oxo (Ref. 97) and 8-carbo (Ref. 83) analogs of the tropanes have been studied and found to exhibit only modest decreases in binding affinity at the DAT.

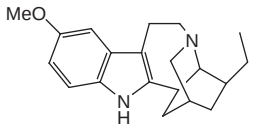
Because of the synthetic difficulties involved in the preparation of compounds containing substituents on other positions of the tropane ring, little is known about the effects of substitution at these positions. Simoni *et al.* reported the synthesis of a 7α-methoxy analog of pseudococaine that exhibited interesting functional antagonism at the DAT (Ref. 98). The low activity of this analog, however, precludes its use as a potential therapeutic treatment. Several recent reports have further investigated the effect of substitution on the 2-carbon bridge of the tropane and found that, in all cases, these compounds exhibit a decrease in binding potency when compared with the unsubstituted analog[81,83,99]. If the substituent that is introduced is a small, polar group, such as a hydroxy or fluoro at the 7α-position, then only a slight decrease in activity results. It is of interest to contrast the results of such 6- and 7-substituted tropanes with the previously discussed 'back-bridged' tropane analogs, as the latter compounds exhibit high binding affinity at the DAT in spite of bearing substitution at these positions.

Recently, a series of piperidine analogs of cocaine have been reported that exhibit high binding potency at the DAT (Ref. 100). For example, the *cis*-3β-carbomethoxy-4β-(*p*-chlorophenyl)piperidine exhibits a 2.5-fold increase in activity at the DAT compared with cocaine. These truncated cocaine analogs reveal that the presence of the tropane ring 2-carbon bridge is not a requirement for activity.

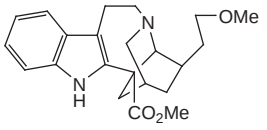
Several preclinical studies are available on tropane analogs for the treatment of cocaine abuse. Childers and coworkers have reported the effects of the 2β-propanoyl-3β-tolyl tropane (PTT) in Rhesus monkeys[101]. These studies showed that this long-acting DAT ligand is effective in decreasing cocaine self-administration and it exhibited generalization to cocaine in drug discrimination studies. Whereas PPT exhibits significant cocaine antagonism in these studies, it was found not to function as a reinforcer when substituted for cocaine, suggesting that it could serve to decrease cocaine craving while exhibiting a low abuse liability. Studies using the potent 3β-2-naphthyl analog (WF-23) in rat models showed a slow onset and very long duration of activity in locomotor assays, with a maximum effect noted at 4 h and persisting for 24 h (Ref. 102). These studies strongly suggest that analogs of the tropane series can be developed to provide therapeutic agents that are capable of assisting cocaine addicts through the critical initial craving stage of treatment programs.

Other potential modes for intervention

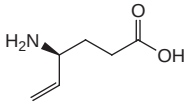
Several other treatments for cocaine addiction have attracted a significant amount of attention. The alkaloid ibogaine (Fig. 7) is being studied as a potential long-lasting therapeutic agent for the treatment of stimulant abuse as well as for alcohol and tobacco addiction[103]. Similar to cocaine, ibogaine exhibits a wide range of actions in the



Ibogaine



18-MC



GVG

Figure 7. *Miscellaneous agents.*

CNS, including inhibition of the DAT and 5-HTT, as well as affinity to the NMDA receptor (antagonist). Its anti-addictive properties apparently arise from these complex pharmacological activities. In animal models, a single administration of ibogaine has been found to reduce the self-administration of cocaine in a few (35%) of the rats tested[104]. In addition to its potentially useful anti-addictive properties, ibogaine also exhibits neurotoxic, tremorgenic and acute hallucinogenic activities that limit its potential as a treatment for cocaine abuse. More recently, the structurally related 18-methoxycoronaridine (18-MC) was reported to inhibit the self-administration of cocaine in rats without the associated neurotoxic effects[104].

The synthesis and release of DA are inhibited indirectly by the antiepileptic drug gamma vinyl-GABA (GVG, also known as vigabratrin). GVG exerts its effects through the irreversible inhibition of GABA transaminase, resulting in an increase in the extracellular levels of the inhibitory neurotransmitter GABA (Ref. 105). Reports have suggested that GVG inhibits the cocaine-induced increase in extracellular DA levels in rats[106] and reduces voluntary alcohol consumption in alcohol-preferring rats[107]. These studies suggest that GVG acts by potentiating inhibitory mechanisms that normally regulate dopaminergic neurotransmission. Compounds that potentiate GABA either directly or indirectly, such as GVG, might be anxiolytic, negatively hedonic or both[108]. Interestingly, GVG has been shown to be more effective at increasing basal brain stimulation reward thresholds (decreasing reward) than at modulating thresholds lowered by cocaine[109].

A wide range of other agents, or a combination of agents, have been investigated as potential treatments for cocaine abuse using the cocaine-agonist strategy. Many of these compounds act indirectly on the DA pathway or through mechanisms that are only poorly understood. Amantadine, for example, increases DA transmission through an unknown mechanism, and clinical trials have suggested that it can reduce cocaine craving[110]. Phentermine, a DA releaser, in combination with fenfluramine, a 5-HT releaser (Phen–Fen), has shown promise in preclinical[111] and open-label clinical studies[112]. Although the cardiotoxicity of fenfluramine precludes further testing using this combination, these studies reveal the potential of a treatment program that combines DA- and 5-HT-releasing properties.

Other candidate compounds for cocaine abuse have been studied and found to exhibit little potential for treatment. The monoamine oxidase inhibitor L-deprenyl has been tested and found to have no effects, either physiological or subjective, when co-administered with cocaine[113]. A number of antidepressants, including the tricyclic amines desipramine and imipramine, as well as the selective serotonin reuptake inhibitor, fluoxetine, have shown some efficacy in open-trials. However, these compounds failed to show significant efficacy in double-blind studies for the treatment of cocaine abuse[114].

Conclusions

A number of potential therapeutic agents for the treatment of cocaine abuse have been identified. To date, none of these therapies have demonstrated pronounced efficacy in double-blind placebo-controlled trials. The lack of effective therapeutic agents has spurred a number of programs to develop pharmacological agents directed at a wide variety of biological targets. Although the exact mechanism responsible for the reinforcing properties of cocaine is not known, it is relatively certain that the DAT activity of cocaine plays a significant role. This idea is further strengthened by the finding that nearly all of the compounds that have displayed some promise as therapeutics for cocaine abuse are reported to act directly or indirectly on the DA pathway. Although the development of cocaine antagonists continues to receive attention, it seems likely that the greatest chance for success is in the development of cocaine agonists, or partial agonists, that exhibit a slow onset of action coupled with a long duration of action. For a pharmacological agent to be considered as a potential treatment for cocaine dependence, it should demonstrate the following characteristics: (1) exhibit no abuse liability itself; (2) suppress the acute reinforcing effects of cocaine;

(3) reduce the symptoms of withdrawal and; (4) most importantly, reduce craving. Thus, while we have come a long way in our understanding of the neurobiology of cocaine abuse, the inquisitive researcher will still find this field affords many opportunities for discovery.

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In short…

Datamonitor (London, UK) has produced a report for **Reuters Business Insight** (London, UK) concerning a forecast of the growth in the number of depressives in the US market. The report combines a survey of US-based pharmaceutical executives with an in-house analysis. The main feature of the report is the forecast that the number of depressives in the CNS market in the US will grow from 41.9 million to 48.1 million by the year 2005, making it one of the main growth areas in the industry over the next five years. Furthermore, it was forecast that Prozac is likely to remain the leading antidepressant in the market until the year 2003.

In the US in 1997, antidepressants accounted for approximately 30% of the CNS market, being worth around $4 billion. The major reason for such a boost in the antidepressant market is because of the massive expansion (by approximately 65% since 1994) of the market for serotonin-selective reuptake inhibitors (SSRIs) to reach an estimated 90% of the market share of antidepressants. Furthermore, because of the increased efficacy of these agents over the older tricyclic antidepressants, prescribers are switching to the more expensive SSRIs.

A number of other factors have influenced the antidepressant market including the increased recognition for the need to manage depression both through therapy and through drug treatment. Moreover, there have been, and still are, significant increases in the size of the population, although the prevalence of depression is almost twice as high in the female than the male population. Additionally, many current antidepressants are now being licensed for a number of other indications such as obesity, and panic and obsessive compulsive disorder.

The full report is available from Reuters Business Insight (tel: +44 171 675 0990, fax: +44 171 675 0991, e-mail: press@rbi-reports.com). Price £495 or $795.