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Perspective

Pharmacotherapies for Treatment of Cocaine Abuse: Preclinical Aspects

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Introduction

Drug abuse, addiction, and dependence represent a major and increasing threat to public health. The 1997 National Household Survey on Drug Abuse (NHSDA) estimated that 76.9 million individuals, aged 12 and older, had used an illicit drug at least once, that 24.2 million had used an illicit drug during the past year, and that 14 million were current users of illicit drugs. However, the household survey is not a very good indicator of drug use among chronic, hardcore drug users, as many of these users are not members of households.[1] Thus, it is likely that the total number of users is much larger.[1] Within the household population, however, there are indicators of increasing illicit drug use. For example, the rate of past-month use of any illicit drug among 12−17-year-olds rose from 9.0% in 1996 to 11.4% in 1997.[1] The economic cost of drug abuse to the U.S. society is enormous and increasing. The health, crime, and other problems created by drug abuse cost society $97.7 billion in 1992, a 50% increase from 1985.[2,3] The estimated cost for 1995 is $109.8 billion, which is almost one-half the size of the Department of Defense budget for 1995.[3] While these numbers on use and cost show the magnitude of the drug abuse problem, the human suffering is incalculable. Illness, crime, domestic violence, reduced productivity, and lost-opportunity are direct consequences of drug abuse.

There is an increasing understanding that drug abuse is a physiologic disorder and that the need for medications for the treatment of drug abuse is tremendous. The terms abuse, dependence, and addiction generally refer to disease states of increasing levels of severity. Abuse is a level where drug taking is creating problems for the individual but where control is largely maintained. In addiction, control is lost. In a general sense, drug addiction or dependence is a chronic relapsing disease, in a social context, with a biological basis. The dramatic advances in our understanding of the biological basis of drug abuse and dependence,[4−10] together with advances in medicinal chemistry and neuropharmacology, support and motivate the search for pharmacotherapies effective as agents for pharmacological intervention. Pharmacotherapies are needed for all levels of drug abuse, as well as for the related problems of relapse and toxicity.

Considerable effort has been devoted to the development of effective treatments for substance abuse disorders, and such research has led to some useful pharmacotherapeutic interventions. For example, methadone (**1**) has been an effective medication and adjunct in treatment for heroin abuse for many years,[11−13] nicotine replacement has been useful for smokers,[14] and naltrexone (**2**) has provided help for alcoholics.[15,16]

Cocaine (**3**) abuse has been an epidemic in the United States since the introduction of crack in the mid-1980s. The 1997 NHSDA estimated that 22.6 million Americans, aged 12 and older, have used cocaine at least once in their lifetime, that 4.1 million used cocaine in the past year, and that 1.5 million are current users—some frequently, others occasionally.[1] In 1995, the estimated number of cocaine-related emergency episodes totaled over 142 000.[1] At present, there are no suitable medications for the treatment of cocaine abuse.

In this Perspective, various medicinal chemistry approaches for the development of medications for

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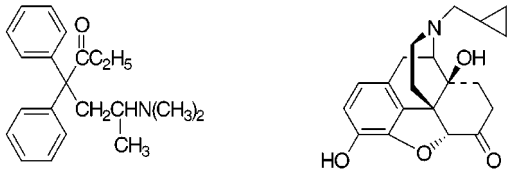
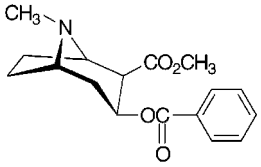


Methadone (**1**)

Naltrexone (**2**)



Cocaine (**3**)

cocaine abuse are presented, including aspects of protein-based therapies such as antibodies and enzymes. Because of the practical limitations of this article, and also because a medication for cocaine (**3**) abusers has not yet been developed, the focus of this Perspective will be on preclinical and development aspects of new medications for cocaine abusers. General concepts will be presented, and an overview rather than an exhaustive review of the literature is intended. The strategies presented are based on the present understanding of the underlying biological mechanism involved in each approach. Nevertheless, this article will focus on pharmacotherapies for treating the medical problems associated with cocaine abuse, rather than on mechanisms of addiction or other treatments. Other aspects of medication development and treatment have been reviewed recently.[17−27]

Properties and Pharmacological Profile of a Desired Medication

In general, certain properties of compounds are required for their development as medications. Efficacy should be demonstrated by models predictive of clinical outcome, but for cocaine abuse no single preclinical measure has yet been shown to be predictive of clinical efficacy. Hence, promising candidate compounds should be tested under a variety of experimental protocols. They must be potent and selective so that effective doses have minimal side effects, and they must be active following the desired route of administration. The compounds should have a suitably long duration of action[28] so as to provide reasonable dosing schedules, and finally, the compounds (particularly substitute agonists), some would argue, must enter the brain slowly.[29−31] This latter point is considered important, because compounds that enter the brain rapidly are associated with high abuse liability. Since treatment medications may be subject to abuse, preclinical evaluations should ensure that the therapeutic drugs have little or no abuse liability. Ideally they should show low potential for self-administration in animal models.

A variety of behavioral animal models are being used in the development of medications for cocaine abuse. These models are summarized in Table 1. Similarly, there are numerous neurochemical assays that are important (Table 2), which have been explained in detail elsewhere.[7,32−36] The behavioral models are powerful tools with which to explore compounds selected from the neurochemical assays. The drug-screening sequence most commonly used in the development of medications

Table 1. Animal Behavioral Models for Drug Screening

drug self-administration
drug discrimination
schedule-controlled responding
intracranial self-stimulation (ICSS)
conditioned place preference
locomotor activity

Table 2. Some Neurochemical/Neurophysiologic/Neuroanatomic Assays

receptor binding
in situ hybridization
receptor autoradiography
immunocytochemistry
microdialysis
voltametry
gene cloning
antisense technology

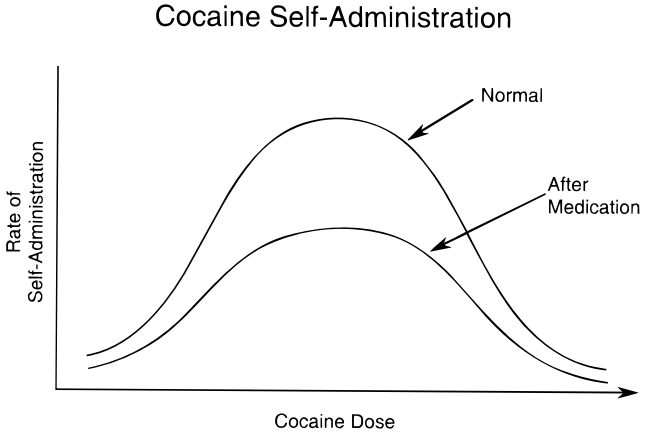


Figure 1. Effect of medications on an ideal dose−response curve for cocaine in self-administration studies. The typical dose−response is an inverted "U". An approach to medications would be to find one that depressed the "U"; this would reduce cocaine intake at all possible available doses.

for cocaine abuse is receptor binding, followed by rodent studies of locomotor activity and drug discrimination, followed by drug self-administration in rats and monkeys.

There has been much discussion about an appropriate pharmacological profile required for a suitable cocaine medication. Mello and Negus[26] suggest that a medication should depress the dose−response curve for cocaine self-administration (Figure 1), which is typically an inverted "U". A medication that depresses the dose−response curve downward would be effective at all concentrations or doses of cocaine, and drug-taking behavior would decrease across a broad range of doses. Medications that weaken the potency of cocaine (a shift of the dose−response curve to the right) may be less effective because the user could compensate for potency changes by adjusting the quantity of cocaine ingested. Moreover, the likelihood of cocaine toxicity would be enhanced if large quantities of drug were taken to overcome the effects of the treatment medications.

The Dopamine Hypothesis

A reasonable approach to develop a medication is to determine what cocaine (**3**) does in the brain and then block or reverse that effect. This requires an understanding of the neuronal circuitry and neurochemistry underlying cocaine's effects and the changes that cocaine

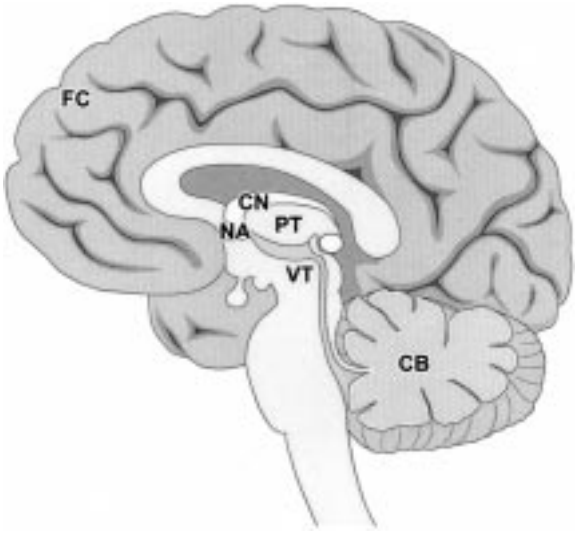


Figure 2. Brain. Certain areas of brain are known to be involved in reward/reinforcement due to drugs. These include the nucleus accumbens (NA), ventral tegmental (VT), and frontal cortex (FC). Other abbreviations are cerebellar (CB), putamen (PT), and caudate nucleus (CN).

causes. While progress has been made on this topic, much remains to be learned. The mesolimbic and mesocortical dopamine systems, which project from the ventral tegmental area to the nucleus accumbens and frontal cortex, respectively, have been identified as involved in psychomotor stimulant reward function (Figure 2).[37] Substantial evidence has accumulated, particularly in animal studies over the last several years, that the dopamine transporter is a key target or "receptor" for cocaine regarding the reinforcing effects of the drug.[38,39] The rationale for the use of dopaminergic drugs to treat cocaine abuse and dependence is based on the dopamine hypothesis of cocaine abuse. This hypothesis proposes that cocaine blocks the reuptake of dopamine by the dopamine transporter (DAT) and, thus, acts as an indirect dopamine agonist (Figure 3).[38,39] The DAT has been cloned and its location in the brain mapped. The increase in dopamine in certain brain regions resulting from cocaine interaction with the DAT is the critical element in cocaine's reinforcing properties. The dopamine hypothesis (Figure 3) has received strong support from a large number of preclinical investigations.[39−42]

For example, dopamine uptake inhibitors and direct-acting dopamine agonists can maintain drug self-administration in laboratory animals.[43−46] In drug-discrimination studies, some dopamine uptake inhibitors substitute completely for cocaine[47,48] and direct-acting dopamine agonists substitute partially for cocaine.[49,50] Conversely, dopamine antagonists can attenuate specific behavioral effects of cocaine in a surmountable manner; this includes its reinforcing effects,[51,52] locomotor activity effects,[53] discriminative stimulus effects,[54−56] and

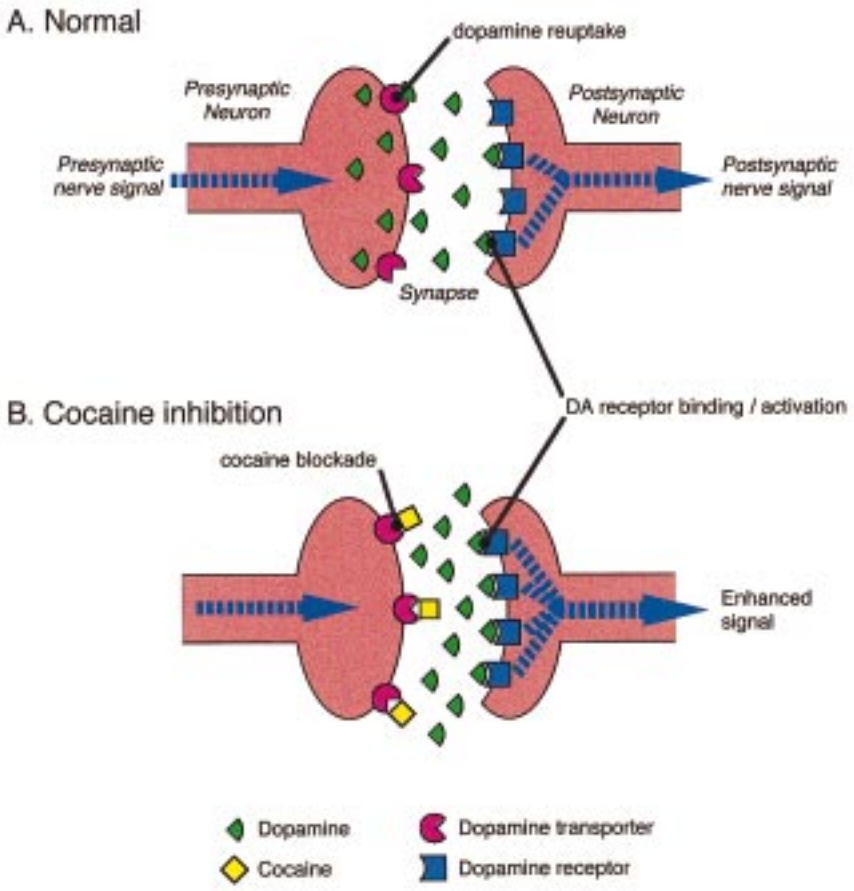


Figure 3. Cartoon representation of the dopamine hypothesis of cocaine's reinforcing effects. This highlights a major but only one approach to medications development. (A) Stimulation of neuron releases DA from the presynaptic terminal into the synapse where it may bind to DA receptors on the postsynaptic terminal, resulting in transmission of the signal; reuptake of DA via the transporter terminates the action. (B) Cocaine blocks the reuptake of DA, flooding the synapse with excess DA thereby causing an enhanced signal. A direct competitive antagonist of cocaine would block cocaine binding but would not block dopamine uptake.

Table 3. Types of Compounds Studied as Potential Medications for Cocaine Abuse[a]

targets	examples of compounds studied
DA uptake inhibitors (selective for DAT)[b]	RTI-113 (**11**), RTI-130 (**13**), RTI-177 (**14**), GBR12909 (**5**)
DA uptake inhibitors (not selective)	WIN 35,065-2 (**4**), RTI-112 (**10**), PTT (**12**), mazindol (**7**), methyl phenidate (**6**), nomifensine (**8**), benztropine (**9**)
DA receptor agonists and partial agonists	apomorphine (**15**), bromocriptine (**16**), SKF38393 (**17**), SKF82958 (**18**), 7-OH DPAT (**19**), quinpirole (**20**)
DA receptor antagonists	SCH23390 (**22**), spiperone (**23**), raclopride (**24**), haloperidol (**25**), SCH39166 (**26**), YM 09151-2 (**27**), nafadotride (**28**), (+)-AJ76 (**29**)
antagonists of cocaine binding that spare DA uptake	desipramine (**21**)
5HT uptake inhibitors	fluoxetine (**30**), alaproclate (**33**)
5HT receptor agonist	quipazine (**32**)
5HT antagonist	ketanserin (**34**), ritanserin (**35**), MDL 72222 (**36**), ondansetron (**37**)
excitatory amino acid (receptor antagonists):	
noncompetitive	MK801 (**38**), ADCI (**39**), ibogaine (**41**)
competitive	NPC 12626 (**40**), CPP (**43**)
excitatory amino acid (glycine site)	(+)-HA-966 (**42**)
strychnine-insensitive (glycine site)	ACPC (**44**), 7-chlorokynuremic acid (**45**)
GABA receptor agonists	baclofen (**46**)
GABA-transaminase inhibitor	vigabatrin (**47**)
opioids:	
kappa-selective agonist	U50,488 (**50**), spiradoline (**51**), enadoline (**53**), cyclozocine (**56**), PD117302 (**57**), bremazocine (**54**), MR2033 (**55**)
kappa-selective antagonist	nor-BNI (**52**)
delta-selective antagonist	naltrindole (**48**), naltriben (**49**)
nonselective antagonist	naltrexone (**2**)
mu/kappa-mixed agonist−antagonist	buprenorphine (**58**)
sigma ligands	BMY14802 (**59**), DuP734 (**60**), rimcazole (**61**), BD1008 (**62**), BD1063 (**63**)
calcium channel blockers	isradipine (**64**)
CRF antagonist	CP-154,526 (**65**)

[a] See text for structures, references, and more details. [b] Selective for the DAT relative to the serotonin and norepinephrine transporters.

rate-altering effects on schedule-controlled behavior.[44,57−59] However, the dopamine hypothesis may be oversimplified. For example, the activity of neurons is not simply related to reward but related to salience or novelty as well (for a recent review on the functional role of mesolimbic dopaminergic neurons, see Schultz et al., 1997).[60] Also, the neurochemical mechanisms involved in the initiation of dependence may be different from those involved in the actual state of dependence itself or even in states of craving, which may precipitate relapse during withdrawal. In addition, Pavlovian and operant-conditioning processes appear to play a major role in the maintenance of drug abuse and dependence, and they may be differentially sensitive to treatment medications. Thus, while the dopamine hypothesis explains some of the addicting process, additional understanding is needed.

Approaches to Medication for Cocaine Abuse

It is important to note that different types of medications may be needed. Overdose must be treated differently from dependence, withdrawal, and relapse, as different mechanisms may be involved in different problems. The optimal medications and treatment regimen for each condition may also be different.

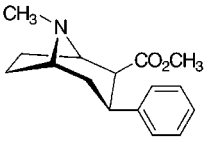
Several strategies have been used in the search for various medications. As mentioned above, one strategy is to identify and characterize the neurochemical effects of cocaine and then try to block or reverse the effects by pharmacologic means. This would certainly be the basis for the strategy of identifying competitive antagonists of cocaine at the dopamine transporter. Another strategy would be similar to that used for methadone (**1**) maintenance for heroin dependence. This approach involves administration of a substitute agonist so that the behavior of the addict can be controlled. This would allow the health care manager and patient to gradually decrease addiction and set in place strategies for long-term abstinence. The indirect modulation of drug reward via serotonergic, glutamatergic, and GABAergic inputs to the mesolimbic dopamine system offers additional targets for medications. Other strategies could involve interventions aimed at other mechanisms of the pharmacological response to cocaine. These include the sigma receptors, opioid receptors, calcium channel blockers, and corticotropin-releasing factor receptors. Table 3 lists several potential types of chemical medications for treatment of cocaine abuse along with specific examples of compounds that have been studied. A final strategy is the use of immunological and enzymatic mechanisms to reduce the penetration of cocaine into the brain. Each of these strategies is addressed in the following sections.

Dopamine System—Direct Approaches

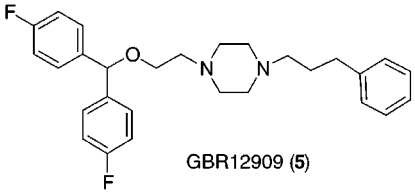
Dopamine Uptake Inhibitors. A key feature of a dopamine uptake inhibitor (substitute agonist) is that it would be a legal and regulated substitute for an illicit drug, and dispensing such a medication by a treatment physician would have the immediate advantage of attracting the drug abuser to the treatment center. It would, therefore, provide a means to an intermediate or long-term care program for the abuser. A substitute agonist would ideally remove craving for the illicit substance and facilitate entry into a program where abstinence is the final goal. This strong rationale has propelled the search for an effective substitute agonist, but none has yet been found.

Animal studies strongly suggest that the dopamine transporter is the critical site of cocaine's reinforcing

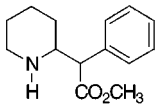
properties.[38,61−64] If these animal models mimic the critical aspects of human use, dopamine uptake inhibitors may very well be useful treatment substances. A large number of cocaine (**3**) analogues and other dopamine transporter inhibitors including analogues of WIN 35,065-2 (**4**), GBR12909 (**5**), methyl phenidate (**6**), mazindol (**7**), nomifensine (**8**), and benztropine (**9**) have been developed in the last 10 years, and these may find



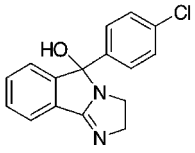
WIN 35,065-2 (**4**)



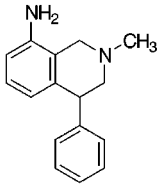
GBR12909 (**5**)



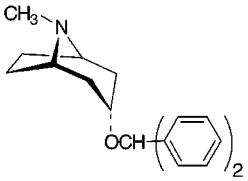
Methylphenidate (**6**)



Mazindol (**7**)



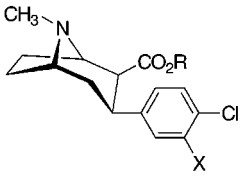
Nomifensine (**8**)



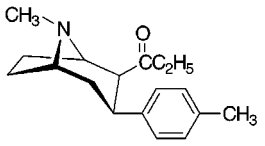
Benztropine (**9**)

importance in treatment of cocaine abuse.[25,65−76] Perhaps the largest class of compounds studied is the 3-phenyltropane analogues, of which many hundreds have been made and tested.[65−68,70,75] The analogues RTI-112 (**10**) and PTT (**12**) are in preclinical evaluation. Like cocaine, RTI-112 (**10**) and PTT (**12**) both have good affinity for all three monoamine transporters, but in contrast to cocaine they enter the brain slowly and are long-lasting. A number of other 3-phenyltropanes are potent, are selective for the dopamine transporter relative to inhibition of the serotonin and norepinephrine transporters, are long-lasting, and also enter the brain more slowly than cocaine,[29] for example, RTI-113 (**11**), RTI-130 (**13**), and RTI-177 (**14**). A study of these compounds will determine if inhibition of dopamine uptake alone is sufficient to serve as a substitute agonist for cocaine abuse. Thus, the 3-phenyltropane class of compounds has some of the basic properties required of medications.

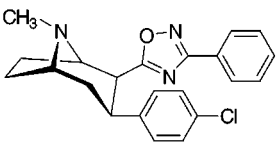
Other dopamine uptake inhibitors include analogues of GBR12909 (**5**), methyl phenidate (**6**), mazindol (**7**), nomifensine (**8**), and benztropine (**9**).[66] Compounds of the GBR series are known to be potent and selective for the dopamine transporter and have been considered as viable substitute agonist medications.[25,77] Preclinical studies of these compounds in nonhuman primates, however, have also indicated the potential for abuse in humans,[44,61] which may be a problem with all substitute agonists. Nevertheless, it is possible that some of the dopamine uptake inhibitors will have an abuse liability significantly less than cocaine. Some would argue that the best efficacy test among the animal models for



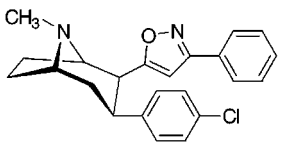
RTI-112 (**10**), X = CH_3, R = CH_3
RTI-113 (**11**), X = H, R = C_6H_5



PTT (**12**)



RTI-130 (**13**)



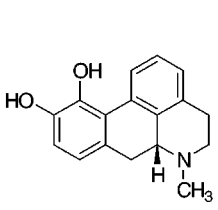
RTI-177 (**14**)

substitute agonists involves drug self-administration in nonhuman primates. Administration of an effective substitute agonist should suppress the self-administration of cocaine. It has been shown that 3-phenyltropanes such as RTI-112 (**10**), RTI-113 (**11**), and PTT (**12**) behave in this manner as does GBR12909.[25,78,79] Thus, compounds that are dopamine uptake inhibitors appear to satisfy the requirement of reducing cocaine intake. Even though no proven substitute agonist exists, many candidates exist in this group of compounds.

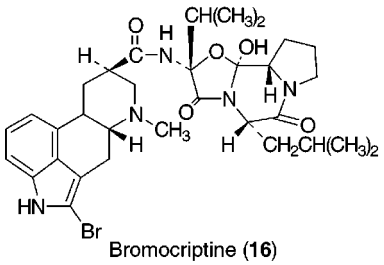
Dopamine Receptor Agonist. The effect of inhibiting neurotransmitter uptake is to stimulate neurotransmitter receptors; thus the use of direct receptor agonists as substitute agonist medications also has been suggested. Data on dopamine receptor agonists have been extensively reviewed.[26] Animal studies indicate that dopamine receptor agonists such as apomorphine (**15**) and bromocriptine (**16**) maintain self-administration in rodents[43,46] and in monkeys,[45,80] respectively. Although the effectiveness of D_1-selective partial agonists [e.g., SKF38393 (**17**)] as reinforcers has been questioned,[45,64] full-efficacy D_1 agonists [e.g., SKF82958 (**18**)] can reliably maintain self-administration in monkeys.[81] A double-blind study using bromocriptine (**16**) for the treatment of cocaine withdrawal showed some improvements in reducing cocaine craving; however, the medication was poorly tolerated leading to a significant dropout rate and consequently is not useful for the treatment of cocaine abuse.[82]

Pretreatment with dopamine agonists selective for the D_3 receptor subtype [e.g., 7-OH DPAT (**19**) and quinpirole (**20**)] potently decreases cocaine self-administration at doses which they are not reliably self-administered themselves.[83] Self et al.[84] have shown that "priming" (an animal model of relapse) was induced by the more selective D_3 agonist 7-OH DPAT (**19**) but not by the D_1 agonist SKF82958 (**18**). Pretreatment with 7-OH DPAT (**19**) enhanced cocaine seeking (i.e., reinstated extinguished cocaine responding), while the D_1 agonist SKF82958 (**18**) prevented cocaine-induced cocaine seeking in rats. These results imply that D_1 agonists can be used as therapeutic agents in humans to prevent relapse. These results suggest that other dopaminergic drugs should be evaluated in relapse prevention models.

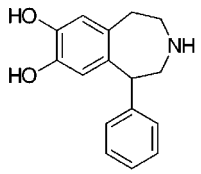
Dopamine Transporter and Receptor Antagonists. It has been proposed that a direct competitive antagonist of cocaine at the dopamine transporter,



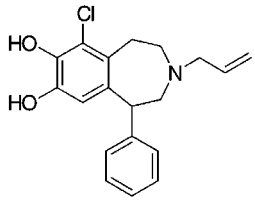
Apomorphine (**15**)



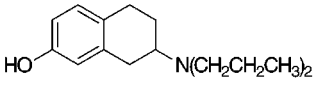
Bromocriptine (**16**)



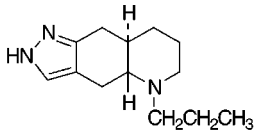
SKF38393 (**17**)



SKF82958 (**18**)

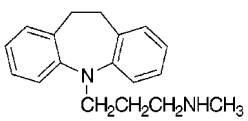


7-OH DPAT (**19**)



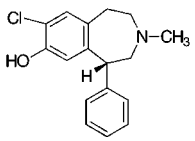
Quinpirole (**20**)

which would block cocaine binding to the transporter but which would not interfere with the uptake of dopamine, might be a useful medication. Thus, a dopamine-sparing cocaine blocker would prevent cocaine from binding and inhibiting uptake, while it would not have any effect on dopamine uptake and the normal function of the dopaminergic synapse (Figure 3B). One way to screen for such a compound in vitro would be to seek compounds that block cocaine binding to the transporter but do not block dopamine uptake, or at least do the latter with a much lower potency. The search for such a compound has been ongoing for several years but has not yet been successful. In fact, since the inhibition of radioligand binding and inhibition of [^{3}H]-dopamine uptake studies are carried out under different conditions, the results are not usually directly comparable. In one structure−activity study, however, the two assays were conducted under identical conditions of time, temperature, and buffer using CHO cells which stably express the human DAT.[85] The most selective compound identified from this study was the tricyclic antidepressant desipramine (**21**) which possessed a K_i uptake/K_i binding ratio = 11.5. Unfortunately, the K_i value for inhibition of [^{3}H]WIN 35,428 binding to the DAT was only 3 μM. A clinical study demonstrated that patients using desipramine as an adjunct treatment for cocaine abuse were no more likely to remain in treatment than those taking placebos.[82] Desipramine-treated patients, however, did have longer periods of abstinence than placebo-treated patients.

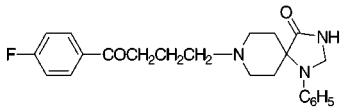


Desipramine (**21**)

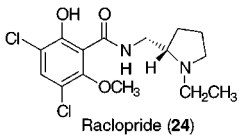
Since the effect of cocaine is to raise dopamine levels in the synapse and to cause an excessive stimulation of dopamine receptors, inhibitors of the dopamine receptors have also been considered for antagonist medications. Indeed, preclinical studies have demonstrated that selective dopamine antagonists can attenuate the behavioral effects of cocaine in a variety of animal models. These studies are summarized in a recent review.[26] The effects of cocaine on schedule-controlled behavior in monkeys are blocked in a dose-dependent manner by the D_1 antagonist SCH23390 (**22**) and the D_2 antagonists spipirone (**23**), raclopride (**24**), and haloperidol (**25**).[58,59,86] Similarly, the discriminative-stimulus effects of cocaine in squirrel monkeys and rhesus monkeys can be attenuated by D_1-selective dopamine antagonists such as SCH39166 (**26**) and SCH23390 (**22**) and D_2 antagonists such as YM 09151-2



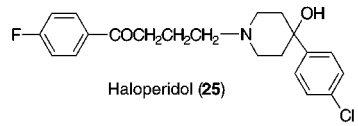
SCH23390 (**22**)



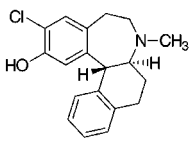
Spiperone (**23**)



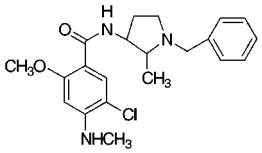
Raclopride (**24**)



Haloperidol (**25**)



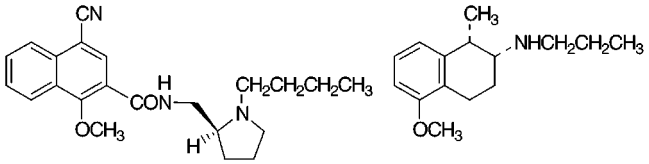
SCH39166 (**26**)



YM 09151-2 (**27**)

(**27**).[87−89] Enhanced dopaminergic activity also has been linked to the reinforcing effects of cocaine in self-administration paradigms,[38,61,90−92] and numerous studies have reported a blockade of the reinforcing effects of cocaine following pretreatment with selective dopamine antagonists.[62,93−97] D_2 dopamine antagonists such as haloperidol (**25**), however, appear to be limited in their ability to block the behavioral effects of cocaine. Behaviorally active doses of this dopamine antagonist produce significant side effects along with modification of the actions of cocaine.[21] Hence, specificity of action may be questionable, which would result in poor patient compliance. There are also some promising results in humans with D_2 antagonists, although the side effects of these drugs, which limit their acceptability in treating schizophrenics, may also limit their acceptability in drug abusers.

As described in the agonist section, there is now evidence that the D_3 receptor plays a role in mediating the reinforcing effects of cocaine. In particular, D_3 agonists were reported to enhance the reinforcing properties of cocaine. Not surprisingly, the D_3 antagonists nafadotride (**28**) and (+)-AJ76 (**29**) were reported to attenuate the behavioral and reinforcing effects of cocaine.[97−99] It is possible that more potent and more selective D_3 antagonists would have value as medications for cocaine abuse.

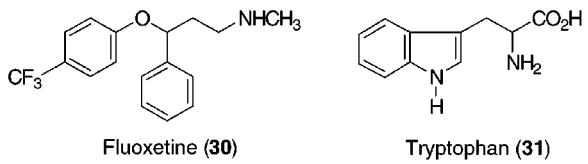


Nafadotride (**28**) (+)-AJ76 (**29**)

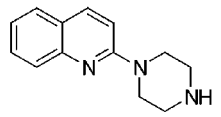
Other Neurotransmitter Systems

Cocaine exhibits a complex pharmacology that includes significant interactions with several neurotransmitter systems in addition to dopamine. Accordingly, compounds from a broad range of drug classes have been characterized in preclinical and clinical studies for their effectiveness as treatment medications in cocaine abuse.

Serotonergic Drugs. Several lines of evidence suggest that serotonin may also be involved in the neurochemical and behavioral effects of cocaine. Cocaine (**3**) binds the serotonin transporter with greater affinity than the dopamine transporter[100] and influences serotonin neurotransmission. Ritz and Kuhar[38,101] reported a negative relationship between the potencies of several cocaine and amphetamine analogues in self-administration studies and their binding potencies to serotonin (5HT) uptake sites. Studies in nonhuman primates have shown that drugs with prominent effects on 5HT uptake or release do not reliably maintain self-administration behavior.[102−104] Consistent with these results, administration of the 5HT uptake inhibitor, fluoxetine (**30**), or the 5HT precursor, L-tryptophan (**31**), decreases iv self-administration of cocaine in rats.[105−107] Pretreatment with selective 5HT uptake inhibitors such as fluoxetine (**30**) or a 5HT receptor agonist with high affinity for $5HT_2$ receptors such as quipazine (**32**) produces an insurmountable attenuation of the behavioral-stimulant effects of cocaine in monkeys.[104]



Fluoxetine (**30**) Tryptophan (**31**)



Quipazine (**32**)

More recently, it has been shown that administration of the 5HT uptake inhibitor, alaproclate (**33**), produces an insurmountable suppression of cocaine self-administration in monkeys (Howell, unpublished data; Figure 4). In contrast, pretreatment with selective $5HT_2$ antagonists such as ketanserin (**34**) enhances the behavioral-stimulant effects of cocaine and increases responding for cocaine self-administration.[104] Selective $5HT_2$ antagonists also increased responding for iv self-administration of the selective dopamine uptake inhibitor GBR12909.[108] The latter results are consistent with biochemical and electrophysiological studies, which indicate that serotonergic modulation of the behavioral effects of cocaine may involve interactions between the serotonergic and dopaminergic systems.[109−111] For example, electrophysiological studies indicate that 5HT exerts an inhibitory influence on the firing rate of dopaminergic neurons,[109−112] and pharmacological studies with ritanserin (**35**) indicate that the inhibition is mediated by the $5HT_2$ receptor subtype.[113] Collectively, these results show that the serotonin system can reliably modulate the behavioral-stimulant and reinforcing effects of cocaine and that the $5HT_2$ receptor subtype may play a significant role.

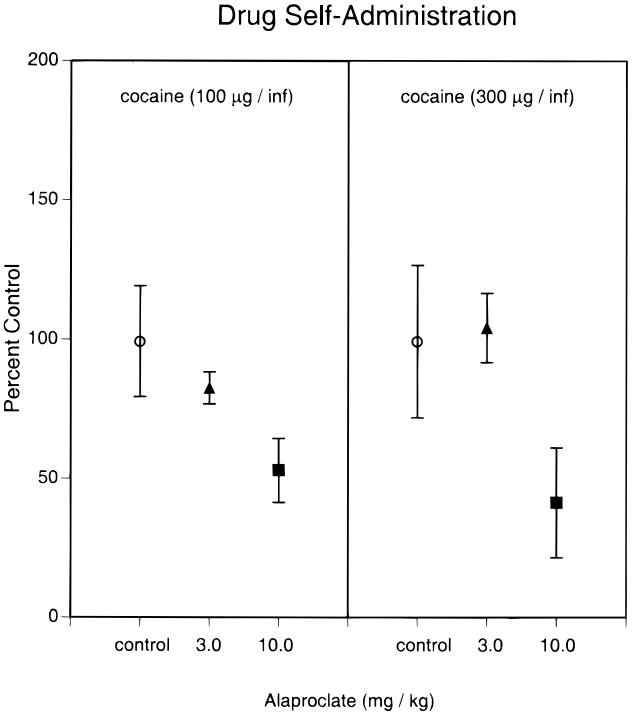
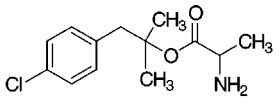
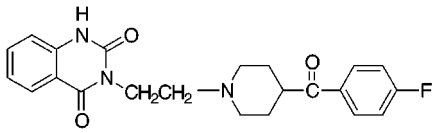


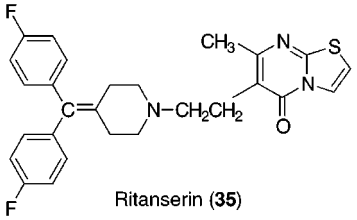
Figure 4. Reduction of cocaine self-administration in squirrel monkeys by a serotonin uptake inhibitor. Data are mean (±SEM) rate of responding maintained by a second-order schedule of iv cocaine self-administration in a group of three squirrel monkeys. Cocaine was self-administered alone or following pretreatment with alaproclate (doses are in mg/kg). Data for drug interactions were derived from at least three consecutive sessions at each dose combination. Alaproclate reduces cocaine self-administration.



Alaproclate (**33**)

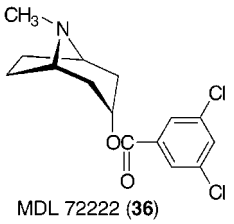


Ketanserin (**34**)

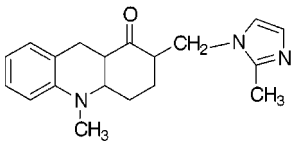


Ritanserin (**35**)

Additional studies have focused on the involvement of the $5HT_3$ receptor subtype in the neuropharmacology of cocaine, but the results obtained are somewhat inconsistent. Several $5HT_3$-selective antagonists, including MDL 72222 (**36**) and ondansetron (**37**), were reported to attenuate cocaine-induced locomotor activity in rodents.[114−116] However, pretreatment with MDL 72222 had no significant effect on cocaine-induced increases in operant behavior in squirrel monkeys.[104] Moreover, MDL 72222 (**36**) and ondansetron (**37**) failed to block the reinforcing[117,118] or discriminative-stimulus[117,119] effects of cocaine in rodents. It is unclear whether these seemingly disparate results involve species and procedural differences or reflect the complexity of the serotonergic system as it relates to the behavioral pharmacology of cocaine.



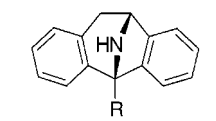
MDL 72222 (**36**)



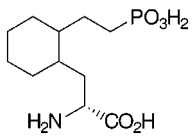
Ondansetron (**37**)

Excitatory and Inhibitory Amino Acids

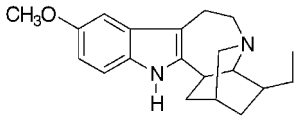
Glutamatergic pathways may also provide useful targets in the treatment of substance abuse. There are several reports indicating the involvement of the NMDA receptor complex in the expression of locomotor-stimulating, stereotypy-stimulating, and reinforcing effects of cocaine.[120,121] The NMDA noncompetitive antagonists, MK801 (**38**) and ADCI (**39**) and the competitive antagonist NPC 12626 (**40**) are reported to block cocaine-induced behavioral activation[122−125] and, in the case of MK801 (**38**), the reward value of self-administration of cocaine.[123,126] However, recent dose-response studies show that the relationships between NMDA antagonism and cocaine self-administration may be rather complex.[127−129] Consistent with the behavioral studies, MK801 (**38**) infused via a microdialysis probe was found to inhibit the cocaine-induced increase in extracellular dopamine in the nucleus accumbens of rats.[130] Since the cocaine-induced increase in extracellular dopamine in the nucleus accumbens is hypothesized to play a role in the reinforcing effects of cocaine, the above studies suggest that the noncompetitive NMDA antagonist class of compounds might reduce the reinforcing effects in humans, and thus be useful medications.



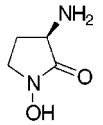
MK801, R = CH_3 (**38**)
ADCI, R = $CONH_2$ (**39**)



NPC 12626 (**40**)



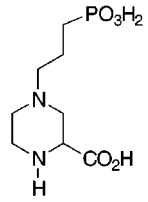
Ibogaine (**41**)



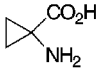
(+)-HA-966 (**42**)

Anecdotal reports indicate that ibogaine (**41**), an indole alkaloid, interrupts addiction to a number of abused substances including cocaine.[131] While the neurochemical bases for these actions remain unclear, the pharmacological profile of ibogaine (**41**) is similar to that reported for an NMDA receptor antagonist and suggests that the potential antiaddictive properties of ibogaine (**41**) are mediated by voltage-dependent block of the NMDA receptor complex. However, pharmacologically relevant concentrations of ibogaine interact with other receptor systems such as the kappa opioid and sigma systems.[132−134] The self-administration of cocaine can also be dose-dependently modified by central administration of the glycine antagonist (+)-HA 966 (**42**) suggesting that the strychnine-insensitive glycine site on the NMDA receptor may be useful in modulation of the reinforcing effects of cocaine.[135]

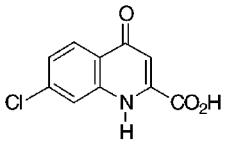
It is well-known that repeated administration of cocaine increases the probability of convulsions. The competitive antagonists CPP (**43**) and NPC 12626 (**40**), as well as MK801 (**38**) and ADCI (**39**), attenuated the convulsive effects induced by cocaine in mice.[21,136] Compounds that act at the strychnine-insensitive glycine site of the NMDA receptor complex, like the partial agonist ACPC (**44**) and the antagonist 7-chlorokynurenic acid (**45**), also protected against convulsions induced by cocaine.[137]



CPP (**43**)

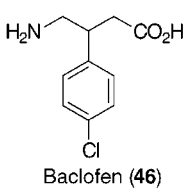


ACPC (**44**)

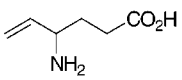


7-chlorokynuremic acid (**45**)

Recent reports suggest that inhibitory amino acid systems may also be involved in the reinforcing effects of cocaine.[138−141] The inhibitory amino acid GABA is known to be widely distributed in the CNS and to modulate basal dopamine release throughout the CNS.[142] Baclofen (**46**), a $GABA_B$ receptor agonist that inhibits the release of dopamine, norepinephrine, serotonin, and glutamate, was shown to suppress cocaine self-administration in rats.[140] A large clinical trial of the use of baclofen (**46**) for treatment of cocaine dependence is planned.[143] A preliminary treatment program using 10 cocaine-abusing males showed that baclofen (**46**) is a well-tolerated and safe medication.[143]



Baclofen (**46**)



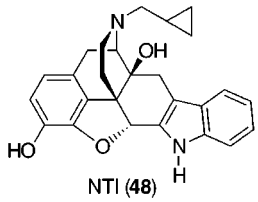
Vigabatrin (**47**)

GABA-transaminase (GABA-T) is thought to be the major enzyme involved in the metabolism of GABA. Inhibition of this enzyme leads to a rapid increase in the concentration of GABA and thus its effects. It is also of interest to note that pretreatment with the GABA-T inhibitor vigabatrin (**47**), which increases GABA activ-

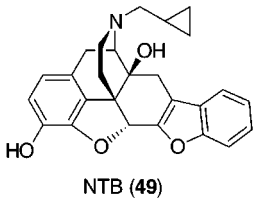
ity, blocked cocaine self-administration and the acquisition and expression of cocaine condition place preference.[139,144] Human trials with vigabatrin are currently being developed to directly examine the effectiveness of this compound in the treatment of cocaine abuse.

Opioid Receptor System. The endogenous opioid system has also been implicated in the reinforcing action of cocaine. As early as 1988, Hertz reported that the endogenous opioid system played a critical role in heroin addiction. Over the last several years, reports from Hertz as well as from other laboratories suggested that the endogenous opioid system may be altered, not only in heroin addiction but also in cocaine and alcohol addiction.[145−147] The effects of opioid ligands on cocaine self-administration in animals under maintenance conditions have been studied, but the results have been inconsistent. The non-subtype-selective opioid antagonist naltrexone (**2**) has produced no change, decreases, and increases in cocaine self-administration in rats.[26] Even though some studies with naltrexone (**2**) in Rhesus monkeys appeared to show decreases in cocaine self-administration, subsequent studies showed no effect.[26]

Results with delta opioid receptor-selective antagonists have also been inconsistent. In some studies naltrindole (**48**) (NTI) and naltriben (**49**) (NTB) were reported to reduce rat intravenous self-administration of cocaine[148] and block cocaine enhancement of response to intracranial stimulation.[149] In other studies naltrindole (**48**) was reported to have no effect on cocaine self-administration in rats[150] and inconsistent effects in Rhesus monkeys.[151]



NTI (**48**)

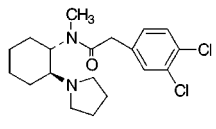


NTB (**49**)

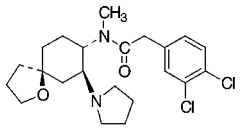
Some opioid agonists studied under maintenance conditions have also been reported to influence cocaine self-administration. The kappa-selective agonists U50,488 (**50**) and spiradoline (**51**) decreased cocaine self-administration without affecting water maintaining responding in rats.[152] The kappa opioid receptor antagonist norbinaltorphimine (nor-BNI, **52**) had no effect on cocaine self-administration under maintenance conditions but fully antagonized the effect of U50,488.[152] The kappa-selective agonists enadoline (**53**), bremazocine (**54**), and MR2033 (**55**) produced decreases in cocaine self-administration in Rhesus monkeys, whereas cyclazocine (**56**), PD117302 (**57**), and (−)-spiradoline (**51**) have no effect on cocaine-maintenance responding.[153] The basis for these differences is unknown.

Similar to the pure opioid receptor antagonist, opioid mixed agonist−antagonists are reported to antagonize the reinforcing effect of cocaine during self-administration. For example, the partial agonist buprenorphine (**58**) reduces the self-administration of cocaine in rats, Rhesus monkeys,[154] and humans.[155,156]

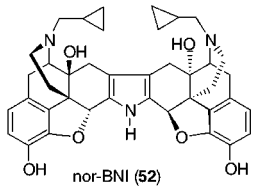
Using a model for the initiation of cocaine self-administration behavior, no effect of naltrexone (**2**) was found in caudate, amygdaloid, or accumbens nuclei, nor in the medial prefrontal cortex.[157] However, blockade



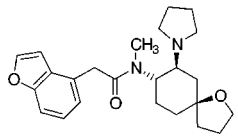
U50, 488 (**50**)



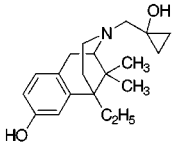
Spiradoline (**51**)



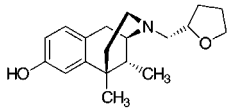
nor-BNI (**52**)



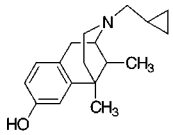
Enadoline (**53**)



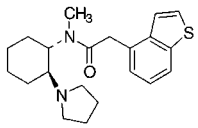
Bremazocine (**54**)



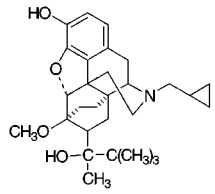
MR2033 (**55**)



Cyclazocine (**56**)



PD117302 (**57**)



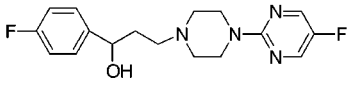
Buprenorphine (**58**)

of endogenous opioid receptors in the ventral tegmental region attenuated cocaine self-administration. The attenuation of self-administration was dependent on the naltrexone (**2**) dose. This suggests that endogenous opioid systems in the ventral tegmental area modulate the reinforcing effect of cocaine.

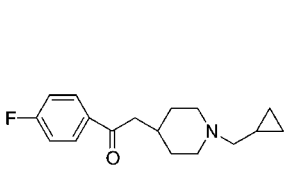
The possible involvement of the endogenous opioid systems in the reinforcing effects of cocaine is further supported by the observation that chronic treatment with the opioid antagonist naltrexone (**2**) facilitates the initiation of cocaine self-administration.[158] In addition, the kappa-selective agonist U50,488 also is reported to facilitate initiation of cocaine self-administration in rats with the dose-response curve shifted to the left.[159] The kappa-selective antagonist nor-BNI (**52**) blocked initiation of cocaine self-administration at threshold doses and shifted the dose-response curve to the right.[160] These results suggest that the kappa opioid system is involved in the modulation of cocaine self-administration behavior, especially during the initiation phase of cocaine dependence.

Sigma Ligands. Reports that sigma ligands modulated dopamine neuronal activity and inhibited the activity of hallucinogens suggested that sigma receptor ligands could be useful to antagonize the effects of cocaine.[161,162] Early studies reported that the putative sigma antagonists, BMY14807 (**59**), DuP734 (**60**), and rimcazole (**61**), inhibited or reduced the locomotor stimulant effects of cocaine at doses that do not alter spontaneous locomotor activity, the development of sensitization to repeated cocaine administration, or the convulsant effects of cocaine.[21,162−164] It is important to note that these compounds have significant affinity for other receptor systems. For example, DuP734 (**60**) has significant affinity for the $5HT_2$ receptor. However, in more recent studies the highly selective sigma receptor ligands, BD1008 (**62**) and BD1063 (**63**), were shown to

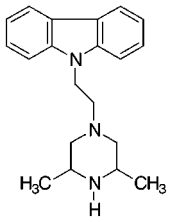
also attenuate the locomotor effect of cocaine.[165] Although these studies suggest that the sigma receptor might be a target for medication development, the mechanism of action of potential therapeutic agents at this site needs further studies.



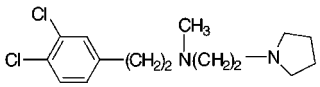
BMY14802 (**59**)



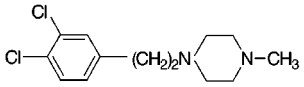
DuP734 (**60**)



Rimcazole (**61**)

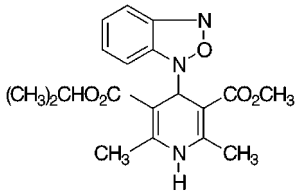


BD1008 (**62**)



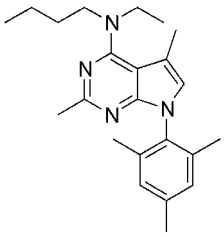
BD1063 (**63**)

Calcium Channel Blockers. Some reports suggest that L-type calcium channel blockers can reduce the rewarding effects of cocaine. For example, the L-type calcium channel blocker isradipine (**64**) attenuated the cocaine-induced dopamine release in the striatum of rats.[166] In other studies isradipine attenuated the condition place preference and the discriminative stimulus properties of cocaine.[167,168] Pretreatment with isradipine (**64**) produced a dose-dependent decrease in intravenous cocaine self-administration.[169,170] Since calcium channel blockers have antihypertensive effects, the potential increase in cardiac output in patients with normal ventricular function could complicate their use as pharmacotherapies for cocaine abuse.



Isradipine (**64**)

Corticotropin-Releasing Factor. Corticotropin-releasing factor or hormone (CRF or CRH), a 41-amino acid neuropeptide that is widely distributed in the brain, is released from the hypothalamus and acts on the anterior pituitary to cause production and release of β-endorphin and ACTH from pro-opiomelanocortin (POMC). CRF is thought to play an important role in the pathophysiology of anxiety and depression.[171] Since anxiety is considered to be a factor in precipitating relapse to chronic cocaine abuse, CRF could be involved in the acute behavioral and neuroendocrine action of cocaine.[172] In a recent report CP-154,526 (**65**), a selective antagonist of the CRF_1 receptor, attenuated stress-induced relapse to drug seeking in cocaine-trained rats.[173] These results suggest that CRF_1 antagonist may have utility in the treatment of relapse to cocaine use. Recently, several new CRF_1 antagonists were reported.[174−176] It will be interesting to evaluate these new analogues as medications for cocaine abuse.



CP-154,526 (**65**)

Protein-Based Therapies. Both active immunization and passive administration of monoclonal antibodies have been used to develop potential protein-based therapies for cocaine addiction. In the first approach, active immunization with a cocaine vaccine is used to generate anti-cocaine antibodies for use in blocking the effects of cocaine.[177,178] This vaccine has been tested in rodents, and the results show that anti-cocaine antibodies bind to cocaine in the circulation, which then retards the ability of cocaine to enter the brain. Furthermore, these anti-cocaine antibodies appear to reduce cocaine self-administration in rats.[177]

Other approaches involve the destruction of cocaine before it has a chance of reaching the brain. Thus, murine monoclonal catalytic antibodies have been developed which cause the metabolic breakdown of cocaine.[179] For example, using a transition-state analogue approach, a catalytic antibody (mAb15A10) was developed which catalyzed the hydrolysis of cocaine to inactive ecgonine methyl ester. In a model of cocaine overdose, mAb15A10 protected rats from cocaine-induced seizures and sudden death in a cocaine dose-dependent fashion.[180] As further proof of the concept, the ecgonine methyl ester concentration was increased more than 10-fold in the plasma of rats treated with the monoclonal antibodies. In a model of cocaine addiction, mAb15A10 completely blocked the reinforcing effects of cocaine in rats. These preclinical findings can be considered as proof of the general concept, but the approach needs further clinical development and evaluation.

Another protein-based approach to cocaine addiction treatment is via enhancing cocaine metabolism with butyrylcholinesterase.[181] Butyrylcholinesterase (BChE) is a major cocaine-metabolizing enzyme present in the plasma of humans and other mammals. Intravenous pretreatment of rats with 5000 IU of horse serum-derived BChE followed by administration of 17 mg/kg cocaine (intraperitoneally) produced a significant attenuation of cocaine-reduced locomotor activity. As further proof of this approach, BChE altered the cocaine metabolic pattern to yield the nontoxic metabolite, ecgonine methyl ester, instead of the usual benzoylecgonine metabolite. Thus, systemic administration of BChE compares favorably to other pharmacokinetic approaches to attenuating cocaine action including active immunization[177,182] and the catalytic antibody approach.[179] Unlike active immunization, which takes weeks to generate a useful antibody titer, BChE or cocaine antibody administration can produce protective effects within minutes after intravenous administration. However, the active immunization approach may be more

effective at retarding cocaine from entering the CNS since these antibodies would be of higher affinity for cocaine.

Studies in Humans—No Dramatic Successes

Given that preclinical results are so promising for some applications, why have there not been successful medications developed for humans? Perhaps with newer compounds, there has not been sufficient time for safety and efficacy studies. But why have so many of the studies with available compounds been negative? The answer to this question is complex, perhaps unsatisfactory, and of course not fully known. However, the situation and the need for such pharmacotherapies are critical, and the search must be continued. A clear challenge for treatment researchers is to find the medications and conditions under which they are useful for humans.

At this point in the medication development process, we are no doubt naive in our understanding and approach to treating the various stages of cocaine abuse. Indeed, cocaine abuse leads to a clinical syndrome, which manifests as a variety of effects that are time-, dose-, and individual-dependent. Therefore, it is unlikely that one medication will be effective at all stages of the addictive process. Consequently, we will need medications (and animal models) for replacement therapy, for the withdrawal period, and during recovery from cocaine addiction when recidivism is a major hurdle for recovery.

A large number of studies using dopaminergic drugs have failed to yield encouraging results. Perhaps these compounds would be effective in combination with other drugs or with behavioral therapies. It could be that the animal models that strongly implicate dopamine in human addictions have been overinterpreted or inappropriately interpreted. Perhaps the assessment of candidates, sample size and statistical power, or evaluation of outcome has been inadequate. For example, the major approach that has been used to determine if a potential medication reduces cocaine use is urine testing. Many studies have been criticized based on the argument that since quantitative urine analysis was not done, a significant reduction in drug intake may not have been noted.[183] For example, a subject who reduced his/her cocaine use from three times a day to once a day may not have been counted as a treatment success without quantitative urine analysis even though such reduction intake is a clear improvement.

Also, other end points or measures of effectiveness may be useful. For example, Berger[184] has shown that a dopamine receptor antagonist (haloperidol) reduces cue-induced craving in humans. These and other results[84] suggest that dopaminergic drugs are useful in relapse prevention, perhaps more so than in terminating ongoing use of cocaine. Thus, additional approaches for evaluating outcome and success of various treatments are needed.

Another reason for possible failure of drugs in clinical trials may be the failure to appropriately test high doses. It has been shown in animal studies that approximately 75% occupancy of DATs is needed to produce detectable locomotor effects,[185−187] presumably because high levels of synaptic dopamine are needed. Similarly, in humans, approximately 50−90% occupancy is needed to observe a "high".[188−190] Thus, it seems that a suitable medication must be able to achieve a high occupancy of dopamine transporter sites under practical, clinical conditions in order to be an effective substitute. Future clinical studies should include in vivo binding with brain imaging to clearly determine occupancy rates.[190,191]

Basic research continues to produce not only novel compounds but also new possible mechanisms, providing new potential strategies for interventions. The challenge to find the medications and the proper conditions under which they are used remains.

Possible Future Directions

Substantial preclinical progress has been made during the past few years toward the development of pharmacotherapies for cocaine abuse. The National Institute on Drug Abuse (NIDA), through its Medications Development Division (MDD), has funded the major portion of the preclinical research and development.[192,193] To provide the total scientific knowledge base required for developing medications for cocaine abuse, continued support by NIDA, MDD is critical. Some possible directions for the future follow.

In contrast to drugs of abuse such as heroin, nicotine, THC, and PCP, cocaine does not act at a neurotransmitter receptor. It has an indirect effect on dopamine receptors by blocking the dopamine transporter. A better understanding of the specific part that the DAT plays in cocaine abuse and in what way the serotonin and norepinephrine transporters modulate reward will be useful in designing new medications. A DAT uptake inhibitor that retained sufficient cocaine properties to overcome its reinforcing properties but lacked the toxic effect and was not abusable could be a medication for cocaine abuse. A number of D_1, D_2, and D_3 agonists and antagonists and DAT uptake inhibitors are effective in reducing cocaine use in animals, and some have low toxicity. Further clarification of the contribution of the D_1−D_5 subtypes of dopamine receptor to the reinforcing effects of cocaine is needed. New information could be useful in the design of antagonists for the D_1−D_5 receptors and, thus, better medications. Similarly, the discovery and development of a compound that binds to the cocaine binding site on the DAT but allows dopamine uptake would be a different type of antagonist and could be a useful medication. However, any dopamine antagonist would suffer from the fact that patients could use higher doses of cocaine in an effort to surmount the antagonist resulting in increasing the cocaine toxicity. Thus, an antagonist is less desirable than a substitute agonist.

Self-administration studies in animals suggest an involvement of the glutamate, GABA, opioid, sigma, calcium channel, and CRF receptor systems in the reinforcing effects of cocaine. Further studies with available compounds that interact with these receptor systems may lead to medications for the treatment of cocaine addiction. In some cases these studies would be aided by the development of a ligand that possessed greater selectivity for the receptor systems or subtypes within the receptor system. Compounds with more desirable pharmacological profiles would also be helpful.

The development of more efficient metabolizing enzymes (i.e., human genetic variants of BChE or genetically engineered variants), specific antibodies for the catalytic degradation and immune binding of cocaine, could also lead to more effective medications. Clearly medicinal chemistry will play an important role in the development of these protein-based therapies since carefully designed and developed hapten for the immunological approach is critical.

There are also possible compounds and directions to be derived from more recent findings. For example, peptides may modulate psychostimulant action,[194] and neurotrophic factors and transcription factors clearly alter relevant circuits.[195,196] Recent studies have demonstrated novel interactions within the ventral tegmental area and its target the nucleus accumbens, between neurotrophic factors and drug abuse.[195] These findings have an important implication for treatment of drug addiction. Finally, the most relevant sites in the brain and the molecular meaning of addiction must be determined. When this latter is accomplished, we may have the ultimate target for intervention.

In the short run, continued evaluation and development of existing compounds seems reasonable and cost-effective. Some of these are approved for use in humans but have not yet been adequately tested for treating drug abuse. Clinical studies are needed to determine the merit of these potential medications. An ongoing reevaluation of outcome measures, doses, and targets also seems essential.

Thus far, most of the clinical studies have been supported by NIDA, MDD. To bring medications for treating cocaine abuse to market, a substantial commitment by pharmaceutical companies will be needed. Due to formidable scientific and marketing issues, regulatory complexities, and financial uncertainties, the pharmaceutical industry has been reluctant to invest in pharmacotherapies for cocaine abuse.[192] Even though substantial progress has been achieved through public support, persuading the private sector to become more involved remains a challenge.

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