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A Review of the Effects of Dopaminergic Agents on Humans, Animals, and Drug-Seeking Behavior, and Its Implications for Medication Development

*Focus on GBR 12909***

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Abstract

Medication development for cocaine abuse has focused on potential mechanisms of action related to the abuse of cocaine. The hypothesis that mesolimbic dopamine (DA) is the key neurochemical mediator of cocaine's addictive and reinforcing effects is well supported by a wide variety of data from animal studies. On the other hand, medications that increase DA or block its actions in humans can produce effects that appear incompatible with this hypothesis. This article reviews these incompatibilities between animal and human data with a focus on the DAergic actions of drugs, including DA reuptake inhibitors, direct DA agonists, DA increasers, and DA antagonists. Possible reasons for these discrepancies are discussed, and the potential role of high-affinity DA uptake inhibitors, such as GBR12909, for pharmacotherapeutic application to treat cocaine abuse is discussed. Since progress in developing pharmacotherapies for treating cocaine addiction in humans is likely to come from understanding its mechanisms of action, it is clear that further research on the effects of cocaine in humans and animals will be critical to the medication development effort.

Index Entries: Dopamine; cocaine, agonists; antagonists, increasers.

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Introduction

A major goal of drug abuse research is to develop effective treatment strategies. The current focus is on the development of pharmacotherapeutic agents to ameliorate cocaine abuse. Many different approaches may be applied to this difficult research problem. One strategy is to develop some *a priori* notions about the mechanisms of action of the abused drugs and then apply this knowledge to the drug-development effort to produce a medicine that would effectively reduce cocaine abuse. Two separate avenues of this approach have been proposed—in one, drugs would be developed to serve as a substitution/replacement therapy (Rothman, 1990), and in the other, drugs would be developed that block the actions of the abused drug. Although both approaches have been tested using animal models, considerably less information is available from human testing. On the other hand, several medications, used for purposes other than treating drug abuse, are known to act through mechanisms similar to those of cocaine, allowing some insight into expected results of these approaches. Some of these agents have also been tested in animal models, allowing the additional benefit of correlating results in animals and humans, which would hopefully enhance the process of discovering effective medications for cocaine addiction.

This article, therefore, reviews current theories of cocaine's reinforcing actions, and then examines data derived from animal and human test studies that are related to this hypothesis. Some speculation on the properties of an "ideal" pharmacotherapeutic agent for cocaine abuse is presented, and data are reviewed that suggest that DA reuptake inhibitors, such as GBR12909, possess effects consistent with these properties.

The DA Hypothesis of Cocaine's Reinforcing Effects

Current hypotheses of mechanisms of action associated with the reinforcing effects of cocaine focus on the mesolimbic DA system as playing a critical role in mediating its effects as well as other events (Johanson and Fischman, 1989; Kuhar et al., 1991). These data include: (1) the high degree of correlation between the potency of cocaine-like drugs as inhibitors of DA reuptake and their potency in tests of self-administration (Ritz et al., 1987; Madras et al., 1989; Spealman et al., 1989); and (2) observations that lesions of the mesolimbic DA system disrupt cocaine self-administration (Roberts et al., 1977; Roberts and Koob, 1982; Koob et al., 1987b; Dworkin et al., 1988). Further support for the DA hypothesis comes from observations that DA antagonists disrupt cocaine self-administration in a predictable manner (Wilson and Schuster, 1972; Johanson et al., 1976; Woods et al., 1978; De La Garza and Johanson, 1982; Ettenberg et al., 1982; Roberts and Vickers, 1984; Koob et al., 1987a). Typically, animals self-administering low doses of cocaine will increase that behavior if higher doses are provided. The effects of DA antagonists often mimic the effects of a dose reduction, although some investigators have suggested that the disruption of cocaine self-administration by DA antagonists results from a nonspecific rate-reducing effect (Woolverton and Balster, 1981; Woods et al., 1987; Johanson and Fischman, 1989; Woolverton and Virus, 1989). In contrast, DA agonists, such as apomorphine, bromocriptine, and piribedil, are self-administered (Baxter et al., 1974; Yokel and Wise, 1978; Woolverton et al., 1984), as are the DA reuptake blockers bupropion (Woods et al., 1983; Lamb and Griffiths, 1990), mazindol (Wilson and Schuster, 1976; Risner and Silcox, 1981), and nomifensine (Spyraki and Fibiger, 1981; Lamb and Griffiths, 1990). However, some of these agents (e.g., mazindol) are not self-administered by all animals tested. This finding suggests that either other actions of these types of drugs counteract the reinforcing effects or simply that binding to the DA transporter is insufficient to produce reinforcing effects. One interesting possibility is that the rate of occupation of the site (i.e., on–off rate) may mediate some of the reinforcing effects of these drugs.

Behavioral Effects of Dopaminergic Agents in Animals and Humans

Several types of agents have effects on DA systems. These drugs can be informally classified as DA reuptake inhibitors, direct DA agonists, DA increasers, and DA antagonists. Some of these agents, DA releasers, such as amphetamine, produce comparable effects in animals and humans under a wide variety of conditions, and will not be discussed further. However, clinical experience with other medications known to increase DA or block its actions reveals some inconsistencies between expected effects in animals and humans. These differences may be the result of many factors and serve as one focus of the current report.

The task of attempting to relate the effects of DAergic drugs on humans to their behavioral effects in animals is complicated by the fact that humans and animals are studied under markedly different circumstances. For example, the behavioral effects of DAergic drugs on animals are often studied under rigidly controlled laboratory conditions using sophisticated behavioral paradigms. In contrast, most data on the effects of DAergic drugs in humans are deduced from their reported effects, or lack of effects, when administered to various patient groups. Thus, a majority of the human data come from naturalistic observations made of other-than-normal healthy humans under circumstances where the cocaine-like effects of these drugs are not the focus of investigation.

Even when the effects of cocaine are studied in humans, a factor that complicates comparison of such human data and corresponding animal data is that the humans studied are usually experienced cocaine users, whereas animal studies typically use cocaine-naive rats. For example, two recent studies have failed to detect cocaine-induced behavioral sensitization in cocaine addicts using paradigms similar to those used in rodents (Nagoshi et al., 1992; Rothman et al., 1994). Although the reasons for these discrepancies remain to be determined, given the role that classical conditioning plays in the addiction process (Childress et al., 1986; O'Brien et al., 1986; Pert et al., 1990; Brown et al., 1992), it is tempting to speculate that prior exposure to cocaine alters the ability to produce cocaine-induced sensitization.

Another factor that complicates comparison of human and animal data is the particular endpoint studied. A number of behavioral paradigms have been used to study cocaine's behavioral effects, including psychomotor stimulant effects, drug discrimination, and self-administration. The self-administration paradigm, which directly assesses the reinforcing effects of drugs, measures various aspects of behavior that result in drug delivery and, thus, is the focus of the current discussion. In self-administration studies, animals are typically prepared with intravenous catheters and trained to operate a manipulandum (press a lever, for example), in order to produce a drug reinforcer. Schedules of reinforcement, specifying the relationship between responding and drug delivery, allow various aspects of behavior to be studied. Cocaine-maintained responding is exceptionally robust and has been successfully studied under a wide variety of different schedule conditions. Important parameters for these studies are the dose of cocaine to be self-administered, the time between repeated doses of cocaine, and, for the assessment of the effects of other drugs (i.e., test agents) on cocaine self-administration, whether the effects of those drugs on comparable behaviors maintained by other reinforcers (i.e., food) can be concurrently assessed. This latter consideration is critical, because the reduction of drug-seeking behavior by a test agent can easily be produced by doses that decrease all other behaviors. Such effects are clearly less interesting and have questionable clinical significance. Thus, comparisons between the clinical effects of drugs and their effects on self-administration behavior will be limited to those cases in which drug effects on self-administration have been assessed using multiple behavioral endpoints.

Cocaine, like all psychoactive drugs, has behavioral effects that are determined by a number of other factors. In animal experiments

with other drugs, these factors have been shown to include the ongoing rate of behavior (Zuccarelli and Barrett, 1980), the event that maintains responding (Hughes and Branch, 1991), the context in which responding occurs (Tatham et al., 1993), and the behavioral and pharmacological history of the animal (Tatham and Barrett, 1993). The reinforcing effects of cocaine have received less attention with regard to these factors, but examples of each are available. To complicate matters further, in addition to its reinforcing actions, cocaine has other behavioral effects that can interact with its ability to support responding. For example, cocaine can serve as a punisher as well as a reinforcer—for some drugs (e.g., amphetamine), these effects have been studied in the same animal. For cocaine, these types of effects appear to interact, suggesting that a history of exposure to one or the other can alter subsequent reinforcing effects.

Although the reinforcing effects of drugs can be measured in humans under controlled laboratory conditions (Fischman and Foltin, 1992), the subjective effects of drug, i.e., euphoria, often provide the primary basis for assessment. Unfortunately, the exact relationship between reinforcement and euphoria is not completely understood, and it is likely that these two effects are indeed separable under certain conditions. Some human studies, for example, indicate that morphine can maintain reinforcing behavior in the absence of positive subjective effects (Lamb et al., 1991). Similarly, it is a well-known clinical fact that people continue to self-administer nicotine, i.e., smoke cigarets, in the absence of positive subjective effects. On the other hand, exposure to the reinforcing effects of benzodiazepines have been shown to modify their subjective effects (Ator and Griffiths, 1993). These types of effects presumably have correlates with human drug abuse. For example, for some individuals, the ingestion of an illegal substance when among friends at a private gathering may be less likely to produce paranoid thoughts than if the substance were ingested among strangers in public. As noted above, although it is difficult to disprove the hypothesis that DAergic agents are not euphorogenic in humans because they are administered in the context of clinical medicine, it is also equally difficult to prove this hypothesis. Moreover, the consideration of context dependency as a major factor in explaining the differences between the animal and the human data should be tempered by the realization that the lack of cocaine-like effects produced by DAergic agents in humans is an empirical observation based on the collective responses of thousands of patients, and is, therefore, a reproducible finding across a myriad of individual "contexts."

At the outset, it must be understood that in surveying the effects of DAergic agents in humans, we focus on the euphoric effects of these medicines. The primary reason for this is that it is a readily deduced endpoint. Moreover, not only is there face validity to the commonsense notion that the positive subjective effects of a drug are related its reinforcing properties, but this has been demonstrated in the human pharmacology laboratory (Fischman and Foltin, 1991, 1992). The occurrence of abuse of these medicines is a less reliable endpoint, since a variety of nonpharmacological factors contribute to the abuse of a drug (Balster, 1991).

Another factor that clearly plays an important role in determining the reinforcing properties of a drug is its rate of entry into the brain (Sellers et al., 1991; Henningfield and Keenan, 1993). Most animal studies use either the ip, sc, or iv route, and self-administration studies most often employ the iv route. In contrast, most DAergic drugs are orally administered to humans. Thus, the fact that DAergic drugs are often administered to animals and humans under markedly different pharmacokinetic circumstances may be an important factor in explaining the apparently different effects of DAergic drugs in animals and humans. However, these pharmacokinetic differences must be balanced by the knowledge that cocaine produces euphoria in humans after intrave-

nous, oral, and inhalational administration (Johanson and Fischman, 1989), that cocaine produces euphoria in the great majority of people who take it (Johanson and Fischman, 1989), and that orally administered cocaine supports self-administration behavior (Meisch et al., 1990; George et al., 1991; Meert et al., 1991). Therefore, when considering the effect of DAergic agents in humans, it is reasonable to test a prediction of the DA hypothesis: DAergic agents should produce euphoria in the majority of people administered these drugs.

DA Uptake Inhibitors

DA uptake blockers prevent the reuptake of DA into the presynaptic terminals, presumably extending the synaptic effects of DA. Cocaine blocks reuptake of DA with moderate affinity, but also blocks the reuptake of serotonin (5-HT) and norepinephrine (NE). There are four DA uptake blockers that are or have been marketed in the United States: bupropion, nomifensine, mazindol, and benztropine. Both bupropion (Wellbutrin™) and nomifensine (Merital™) have been prescribed as antidepressants. Nomifensine was taken off the market because it produced severe allergic reactions in some patients. Mazindol (Sanorex™) is prescribed for the treatment of obesity. Benztropine (Cogentin™) is commonly prescribed for the treatment of movement disorders (Bianchine, 1980). All of these medications are more potent than cocaine in inhibiting [^{3}H]DA reuptake into striatal synaptosomes (Andersen, 1987). The inclusion of benztropine in this class of DAergic drugs is debatable. Although benztropine is more potent than cocaine as an inhibitor of [^{3}H]DA uptake (Andersen, 1987) and increases extracellular DA during in vivo microdialysis studies (Church et al., 1987; Nomikos et al., 1990), it is also a potent anticholinergic drug, and it is this pharmacological effect that is often cited as the mechanism responsible for its efficacy in treating movement disorders (Baldessarini, 1990). Thus, it is possible that the doses of benztropine generally administered to humans are below the range that blocks DA reuptake and any resulting euphoria. Another drug that exhibits DA reuptake blocking effects, GBR12909, has been tested in Europe as an antidepressant and was found to produce sedation, rather than stimulant effects (Sögaard et al., 1990). GBR12909 is several hundred times more potent than cocaine in inhibiting [^{3}H]DA uptake (Andersen, 1987).

Clinical Effects

Like cocaine, one would predict that these agents should produce euphoria in humans. However, the prescribing literature for these drugs do not mention the occurrence of euphoria as either a primary, or a side effect (Hadler, 1972; Bianchine, 1980; Rickels et al., 1982; Stern et al., 1982; Chait et al., 1987), and mazindol is reported to be dysphoric in humans (Chait et al., 1987). Where the subjective effects of bupropion and nomifensine were specifically examined, there was no mention of drug-induced euphoria (Parrott et al., 1982; Hamilton et al., 1983; Peck and Hamilton, 1983; Miller and Griffith, 1983; Yakabow et al., 1984; Shekim et al., 1989). The studies of Peck and Hamilton (1983) showed that oral administration of 200 mg of bupropion or 100 mg of nomifensine did not produce amphetamine-like CNS-stimulant activity in normal volunteers. Supporting these results were the studies of Miller and Griffith (Griffith et al., 1983; Miller and Griffith, 1983), which demonstrated that bupropion at oral doses up to 400 mg did not produce amphetamine-like subjective effects in experienced abusers of amphetamine. As noted above, mazindol, as reported by Chait et al. (1987) is actually dysphoric in humans.

Benztropine is also an interesting medicine because it is known to be abused by schizophrenics. Although it is tempting to speculate that it is abused because of its interaction with the DA transporter, this is unlikely in view of the fact that other anticholinergic drugs, such as trihexyphenidyl, which do not block DA uptake, are also abused by schizophrenics. This nicely illustrates that the occurrence of

abuse does not necessarily provide information as to the underlying neurochemical mechanisms responsible for the abuse.

A common assumption in the clinical literature is that drugs described as "DA uptake blockers" actually block DA uptake when administered to humans. Clearly, this assumption is crucial to the arguments made above. In the case of the tuberoinfundibular DA pathway, occupation of DA transporters can be reasonably deduced to have occurred if the drug inhibits prolactin secretion. However, occupation of hypothalamic DA transporters does not necessarily mean that DA transporters in the mesolimbic areas are also occupied. Positron emission tomography (PET) is probably the "gold standard" for demonstrating occupation of mesolimbic DA transporters by a DA uptake inhibitor in humans. Indeed, preliminary PET data suggest that 6 mg of oral mazindol produces significant occupation of the DA transporter in vivo (Wong et al., 1993).

In light of these considerations, the assumption that clinical doses of mazindol and bupropion actually occupy mesolimbic DA transporters is equivocal. Although one study reported that mazindol decreased prolactin (Thompson et al., 1981), another study reported no effect (Sekiya et al., 1984). The ineffectiveness of mazindol in this latter study cannot be attributed to an inadequate dose, since mazindol administration produced significant elevations in plasma ACTH, β-endorphin, β-lipotropin, and growth hormone. With regard to bupropion, low and modest doses (12.5 and 100 mg p.o.) do not decrease prolactin levels (Whiteman et al., 1983). Orally administered nomifensine presents the strongest case for occupation of DA transporters. Nomifensine is well known to decrease prolactin levels (Masala et al., 1980; Agnoli et al., 1981; Camanni et al., 1981; Dallabonzana et al., 1982) and was widely used as a diagnostic tool in the diagnosis of hyperprolactinemia (Minuto et al., 1984). Importantly, trace iv doses of [^{11}C]nomifensine produce detectable occupancy of striatal DA transporters in humans as measured by PET (Tedroff et al., 1988). Although orally administered nomifensine is not reported to produce euphoria, there is one report that 100 mg of nomifensine administered iv produced "euphoria" in three of five subjects (Whiteman et al., 1983).

As noted above, GBR12909 has been tested in humans in Europe as an antidepressant and was found to produce sedation, rather than stimulant effects (Sögaard et al., 1990). Although the simplest explanation for the lack of cocaine-like effects would be poor penetration into the brain, PET studies clearly show that GBR12909 analogs do occupy the DA transporter at trace doses (Kilbourn et al., 1989).

The observations reviewed above emphasize the need for PET studies to determine if oral doses of DA uptake inhibitors occupy the DA transporter after acute and chronic administration. More generally, these data indicate the need for additional human research to determine the reasons for the apparent non-euphoric effects of nomifensine, including studies with intravenous nomifensine and GBR12909.

Effects on Cocaine Self-Administration

Few studies have examined the effects of DA reuptake inhibitors on cocaine self-administration behavior. In one, Kleven and Woolverton (1993) compared the effects of continuous (24-h) infusion of mazindol (0.4–3.2 mg/kg), sertraline (0.1–8.0 mg/kg), and fluoxetine (0.4–3.2 mg/kg) on rhesus monkeys where responding was maintained under multiple FR30 response schedules of food presentation and cocaine (0–0.1 mg/kg/inj) delivery. All three drugs were able to decrease cocaine-maintained behavior, but food-maintained behavior was also affected. Fluoxetine (primarily a 5-HT uptake inhibitor) decreased food-maintained behavior to a greater extent than drug-maintained behavior, demonstrating a lack of specificity for cocaine-maintained responding. Similarly, the 5-HT uptake inhibitor sertraline decreased food-maintained behavior to a greater extent than drug-maintained behavior

in three of the four monkeys tested. The results with mazindol, which blocks both 5-HT and NE uptake, were equivocal with respect to specificity. Another study compared the ability of GBR12909 and cocaine to decrease responding maintained by cocaine (Skjoldager et al., 1993); however food-maintained controls were not studied.

Direct DA Agonists

DA agonists available for use in humans include pergolide and bromocriptine, which act equally at D_1 and D_2 receptors. Their primary therapeutic use is in the treatment of Parkinson's disease, acromegaly, and hyperprolactinemia. In addition, bromocriptine has been used to treat cocaine craving (Dackis et al., 1985). In that they are self-administered by animals (Woolverton et al., 1984), one might expect them to produce cocaine-like effects in humans. However, although the *Physician's Desk Reference* (1991) reports a variety of neuropsychiatric side effects, euphoria is not among them.

In contrast to the DA uptake blockers, it is difficult to argue that the lack of cocaine-like effects of DA agonists results from inadequate receptor occupancy at therapeutic doses. The therapeutic effects of these drugs are presumed to depend on occupation of DA receptors. It is possible that the euphoric effects of these drugs are attenuated by their emetic effects, since humans have a highly sensitive chemotactic trigger zone. However, although some patients experience significant nausea, the great majority do not experience euphoria. Moreover, nonhuman primates, which are also sensitive to the emetic effects of DA agonists, self-administer DA agonists (Woolverton et al., 1984). Another possibility is that different classes of DA agonists will produce different profiles of effect. For example, Woolverton et al. (1984) found that apomorphine, piribedil, propylbutyldopamine, and bromocriptine were self-administered by at least half the animals tested, whereas SKF38393 failed to maintain self-administration. This pattern of results suggested activity at D_2 receptors was more closely related to the reinforcing effects of these agents.

One study assessed the effects of bromocriptine on responding maintained by both food and cocaine delivery (Kleven and Woolverton, 1990a). Bromocriptine selectively decreased cocaine-maintained responding, at doses noted to produce behavioral agitation. The authors concluded that although this drug was capable of selectively decreasing drug-maintained responding, it did so apparently through mechanisms unrelated to the reinforcing effects of cocaine.

DA Increasers

This group of agents includes the monoamine oxidase (MAO) inhibitors and L-DOPA. The MAO inhibitors commonly used in the US are phenelzine, tranylcypromine, and selegiline (L-Deprenyl). Whereas phenelzine and tranylcypromine inhibit both MAO types A and B, selegiline is a selective inhibitor of MAO type B (Murphy, 1978; Murphy and Kalin, 1980; Murphy et al., 1984). Phenelzine and tranylcypromine are effective antidepressants (Baldessarini, 1990). Selegiline is approved by the FDA only for the treatment of Parkinson's disease (Cedarbaum and Schleifer, 1990). Preliminary data suggest it might also have antianxiety and antidepressant properties (Tariot et al., 1987). Its mechanism of action in treatment of Parkinson's disease is thought to result from inhibition of MAO type B, which metabolizes DA. This results in an increase in the synaptic concentration of DA (Cedarbaum and Schleifer, 1990). In support of this hypothesis, in vivo microdialysis studies in rats have shown that MAO inhibitors substantially increase the concentration of extracellular DA (Butcher et al., 1990; Colzi et al., 1990). Moreover, studies with patients with Alzheimer's disease (Sunderland et al., 1987) demonstrated that administration of selegiline decreased the CSF levels of the DA metabolite, homovanillic acid (HVA), presumably as a result of inhibi-

tion of MAO. Similar results were observed in the CSF of monkeys treated chronically with the selective MAO type A inhibitor, clorgyline (Cox et al., 1991).

Since MAO inhibitors increase the synaptic concentration of DA, the DA hypothesis would predict that they should have cocaine-like effects. Indeed, in rats trained to discriminate 5 mg/kg of cocaine from saline, Colpaert et al. (1980) found that the cocaine introceptive cue generalized to Deprenyl and tranylcypromine, consistent with the notion that these agents act to increase mesolimbic DA. However, the side effect profile of these medicines does not include euphoria (PDR, 1991). Indeed, most patients find that these drugs are unpleasant to take because of a variety of side effects. Similarly, L-DOPA is prescribed to patients with Parkinson's disease because it increases synaptic DA, yet it, too, does not consistently produce euphoria (Cedarbaum and Schleifer, 1990).

It should be noted that Resnick and Resnick (1986) reported, in an open-label study, some success in treating cocaine addicts with the MAO inhibitor phenelzine. Thus, the ability of MAO inhibitors and the direct DA agonists to attenuate cocaine craving (Dackis et al., 1985) is consistent with a role for DA in cocaine addiction.

Amantadine, which is usually described as a DA releaser and is used to treat Parkinson's disease and extrapyramidal side effects (Baldessarini, 1990), is not known to produce euphoria in humans. In baboons, amantadine was not self-administered and did not effect cocaine self-administration (Sannerud and Griffiths, 1988). Clinical trials with amantadine have demonstrated at most modest efficacy (Weddington et al., 1991; Ziedonis and Kosten, 1991; Kolar et al., 1992; Kosten et al., 1992).

DA Antagonists

This group of agents include the relatively large number of medicines used mainly in the treatment of schizophrenia. (The reader is referred to a textbook for a more thorough description of the antipsychotic drugs [Baldessarini, 1990].) The increasing number of DA receptor subtypes (Sokoloff et al., 1990; van Tol et al., 1991; Sunahara et al., 1991) complicates the task of deciding which receptor(s) might mediate the reinforcing effects of cocaine. However, DA antagonists appear to attenuate cocaine self-administration in animals, as is predicted by the DA hypothesis of the reinforcing effects of cocaine.

Evidence that antipsychotics block cocaine-induced euphoria in humans is either negative, lacking, or inconclusive. Gawin (1986) contributed a case report that noted that

> four cocaine abusers with histories of stimulant-induced paranoid psychoses reported selective reduction in psychotic symptoms but not euphoria when treated with dopamine blockers. This provides preliminary evidence against efficacy of neuroleptics in cocaine abuse prevention, and suggests euphoria and paranoia may have discriminable neurophysiological substrates.

Sherer et al. (1989) reported that haloperidol (8 mg im) partially reduced the "high," but not the rush induced by iv cocaine. This finding is difficult to interpret, since it is not clear if the sedating effect of haloperidol contributed to the partial amelioration of the cocaine-induced high. In an open-label study of the effectiveness of flupentixol deconoate for treating cocaine abuse in crack addicts, Gawin et al. (1989) noted that

> subjects treated informally before this trial at higher doses (30 to 80 mg) ...often reported diminished intensity or duration of cocaine's euphoric effect, but not complete blockade, when cocaine smoking was resumed.... [This] may not occur in a clinically meaningful magnitude in the low doses [used in this study] (p. 324,325).

Indirect evidence that antipsychotic medications do not attenuate the euphoric effects of cocaine comes from studies that indicate that

schizophrenic patients, many of whom are taking antipsychotic medication, abuse cocaine (Schneier and Siris, 1987; Brady et al., 1990; Bunt et al., 1990; Sevy et al., 1990; Dixon et al., 1991). Moreover, the fact that many of these patients presumably engage in repetitive drug-taking behavior suggests that drug reinforcement behavior is also not affected by antipsychotic medications. This last point is well illustrated by the case of a cocaine-abusing patient with schizophrenia who was evaluated in an emergency room setting by one of the authors (R.B.R.):

> This 26 year old white male, who was in police custody for snatching a purse, was initially evaluated because he needed to be supplied with his usual medication: chlorpromazine (100 mg p.o. qam and 200 mg p.o. qhs), and sertraline (25 mg p.o. bid). This patient was diagnosed with paranoid schizophrenia in 1988, and had been on chlorpromazine since then, and on sertraline for the last month. The patient had been hospitalized several times in the last three years for suicide attempts which followed approximately 3-day binges of crack cocaine use. He admitted to three "on the record attempts" which involved an overdose of 51 thorazine pills, cutting all the tendons of one wrist, and slicing the veins on an arm with a razor blade. The patient stated that he was released one week ago from a local psychiatric hospital where he had been admitted following a suicide attempt. He also admitted to several other "off-the record" suicide attempts, which generally involved taking an overdose of chlorpromazine, but which did not lead to a hospitalization.
>
> The patient said that he spent $800 over the last 3 days on crack cocaine. He was specifically asked whether or not he took his chlorpromazine during a cocaine binge. He replied that he made sure to take this medication in the morning and the evening, since it helped control certain effects of crack which he found unpleasant. In particular, he indicated that although chlorpromazine did not block the cocaine-induced high, it decreased cocaine-induced auditory hallucinations and paranoid ideations which he typically experienced when smoking crack. He indicated that he would often take 2 extra pills (200 mg) at night time to help him go to sleep, or as a deliberate overdose if he felt suicidal.

Thus, although the hypothesis that DA antagonists block cocaine-induced subjective effects in humans has not been rigorously tested, the currently available data suggest that they do not. Alternative explanations for this discrepancy include the possibility that the addictive effects of cocaine in humans are mediated by other than D_2 receptors, or perhaps that patients with schizophrenia respond differently to cocaine than normals. Clearly, this issue calls for careful study by clinical investigators.

The majority of studies that examined the effect of drugs on cocaine-maintained responding have tested DA antagonists. The earliest studies showed that DA antagonists could either increase or decrease cocaine-maintained responding (Wilson and Schuster, 1973). Until the biphasic nature of the cocaine self-administration dose–effect curve was fully appreciated, this at times appeared to suggest that DA antagonists could increase the reinforcing efficacy of cocaine. Recent studies have shown that the dose–effect function for cocaine maintenance is shifted to the right (sometimes slightly downward also) by DA antagonists (Bergman et al., 1990). This effect appears to occur with both D_1 and D_2-type antagonists. In order to compare the rate-decreasing effects of DA antagonists, another study reported the effects of SCH23390 on food- and cocaine-maintained responding (Kleven and Woolverton, 1990b). Although the results seemed to suggest that this D_1 antagonist electively decreased drug-maintained responding, this selectivity diminished with repeated dosing. These results emphasize the importance of repeated exposure to

drug effects, since presumably therapeutic agents will require continuous use.

Conclusions

The data reviewed here about the role of DA in mediating the effects of cocaine in humans provoke more questions than answers. Nevertheless, some tentative conclusions can be reached. Although the animal studies suggest that DA is a key neurochemical mediator of the reinforcing effects of cocaine, interpretations arising from the human data are less clear. With the exception of cocaine and amphetamine-like drugs, most of the drugs interacting with DAergic systems reviewed here do not produce euphoria in humans and are not apparently abused to any significant degree.

For any class of DAergic medicines, various arguments can be made as to why particular agents do not produce effects in humans as predicted by the DA hypothesis. According to this viewpoint, the DAergic agents reviewed in this article are the exceptions to the rule, and in some sense are selected to be noncocaine-like because cocaine-like DAergic drugs would most likely not, because of their high abuse liability, be widely marketed.

Another viewpoint is that the lack of cocaine-like effects shown by every clinically available member of several classes of DAergic drugs suggests that the DA hypothesis, as specifically described in this article, is probably too simple to explain the effects of cocaine in humans completely, and that further research is needed to resolve these differences.

A third and related possibility is that the endpoints generated by various animal models do not extrapolate in a straightforward manner to the human situation. For example, Ritz et al. (1987) showed, for a large number of drugs, that their potency at the DA transporter and their potency as reinforcers in self-administration paradigms are highly correlated. Why might this important finding, which lends considerable support to the DA hypothesis, not extrapolate in a straightforward manner to the human situation? One obvious limitation to the correlation is that the large majority of drugs considered in the correlation have never been given to humans. A less obvious limitation is that the pharmacological endpoint plotted, response rate in a substitution paradigm, is not the key endpoint we might anticipate to be predictive of their effects in humans. In humans, we would want to know how good a reinforcer a drug is, i.e., does it pack the same "punch" as does cocaine? In more precise pharmacological terms, we would like to know the reinforcing efficacy of these drugs. However, response rates in a substitution paradigm may not be the best measure of the efficacy of a drug as a reinforcer (Johanson and Fischman, 1989). Indeed, there is no generally accepted method of determining reinforcing efficacy. These considerations support the notion that endpoints generated by various animal models may not extrapolate in a straightforward manner to the human situation. Given the general paucity of human data that can be directly compared to animal experiments, there is clearly a need for additional research to validate the ability of animal models to predict the actions of drugs in humans.

A hypothesis consistent with both the human and animal data is that mesolimbic DA does mediate the addictive and euphorogenic effects of cocaine, but that only certain DAergic agents produce euphoria in humans (Rothman, 1990). This hypothesis clearly creates a secondary research question as to why these differences among DAergic agents exist. Although there are a variety of hypotheses to test, the pharmacokinetic hypothesis (*see* Introduction), in the authors' opinion, deserves particular attention, because it can be readily tested by varying the infusion rate of the test drug.

Although we do not yet know why some DAergic drugs lack cocaine-like effects in humans, that this occurs suggests the possibility of pharmacotherapeutic intervention. For example, in a paper focused primarily on the DA reuptake inhibitors (Rothman, 1990), we divided DA reuptake inhibitors into two

classes. Type 1 blockers refer to drugs that produce euphoria in humans, i.e., cocaine-like drugs. Type 2 blockers refer to drugs like mazindol, nomifensine, GBR12909, and bupropion, which are not abused. Assuming that the initiating event for cocaine-induced euphoria is the binding of cocaine to the DA transporter, then it follows that administration of a type 2 DA reuptake blocker should block the binding of cocaine to the DA transporter, and thereby attenuate cocaine-induced euphoria. The identification of a drug with these properties may functionally represent a competitive antagonist. Undoubtedly it would be an important research tool. However, as a medication, it might have limited therapeutic uses, since a patient could overcome its inhibition by self-administering more cocaine, thereby increasing the probability of increased toxic side effects, which would not be blocked by the competitive antagonist.

An alternative approach is to develop a type 2 agent that binds with high affinity to, and dissociates slowly from, the DA transporter. If the dissociation rate were slow enough, the agent would behave as a noncompetitive inhibitor, creating insurmountable inhibition of those cocaine effects that are initiated by its binding to the DA transporter. A sustained increase in mesolimbic DA produced by such an agent might serve to provide the cocaine addict with some relief from cocaine craving, which some investigators suggest is related to a relative functional deficiency of DA (Dackis and Gold, 1985). Moreover, if the addictive effects of cocaine result from its rapid entry into the brain and a consequent rapid increase in synaptic DA, then a slow-on, slow-off reuptake inhibitor might not produce a cocaine-like high, yet still block cocaine.

A key issue is what type of preclinical studies will identify putative type 2 DA reuptake inhibitors as possible candidates for human study. One possible set of criteria for identifying a type 2 DA reuptake inhibitor is that it should have the behavioral profile in animals that is expected of a DA uptake inhibitor. It should act as a classical locomotor stimulant, i.e., stimulate locomotor activity, generalize to a cocaine-induced interoceptive cue in drug discrimination studies, and be self-administered in a substitution paradigm. A key characteristic is that a putative type 2 DA reuptake inhibitor should be less reinforcing than cocaine. In this regard, it should be noted that the substitution paradigm does not measure reinforcing efficacy. Therefore, other approaches, such as an acquisition study, a progressive ratio paradigm, or a choice paradigm (Johanson and Fischman, 1989) will be needed to provide measurements of reinforcing efficacy. It will be crucial, when examining the effects of a putative type 2 DA reuptake inhibitor on cocaine-induced effects, to manipulate the pharmacokinetic profile of the test agent. For example, the effect of a test drug administered iv over 15 s may be entirely different from its effect when administered iv over a 30-min period, or orally, since the latter methods accentuate a slow-on method of drug delivery.

These and additional considerations *(see below)* led us to investigate the high-affinity inhibitor of DA reuptake, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]-piperazine (GBR12909) and its analogs (Rothman et al., 1989, 1991), as possible prototypical noncompetitive inhibitors. Published data have shown that these agents produce the spectrum of cocaine-like pharmacological actions expected of a DA uptake inhibitor including:

1. Stimulation of locomotor activity (Andersen, 1989);
2. Maintenance of iv self-administration in monkeys trained to self-administer cocaine (Howell and Byrd, 1991);
3. Increasing fixed-interval responding in squirrel monkeys (Howell and Byrd, 1991) and in rodents (Kelley and Lang, 1989); and
4. Substitution for cocaine in animals trained to discriminate cocaine from saline (Kleven et al., 1990; Cunningham and Callahan, 1991).

In addition, monkeys trained to discriminate GBR12909 from saline generalize to cocaine (Melia and Spealman, 1991).

However, GBR12909 differs from cocaine in several important ways, including:

1. A slower onset of action and much longer duration of action (Kelley and Lang, 1989; Rothman et al., 1991, 1992);
2. A much higher affinity for, and slower dissociation rate from, the DA transporter (Reith et al., 1981; Andersen, 1987; Rothman et al., 1991);
3. The ability to antagonize the ability of cocaine to elevate extracellular levels of DA (Rothman et al., 1991);
4. A nonstimulant-like profile of action in normal human volunteers following oral administration (Sögaard et al., 1990); and
5. Apparent lower in vivo efficacy as a motoric stimulant in rats, as compared to cocaine (Rothman et al., 1992).

It is appropriate to review here findings that challenge traditional notions regarding the actions of transmitter uptake blockers. Neurotransmitter transporter molecules belong to a family of membrane proteins that translocate a substance across the cell membrane. Inhibitors of the transport process can be conceptualized as plugging a channel. According to this notion, it would not be possible to synthesize a drug that would partially inhibit the transport process (a partial agonist) or perhaps block the binding of another inhibitor without inhibiting transport by itself (an antagonist).

Several lines of evidence suggest that the "plug" hypothesis may be an oversimplification. In particular, this conceptualization does not take into account the possibility that different uptake inhibitors may bind to different domains of an uptake binding site on the transporter molecule. A straightforward prediction of the "plug" hypothesis is that there should be a one-to-one relationship between potency of an agent as an uptake inhibitor and its K_i value at the uptake inhibitor binding site (i.e., the plug). Although most studies demonstrate a significant correlation between these two measurements, notable exceptions to this prediction can almost always be identified as compounds that are located off the correlation curve (Andersen, 1987; Boja et al., 1992). This discrepancy is also observed in vivo, where different DA uptake blockers produced markedly different effects on extracellular DA levels (Westerink et al., 1987). Moreover, several observations are difficult to reconcile with the "plug" hypothesis, including the differential protecting effect of amphetamine and cocaine against NEM alkylation of [^{3}H]mazindol binding sites (Johnson et al., 1992), noncompetitive inhibition of in vivo [^{3}H]BTCP binding to the DA transporter by cocaine and dopamine (Maurice et al., 1991), and uncompetitive inhibition of DA uptake into striatal synaptosomes by cocaine (McElvain and Schenk, 1992).

Moreover, Akunne et al. (1992) presented strong evidence that paroxetine, which is a high-affinity and selective inhibitor of [^{3}H]5-HT uptake, binds to a different domain than does [^{3}H]cocaine on the 5-HT transporter: Pretreatment of guinea pig brain membranes with paroxetine increased the K_d of [^{3}H]cocaine binding and also increased the [^{3}H]cocaine dissociation rate, consistent with what was termed a pseudoallosteric model. According to this model, occupation of the uptake inhibitor binding site with paroxetine before the addition of [^{3}H]cocaine forces the [^{3}H]cocaine to bind to a portion of the binding site domain at which it has lower affinity and a faster dissociation rate. The ability of [^{3}H]cocaine to bind to the 5-HT transporter even after the prebinding of paroxetine strongly supports the existence of different binding domains. Other data supporting the existence of binding domains come from ligand binding studies, which demonstrate, for certain compounds, large quantitative differences in their K_i values as measured with different radioligands (Dersch et al., 1994), and the identification of mutant cDNAs of the DA transporter, which exhibit decreased transport of [^{3}H]DA without any decrement in [^{3}H]CFT binding (Kitayama et al., 1992).

In view of these considerations, it is perhaps not surprising that the in vivo data we have obtained with GBR12909 are not compatible with the "plug" hypothesis. For example, doses

of GBR12909 and cocaine that produce equivalent motoric responses do so at markedly different in vivo occupancies of the DA transporter: 100 vs approx 50% (Rothman et al., 1992). Similarly, systemic doses of GBR12909, which produce threshold elevations of extracellular DA, attenuate the ability of cocaine to elevate extracellular DA (Rothman et al., 1991).

We have discussed elsewhere possible mechanisms that might explain these interesting properties of GBR12909 (Rothman et al., 1992). Regardless of which mechanism might explain the observation that behaviorally equivalent doses of GBR12909 occupy considerably more DA transporters than does cocaine, such a drug could turn out to be therapeutically useful as either substitution therapy for, or an antagonist of, cocaine. For example, such a drug could completely occupy the DA transporter, and thereby block the reinforcing effects of cocaine (Ritz et al., 1987), yet have its own dopaminergic effects attenuated by some other action.

In summary, further preclinical and clinical research will be required to determine the reasons for the discrepancies between the effects of DAergic drugs in humans and in animals. These apparent differences point to the need for testing the DA hypothesis in humans. Clinical research in this area will provide one pathway to validating the various animal models presently used to identify possible treatment medications for cocaine addiction. Since progress in developing pharmacotherapies for treating cocaine addiction in humans is likely to come from understanding its mechanisms of action, it is clear that research on the effects of cocaine in humans will be critical to the medication development effort.

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