CNS Drug Reviews
Vol. 10, No. 3, pp. 230–242


# Dihydrexidine — The First Full Dopamine $D_1$ Receptor Agonist

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**Keywords:** Dopamine — Dopamine agonist — Dopamine $D_1$ receptor agonist — Dihydrexidine.

## ABSTRACT

The functional role of dopamine $D_1$ receptors is still controversial. One reason for this controversy is that for a long time the only available agonists for in vivo characterization of dopamine $D_1$ receptors were benzazepines. Among them was the prototype dopamine $D_1$ receptor partial agonist, SKF 38393. The lack of a selective and fully efficacious dopamine $D_1$ receptor agonist hampered basic research on dopamine $D_1$ receptors and left the potential clinical utility of dopamine $D_1$ receptor agonists elusive. The research situation improved when the first potent full dopamine $D_1$ receptor agonist dihydrexidine, a phenanthridine, was introduced in the late 1980s. In contrast to SKF 38393, dihydrexidine was shown to stimulate cyclic AMP synthesis just as well or better than dopamine, and potently displaced [$^3$H]SCH 23390 from rat and monkey striatal membranes. Also, dihydrexidine was the first dopamine $D_1$ receptor agonist that had potent antiparkinsonian activity in a primate model of Parkinson's disease. This finding suggested clinical utility for dopamine $D_1$ receptor agonists in Parkinson's disease and that this utility might be critically dependent on the intrinsic efficacy of the drug. Clinical utility for dopamine $D_1$ receptor agonists in other central nervous disorders might also be dependent on the intrinsic efficacy of the drug. However, even though studies with dihydrexidine as a pharmacological tool have pointed to the clinical use for dopamine $D_1$ receptor agonists, dihydrexidine's unfavorable pharmacokinetic profile and various adverse effects are likely to restrict or even preclude its use in humans. This review article provides an updated overview of the pharmacology of dihydrexidine and discusses possible clinical utility of dopamine $D_1$ receptor agonists in various central nervous system disorders.

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## INTRODUCTION

Dopamine plays a fundamental role in human behavior through its involvement in central functions such as psychomotor activation, cognition and reward. Furthermore, dopamine is implicated in the pathophysiology of schizophrenia and Parkinson's disease. Dopamine binds to and acts through receptors belonging to two subfamilies of dopamine receptors: dopamine $D_1$-like ($D_1$ and $D_5$) and dopamine $D_2$-like ($D_2$, $D_3$, and $D_4$) (10) (throughout this review, the terms $D_1$ and $D_2$ receptors will be used to denote the two respective receptor families).

Today it is believed that the role of dopamine in such functions as locomotion and cognitive performance involves both dopamine $D_1$ and $D_2$ receptors. Historically, however, dopamine $D_2$ receptors attracted more interest than dopamine $D_1$ receptors, and extensive work on the physiology and pharmacology of dopamine $D_2$ receptors has been carried out over the years. The focus on dopamine $D_2$ receptors can be explained by the clinical success of drugs that target dopamine $D_2$ receptors in the treatment of schizophrenia and Parkinson's disease, as well as by the wide range of selective and efficacious ligands for this receptor. Dopamine $D_1$ receptors have been studied far less and their properties require further exploration.

One reason for the lack of information on dopamine $D_1$ receptors, is that for a long time benzazepines were almost the only available agonists and antagonists for *in vivo* characterization of dopamine $D_1$ receptors. Among them were SKF 38393 and SCH 23390, the prototype dopamine $D_1$ receptor agonist and antagonist, respectively. Furthermore, the benzazepine agonists are partial rather than full agonists or their *in vivo* potency is low, probably because of poor penetration of the blood-brain barrier (9). Thus, even though the use of both SKF 38393 and SCH 23390 has kept the dopamine $D_1$ receptor field alive, the lack of a selective and fully efficacious dopamine $D_1$ receptor agonist has severely hampered basic research on dopamine $D_1$ receptors, and left the potential clinical utility of dopamine $D_1$ receptor agonists elusive.

The research situation improved when two separate classes of novel full dopamine $D_1$ receptor agonists were introduced almost simultaneously — the phenanthridines and the isochromans (29). Dihydrexidine, a phenanthridine, introduced in the late 1980s, is the first potent full dopamine $D_1$ receptor agonist (5,27,29,30), but the isochromans, exemplified by A 68930, also display full dopamine $D_1$ receptor agonism *in vivo* (8). Two earlier described agonists (not of the benzazepine family), SKF 89626 and CY 208-243, were introduced as full dopamine $D_1$ receptor agonists but their status as full agonists was later questioned (29,59).

In contrast to SKF 38393, dihydrexidine was shown to stimulate cyclic AMP synthesis just as well or better than dopamine. It also potently displaced [$^3$H]SCH 23390 from rat and monkey striatal membranes (35, 58). It has been hypothesized at the time of dihydrexidine's development that a full (rather than partial) agonist at dopamine $D_1$ receptors, might have antiparkinsonian effects. Indeed, in an initial study in a primate model of Parkinson's disease, dihydrexidine, in contrast to SKF 38393, had potent antiparkinsonian properties (54). The notion of treating Parkinson's disease with full dopamine $D_1$ receptor agonists gained further support with the isochromans, and later with ABT-431 (prodrug of A 86929 and similar in structure to dihydrexidine), all of which had potent antiparkinsonian effects, similar to those of dihydrexidine (21,52). Altogether, this indicated that a full

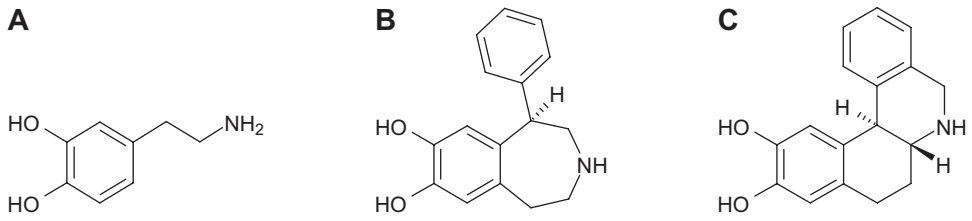


**Fig. 1.** The chemical structures of dopamine (A), SKF 38393 (B), and dihydrexidine (C).

dopamine $D_1$ receptor agonism is required to achieve antiparkinsonian effects, and that the possible clinical utility might be critically dependent on the intrinsic efficacy of the drug.

These "novel" and other aspects of dopamine $D_1$ receptor function can apparently be elucidated with a full, but not a partial dopamine $D_1$ receptor agonist, like SKF 38393. The use of dihydrexidine, as well as of other full dopamine $D_1$ receptor agonists, may, therefore, modify our understanding of dopamine $D_1$ receptor function.

This article provides an updated overview of the pharmacology of dihydrexidine. This drug represents a prototype of a full dopamine $D_1$ receptor agonist. The possible clinical utility of full dopamine $D_1$ receptor agonists in various central nervous disorders is discussed below.

## CHEMISTRY

In the late 1980s David E. Nichols synthesized a series of novel ligands for dopamine receptors that included certain trans-hexahydrobenzophenanthridines. The biological activity of these compounds has been found to range from potent agonism, like that of dopamine itself at dopamine $D_1$ and $D_2$ receptor subtypes, to a specific dopamine $D_1$ receptor antagonism. These studies culminated in the synthesis of dihydrexidine (racemic trans-10,11-dihydroxyhexahydrobenzo [a] phenanthridine), the first compound that was shown to be a potent, bioavailable, full dopamine $D_1$ receptor agonist (27). Dihydrexidine represents structurally a class of conformationally rigid dopamine receptor ligands with β-phenyldopamine moiety. The chemical structures of dihydrexidine, dopamine and SKF 38393 are shown in Fig. 1.

## PHARMACOKINETICS

There is very little information on the pharmacokinetics of dihydrexidine in the literature. Generally, dihydrexidine enters the brain readily and is fully bioavailable by parenteral administration. However, dihydrexidine has poor oral bioavailability and a relatively short half-life of 1 to 2 h (29). Such properties limit its clinical use. In addition, various adverse effects of dihydrexidine have been reported in a clinical study in patients with Parkinson's disease (see below). No active metabolites of dihydrexidine are known.

# PHARMACOLOGY

## *In Vitro* Pharmacology

### *Receptor binding*

The binding profile of dihydrexidine at dopamine receptors has been examined thoroughly, starting with the seminal report on dihydrexidine as a potent full dopamine $D_1$ receptor agonist (27). In radioligand binding studies, using displacement of the selective dopamine $D_1$ receptor antagonist [$^3$H]SCH 23390, dihydrexidine shows high affinity (low nM) for dopamine $D_1$ receptors in striatal membranes of rats, monkeys or humans, and in membranes from neuroblastoma cells expressing the dopamine $D_1$ receptor. The rank order of potency of dopamine $D_1$ receptor agonists, competing for [$^3$H]SCH 3390-labelled sites, is A 68930 > SKF 82958 ≥ dihydrexidine > SKF 38393 > dopamine.

Although dihydrexidine exhibits high affinity and specific binding to dopamine $D_1$ receptors, at which it functions as a full agonist, it also has affinity for dopamine $D_2$ receptors (14,27,35–37). Dihydrexidine binds to dopamine $D_2$ receptors in membranes from rat striatum, labelled with the selective dopamine $D_2$ radioligand [$^3$H]spiperone ($K_i \approx 100$ nM). This indicates that dihydrexidine is approximately 10-fold more selective for dopamine $D_1$ than for $D_2$ receptors (35,36). The reported binding affinities of dihydrexidine for dopamine $D_1$ and $D_2$ receptors are listed in Table 1. In this context, it is important to keep in mind that data obtained in various *in vitro* binding assays are not necessarily valid *in vivo*. It is difficult to predict what the *in vitro* affinity for dopamine $D_2$ receptors by dihydrexidine implies *in vivo*. It is, however, conceivable that dopamine $D_2$ receptor binding properties of dihydrexidine could contribute to the net effect of this compound *in vivo*. In addition to dopamine $D_1$ and $D_2$ receptors, dihydrexidine displays affinity also for $\alpha_2$-adrenoceptors with an estimated $K_i$ value of 230 nM (35).

It should also be noted that dihydrexidine does not distinguish specifically between dopamine $D_1$ and $D_5$ receptors within the dopamine $D_1$-like receptor family. It is, therefore, not possible to state definitively which of the two dopamine $D_1$ receptor subtypes is primarily involved in the *in vivo* effects of this drug.

### *Functional* in vitro *assays*

To examine functional effects of dihydrexidine *in vitro*, measurements of cyclic AMP accumulation have been commonly used. In such experiments, dihydrexidine behaves as a

*TABLE 1. $IC_{50}$ values in nM (mean ± S.E.M.) for dihydrexidine binding at dopamine $D_1$ and $D_2$ receptors, in competition experiments using either [$^3$H]SCH 23390 ($D_1$) or [$^3$H]spiperone ($D_2$) as radioligands*

| [$^3$H]SCH 23390 | [$^3$H]spiperone | Species | Reference |
|---|---|---|---|
| 10 | 660 | Rat | 27 |
| 10 ± 1 | 122 ± 10 | Rat | 35 |
| 9.7 ± 3.2 (20.2 ± 3.3) | | Rat (Monkey) | 58 |
| 35.7 ± 7.3 | | Human postmortem | 15 |
| 2.3 | 43.8 | Rat | 37 |
| 4.59 ± 0.28 | 43.2 ± 3.2 | Rat | 14 |
| 6.2 ± 1.1 | 50 ± 18 | Rat | 36 |
| | 2,607 ± 471 | MN9D cells transfected with $D_{2L}$ receptors | 22 |

full dopamine $D_1$ receptor agonist and thus increases cyclic AMP synthesis in homogenates and slices from rat striatum. These effects are completely blocked by SCH 23390 (15,27,35). Also, in molecular expression systems that are transfected with dopamine $D_1$ receptors, the effects of dihydrexidine appear to be similar to those of dopamine (5,15,28, 35,58,59).

Some studies have addressed *in vitro* functional effects of dihydrexidine mediated not only by dopamine $D_1$ but also by $D_2$ receptors. Thus, in addition to stimulation of cyclic AMP accumulation through dopamine $D_1$ receptors, dihydrexidine has been shown to augment forskolin-stimulated cyclic AMP accumulation in the presence of a dopamine $D_2$ receptor antagonist (35), an effect mediated apparently by activation of dopamine $D_2$ receptors by dihydrexidine. Furthermore, dihydrexidine inhibits dopamine $D_1$ receptor-stimulated cyclic AMP efflux much like other dopamine $D_2$ receptor agonists. It also inhibits adenylyl cyclase by activating dopamine $D_2$ receptors expressed in striatum (23). Moreover, two recent papers described somewhat unusual or atypical properties of dihydrexidine at dopamine $D_2$ receptors (22,36). These findings indicated that dihydrexidine might act as a dopamine $D_2$ receptor agonist (inhibition of adenylyl cyclase and prolactin release) as well as a dopamine $D_2$ receptor antagonist (blockade of quinpirole-induced inhibition of dopamine release and of dopamine-stimulated G protein-coupled inwardly rectifying potassium [GIRK] channel activity). The same reports claim that dihydrexidine alone has no effect on dopamine release, firing or synthesis. It appears, therefore, that as a dopamine $D_2$ receptor agonist, dihydrexidine activates only certain isoforms or specific conformations of dopamine $D_2$ receptors that are postsynaptic in nature, a phenomenon that has been described as "functional selectivity. "

## Electrophysiology and Biochemistry

There are only a few reports on the electrophysiological or biochemical effects of dihydrexidine. Consistent with the dopamine $D_1$ receptor-mediated effects, dihydrexidine has no effect on the firing rates of midbrain dopamine neurons and does not antagonize quinpirole-induced inhibition of firing rates (43). Zhen et al described activation of c-Jun by dihydrexidine (63). In the same study dihydrexidine is described to activate p38 mitogen-activated protein kinase in SK-N-MC neuroblastoma cells. In a recent publication (19) dihydrexidine is reported to induce a strong increase in SCH 23390-sensitive c-Fos expression in the rat medial prefrontal cortex. Dihydrexidine produced this effect at a dose that produces dopamine $D_1$ receptor-mediated behavioral effects in rats. At the same dose the effects of dihydrexidine on c-Fos expression in subcortical dopamine systems (nucleus accumbens and caudate putamen) were less marked.

## *In Vivo* CNS Pharmacology. Effects of dihydrexidine on motor functions

### *Locomotor activity*

The role of dopamine in the psychomotor behavior of mammals is well established. Generally, compounds that produce an overall enhancement of dopamine transmission in the brain cause locomotor stimulation in rodents (3). This is true for amphetamine or apomorphine, and the stimulatory effects of these drugs on locomotion have been linked to the activation of dopamine $D_2$ receptors. However, these drugs also activate dopamine

$D_1$ receptors. The studies with the classical dopamine $D_1$ receptor agonist SKF 38393, as well as with other benzazepine agonists, suggest that dopamine $D_1$ receptors may play a role in locomotor activation, possibly in synergy with dopamine $D_2$ receptors (33).

In rats, however, dihydrexidine either suppresses, or has no effect on locomotor activity, depending to some extent on whether rats are habituated to the experimental conditions (i.e., whether the baseline activity of rats was high or low before the locomotor test) (9,19). Furthermore, in a recent study, the dose-dependent locomotor suppression by dihydrexidine was specifically antagonized by a dopamine $D_1$, but not $D_2$, receptor antagonist. This finding indicates a specific inhibitory role of dopamine $D_1$ receptor stimulation on locomotor activity (19). In monkeys, similar results have been obtained, i.e., dihydrexidine either does not promote locomotor stimulation, or decreases locomotor activity (17). The notion of inhibitory actions of dopamine $D_1$ receptor stimulation on locomotor activity is strongly supported by the results obtained with A 68930, another novel full dopamine $D_1$ receptor agonist, which also causes SCH 23390-sensitive suppression of locomotion (1,44,46). A recent study indicates that such inhibitory effects of dihydrexidine and A 68930 might be mediated through activation of dopamine $D_1$ receptors in the prefrontal cortex (19).

The inhibitory effects on locomotor activity in rats have not been observed in the initial behavioral studies with dihydrexidine. Darney et al (7) reported in the early 1990s that dihydrexidine causes locomotor stimulation in rats. This motor stimulatory effect was blocked by dopamine $D_1$ and dopamine $D_2$ receptor antagonists. Apparently dihydrexidine induces locomotor stimulation by activating dopamine $D_2$ as well as dopamine $D_1$ receptors. Since dihydrexidine has affinity for dopamine $D_2$ receptors, it is conceivable that at doses used by Darney et al. (7) dihydrexidine activated dopamine $D_2$ receptors as well. It has been reported that the full dopamine $D_1$ receptor agonist A 68930, administered together with a dopamine $D_2$ receptor agonist, produces a marked locomotor stimulation in rats, even when the dose of A 68930 alone causes locomotor suppression (44).

## *Stereotypic behavior*

Excessive brain dopamine activity generally results in stereotypic, or repetitive, behaviors in mammals. In rats, such behaviors include intense sniffing, vacuous chewing, and increased rearing or grooming. Many of these behaviors have been linked to dopamine $D_2$ receptor activation, with the notable exception of grooming. As shown in studies with SKF 38393, grooming appears to be mediated mainly through dopamine $D_1$ receptors (33,34). It should be noted, however, dopamine $D_1$ and $D_2$ receptors interact functionally in many of these stereotypies, which thus can be antagonized by both dopamine $D_1$ and $D_2$ receptor antagonists. Consistent with the notion that grooming is a dopamine $D_1$ receptor-mediated effect, dihydrexidine produces modest grooming behavior, but not other marked stereotypies in rats (9,19), even though an increased sniffing has been reported (7,9). Thus, at moderate doses dihydrexidine does not induce any excessive stereotypies, while at higher doses dihydrexidine-induced stereotypies may be due to activation of dopamine $D_2$ receptors. In fact, a recent study demonstrated that dihydrexidine potently blocks amphetamine-induced hyperactivity/stereotypies (19). This finding is in line with the notion that brain dopamine $D_1$ receptors might be inhibitory in nature, at least with respect to various psychomotor behaviors such as locomotor activity.

### *Animal models of Parkinson's disease*

As stated in the Introduction, it was hypothesized that a full agonist, in contrast to a partial agonist at dopamine $D_1$ receptors, might exert antiparkinsonian effects in animal models as well as in patients. The first study reported a dramatic antiparkinsonian effect of dihydrexidine in MPTP-induced parkinsonism in monkeys (54). These initial observations were confirmed by other studies with dihydrexidine in primate models of Parkinson's disease (17,20,49). Isochromans, another class of full dopamine $D_1$ receptor agonists, were also reported to have antiparkinsonian effects (21). Moreover, the antiparkinsonian effects of the isochromans (which have a negligible affinity for dopamine $D_2$ receptors) should allay the concerns that not only dopamine $D_1$ receptor agonism but also dopamine $D_2$ receptor agonism might be involved in the antiparkinsonian effects of dihydrexidine (17). Altogether, such observations were promising and the way seemed clear for clinical trials with dihydrexidine. It should be noted that the antiparkinsonian effects of dihydrexidine and other dopamine $D_1$ receptor agonists, like A 68930, do not necessarily lead to locomotor stimulation in animal models of Parkinson's disease as both dihydrexidine and A 68930 suppress locomotor activation. This apparent discrepancy could indicate that different brain regions and different underlying mechanisms are involved in locomotor activity and in antiparkinsonian effects in animal models of Parkinson's disease.

## Other Behavioral Effects of Dihydrexidine

### *Body core temperature*

It is widely accepted that central activation of dopamine receptors decreases body temperature in rats (25). This decrease has generally been linked to dopamine $D_2$ receptor activation, as selective dopamine $D_2$ receptor antagonists block hypothermia produced by intracerebral injection of dopamine, or by systemic administrations of the non-selective dopamine receptor agonist apomorphine. The role of dopamine $D_1$ receptor in the control of body temperature is rather unclear. In some studies SKF 38393 has no effect on body temperature, whereas other studies reported an increase in body temperature, albeit by very high doses of SKF 38393 (11,38,47,57). The effects of dihydrexidine on body temperature of rats have been reported in one study (45). The results of this study indicate that dihydrexidine produces hypothermia. This hypothermic effect could be differentiated pharmacologically from hypothermia produced by activation of dopamine $D_2$ receptors, since it was antagonized by dopamine $D_1$, but not $D_2$, receptor antagonists (45). This would indicate a specific dopamine $D_1$ receptor-mediated hypothermic effect of dihydrexidine. A 68930, another selective full agonist at dopamine $D_1$ receptors, also produces an SCH 23390-sensitive hypothermia in rats (44,47).

### *Drug discrimination*

In a recent study the effects of dihydrexidine were studied in rats trained to discriminate SKF 38393 from vehicle (16). Dihydrexidine could fully substitute for SKF 38393, whereas the dopamine $D_2$ receptor agonist PD 128,907 could not. Furthermore, the dopamine $D_1$ receptor antagonist SCH 23390 blocked the effect of dihydrexidine. Other full dopamine $D_1$ receptor agonists in the study, including ABT-431, also substituted for SKF 38393.

### *Cognitive performance*

Dopamine is a fundamental regulator of various cognitive functions (39). For example, a great deal of evidence indicates that dopamine $D_1$ receptors in the prefrontal cortex are critically involved in working memory. Thus, local injections of selective dopamine $D_1$, but not dopamine $D_2$, receptor antagonists into the prefrontal cortex of primates impairs working memory (48), whereas local administration of dopamine $D_1$ receptor agonists into the prefrontal cortex of rats result in enhanced cognitive functioning (12). It has also been shown that antipsychotic-induced working memory deficits can be reversed by dopamine $D_1$ receptor agonists (6).

Consistent with such results, dihydrexidine has been shown to alleviate cognitive deficits or enhance cognitive performance in a number of animal models of cognition. In rats, dihydrexidine has been shown to improve passive avoidance performance and block scopolamine-induced cognitive deficits in the same test (53). In monkeys, dihydrexidine has been shown to improve working memory measured by delayed response performance (49). This effect was blocked by SCH 23390. Also, in the MPTP-treated monkey, dihydrexidine dose-dependently improved delayed response deficits caused by the lack of dopamine (49). In contrast to these findings, neither dihydrexidine nor the dopamine $D_1$ receptor antagonist SCH 23390 had any effect on cognitive performance in another working memory paradigm, the radial maze test (60).

There are also reports of cognitive impairment after treatment with dihydrexidine in various working memory tests (2). Such impairments are not necessarily contradictory to the notion of beneficial effects of dopamine $D_1$ receptor agonism on cognitive performance. These impairments may have been caused by excessive dopamine $D_1$ receptor stimulation (by very high doses of dihydrexidine, for example), and would indicate that there is a range at which dopamine $D_1$ receptor stimulation is optimal with respect to cognitive functioning.

### *Social/emotional reactivity*

There have been a number of reports dealing with dopamine-mediated social or emotional reactivity in rats, and the effects of dihydrexidine. High social reactivity has for example been found after isolation, and previous research has suggested the involvement of dopamine in such isolation-induced behavior. Studies with dihydrexidine suggested that dopamine $D_1$ receptors have an important role in social reactivity (13,26).

## HUMAN STUDIES AND THE POTENTIAL CLINICAL UTILITY OF DOPAMINE $D_1$ RECEPTOR AGONISTS

### Parkinson's Disease

The specific role of dopamine $D_1$ or $D_2$ receptors in Parkinson's disease remains unclear. Basically all drugs used in the treatment of Parkinson's disease involve activation of dopamine $D_2$ receptors, with a possible enabling role of activation of dopamine $D_1$ receptors. The development of dihydrexidine was based on the expectation that a full dopamine $D_1$ receptor agonist, in contrast to a partial agonist, would exert potent antiparkin-

sonian effects. Studies of this compound in primate models of Parkinson's disease indicated that this notion might indeed be correct. Dihydrexidine has been found to be the first dopamine $D_1$ receptor agonist with antiparkinsonian efficacy in MPTP-treated monkeys (54). A subsequent controlled proof-of-principle trial in parkinsonian patients was consistent with the animal studies, and showed that monotherapy with dihydrexidine had promising antiparkinsonian effects in patients (4). Unfortunately, the study required dose limitations because of adverse effects of dihydrexidine, including hypotension and tachycardia. This finding, together with dihydrexidine's unfavorable pharmacokinetic profile, that includes its low oral bioavailability, is likely to restrict or even preclude the use of this drug in humans. There have been no recent studies with dihydrexidine or other dopamine $D_1$ receptor agonists in parkinsonian patients, so that the potential usefulness of dopamine $D_1$ receptor agonism in the treatment of Parkinson's disease remains unproven.

## Schizophrenia

Several lines of evidence indicate that a dysfunctional prefrontal cortex, or hypofrontality, may underlie many of the symptoms that schizophrenic patients display. In particular, cognitive deficits and negative symptoms have been linked to hypofrontality (6,40). In view of the role of prefrontal dopamine $D_1$ receptors in cognition, cognitive symptoms in particular might respond well to treatment with dopamine $D_1$ receptor agonists. However, negative symptoms such as emotional indifference and social withdrawal may also be amenable to treatment with dopamine $D_1$ receptor agonists, as such symptoms appear to be a result of hypodopaminergic function.

Hypofrontality in schizophrenic patients may also be linked to dysregulation of subcortical dopamine systems that could possibly give rise to positive symptoms as well (24). Indeed, the prefrontal cortex appears to control subcortical dopamine systems, and several animal studies indicate that prefrontal dopamine $D_1$ receptors may be inhibitory in nature with respect to dopamine release in the nucleus accumbens and thus locomotion (41,42, 55,56). Furthermore, a recent study on regional blood flow predicted exaggerated striatal dopamine function in schizophrenic patients that displayed reduced prefrontal activity (31). In this context, it is interesting to note that experimental findings in rats of inhibition of locomotor activity and d-amphetamine-induced hyperactivity by dihydrexidine are accompanied by a pronounced increase in c-Fos expression in the prefrontal cortex (19 and see above).

## Attention-Deficit/Hyperactivity Disorder

Animal and human studies strongly indicate that dopamine has a critical role in attention-deficit/hyperactivity disorder, and the most effective current treatment for attention-deficit/hyperactivity disorder is amphetamine and methylphenidate. Moreover, a great deal of evidence indicates that dopamine $D_1$ receptors specifically might be involved in attention-deficit/hyperactivity disorder. For example, a recent linkage study found a relationship between the dopamine $D_1$ receptor gene and attention-deficit/hyperactivity disorder (32). Furthermore, some of the motor disturbances observed in children with attention-deficit/hyperactivity disorder are "mimicked" in dopamine $D_1$ receptor-knockout mice, which display motor hyperactivity (62). In view of the inhibitory actions of dihydre-

xidine, as well as of A 68930, on psychomotor activation in animals, dopamine $D_1$ receptor agonism might be an attractive approach to the treatment of attention-deficit/hyperactivity disorder. It is also tempting to speculate that amphetamine might produce some of its "calming" effects on children with attention-deficit/hyperactivity disorder by activating dopamine $D_1$ receptors.

## Cognitive Disorders

As already mentioned, it is highly likely that dopamine $D_1$ receptors play a role in cognition. This makes the use of dopamine $D_1$ receptor agonists an obvious approach to the treatment of cognitive deficits. As cognitive deficits are present in many disease states, a dopamine $D_1$ receptor agonist could be useful in several different clinical disorders, including cognitive dysfunction associated with aging, schizophrenia or Parkinson's disease.

## Substance Abuse

As with dopamine $D_2$ receptor agonists, it has been demonstrated that rodents self-administer dopamine $D_1$ receptor agonists (51). However, dopamine $D_1$ receptor agonists prevent cocaine-seeking behavior in rodents, which is in sharp contrast to dopamine $D_2$ receptor agonists (that enhance such behavior) (50). Thus, even though both dopamine $D_1$ and $D_2$ receptors mediate reinforcing effects, they produce opposing effects on cocaine-seeking behavior. This would favor dopamine $D_1$ receptor agonists over dopamine $D_2$ receptor agonists in the treatment of cocaine abuse, and possibly other types of drug abuse as well. In this context, it should be noted that dihydrexidine has been shown to partially substitute for cocaine in a discrimination study in rats (61). In support of the animal studies, ABT-431 (or adrogolide, a prodrug of the dopamine $D_1$ receptor agonist A 86929) has been reported to reduce cocaine craving in human cocaine abusers (18).

# CONCLUSIONS

Dihydrexidine has proven to be a useful tool to characterize dopamine $D_1$ receptor functions, and to broaden our understanding of this receptor subtype. For example, as described in the review, truly new aspects of dopamine $D_1$ receptor function have been delineated with the help of dihydrexidine. However, the authors of this review consider A 68930, an isochroman, to be more potent, selective and efficacious than dihydrexidine. This notion is based on behavioral studies where we often tested both compounds in parallel.

Furthermore, even though studies with dihydrexidine and other dopamine $D_1$ receptor agonists, as pharmacological tools, have pointed to the clinical uses for dopamine $D_1$ receptor agonists, dihydrexidine is not likely to be used clinically because of various pharmacokinetic limitations and adverse effects. Thus, as it stands, no dopamine $D_1$ receptor agonist has yet made it to the clinic, and the clinical utility of dopamine $D_1$ receptor agonists remains elusive.

## ADDENDUM

The following are chemical names of compounds mentioned in the text by code number only:

**ABT-431**, (–)-trans-9,10-diacetyloxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene HCl;
**A 68930**, (1R,3S)-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman HCl;
**A 86929**, (–)-trans-9,10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena-[c]phenanthrene HCl;
**CY 208-243**, (–)4,6,6a,7,8,12b-hexahydro-7-methyl-indolo-(4,3-ab)phenanthoridine;
**PD 128,907**, (+)-(4aR,10bR)-3,4,4a,10b-Tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol HCl;
**SCH 23390**, R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl;
**SKF 38393**, (±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol HCl;
**SKF 82958**, 6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HBr;
**SKF 89626**, 4-(3,4-dihydroxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine HBr.

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