

# D<sub>1</sub> and D<sub>2</sub> Dopamine Receptors Independently Regulate Spontaneous Blink Rate in the Vervet Monkey<sup>1</sup>

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## ABSTRACT

Previous studies have revealed the involvement of a dopaminergic link in the regulation of spontaneous eye blink rate in primates. Based on the effect of dopamine D<sub>2</sub> receptor-selective drugs and the anecdotal failure of the partial D<sub>1</sub> agonist, SKF 38393, to alter blink rate in monkeys, it was assumed that D<sub>1</sub> dopamine receptors did not control blink rate. The recent availability of dihydrexidine, a full D<sub>1</sub> agonist, prompted us to re-evaluate the role of D<sub>1</sub> and D<sub>2</sub> receptors in the regulation of blink rate. African green monkeys (*n* = 5) were used in all studies. Dihydrexidine produced a rapid and dose-dependent (up to 1 mg/kg, i.m.) increase in blink rate. The elevation in blink rate elicited by 0.3 mg/kg dihydrexidine was completely reversed by prior administration of a specific D<sub>1</sub> antagonist, SCH 23390 (0.01 mg/kg, i.m.), but was unaffected by prior administration of a

specific D<sub>2</sub> antagonist, remoxipride (1 mg/kg, i.m.). Treatment with the specific D<sub>2</sub> agonist, (+)-4-propyl-9-hydroxynaphthoxazine, led to a rapid and dose-dependent (up to 0.01 mg/kg, i.m.) increase in blink rate. The raised blink rate produced by (+)-4-propyl-9-hydroxynaphthoxazine (0.001 mg/kg) was abolished by pretreatment with remoxipride, but was not influenced by pretreatment with SCH 23390. These data indicate that spontaneous blink rate in the primate can be regulated by both D<sub>1</sub> and D<sub>2</sub> dopamine receptors. Furthermore, the receptor subtypes appear to affect blink rate in the same direction, yet function independently. Measurement of blink rate may provide a noninvasive method to assess the potency and selectivity of dopamine agonists and antagonists in primates.

Spontaneous eye blinks are distinguished from reflex blinks by the absence of an identifiable external stimulus, and from voluntary blinks by the absence of a conscious decision to blink. Spontaneous blink in primates occurs at a rate greater than that required to maintain the corneal tear film (Doane, 1980). Other functions of blinking are more speculative, although studies have indicated that spontaneous blink rate can be affected by certain behavioral (*e.g.*, anxiety, tension) and cognitive states (*e.g.*, activation, attention) (Ponder and Kennedy, 1927; Meyer *et al.*, 1953; Stern *et al.*, 1984; Lawrence and Redmond, 1991). Although the neuronal circuitry involved in the generation of spontaneous blinks is not known, the participation of several brain regions is apparent (see Karson, 1988; Watson and Rapcsak, 1989). The involvement of the mesostriatal dopamine pathway is suggested by the observation that

decreased blink rates occur in both Parkinson's disease and in mild parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Hall, 1945; Karson *et al.*, 1984; Lawrence and Redmond, 1991). In fact, the decrease in the rate of spontaneous blinking in parkinsonian patients appears to parallel the severity of the disease (Karson *et al.*, 1982).

Further support for a dopaminergic link in the regulation of blink rate derives from pharmacological studies in monkeys. Sulpiride, a selective D<sub>2</sub> dopamine receptor antagonist, is able to block the increase in blink rate induced either by apomorphine, a nonselective dopamine agonist (Karson, 1983) or by PHNO, a high-potency selective D<sub>2</sub> agonist (Lawrence and Redmond, 1991). These data are consistent with the importance of D<sub>2</sub> receptors in the modulation of blink rate. The role of D<sub>1</sub> dopamine receptors in the central nervous system, however, is understood less well, although the recent availability of drugs with relatively high affinity and selectivity for the D<sub>1</sub> receptor has been a boon to this area of research (Iorio *et al.*, 1983; Mailman *et al.*, 1984; Waddington and O'Boyle, 1989; Clark and White, 1987). One major deficiency with the pharmacological agents presently available is that the D<sub>1</sub>-selective agonists

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**ABBREVIATION:** PHNO, (+)-4-propyl-9-hydroxynaphthoxazine.

(e.g., SKF 38393 or fenoldapam) are, based on the stimulation of dopamine-sensitive adenylate cyclase, only partial agonists at the  $D_1$  receptor (Setler *et al.*, 1978). Thus, the indication that SKF 38393 is without effect on spontaneous blink rate (unpublished data, cited in Karson, 1988) may reflect deficiencies in the available drugs as much as a lack of involvement of  $D_1$  receptors.

The recent synthesis of dihydrexidine, a new drug with full efficacy at the  $D_1$  receptor (Brewster *et al.*, 1990; Lovenberg *et al.*, 1989) provided a tool for us to examine the issue of  $D_1$  receptor involvement in spontaneous blink rate in nonhuman primates. This study is of importance not only to understand the neurochemistry of spontaneous blink rate, but also because blink rate has been suggested to be a functional marker of central dopamine function (Karson, 1983) and a sensitive mirror of general cognitive factors, such as attention and activation (Stern *et al.*, 1984). In addition, the study will indicate whether mechanisms involving  $D_1$  receptors could be attributed to the altered blink rate observed in Parkinson's disease (see above), schizophrenia (Stevens, 1978; Karson, 1983; Helms and Godwin, 1985; Karson *et al.*, 1986), Huntington's disease (Karson *et al.*, 1984), Tourette's syndrome (Bonnet, 1982), seasonal affective disorder (Depue *et al.*, 1988), stereotyped behavior in man (MacLean *et al.*, 1985) and after administration of neuroleptic drugs (Karson *et al.*, 1981; Bartkó *et al.*, 1990). This study, performed with selective  $D_1$  and  $D_2$  agonists and antagonists, also allowed the examination of a possible  $D_1/D_2$  receptor interaction in the regulation of a primate motor function that can be reliably quantified in a noninvasive manner.

## Methods

The subjects were five young adult male (weight range: 5.2–6.2 kg) African green monkeys (*Cercopithecus aethiops sabaeus*) trapped on the island of St. Kitts in the West Indies. They were untreated except for the acute administration of drugs in the study of blink rate. The monkeys were housed individually in their own cages for the year before the study. They were habituated to daily observations during a previous study (Lawrence and Redmond, 1991) and were re-acclimatized to the procedure a few days before the start of drug administration. A blink was defined as an apposition of the eyelids lasting no longer than half a second, as estimated by the observer. The measurement of blink rate was as described previously (Lawrence and Redmond, 1991). Briefly, blinks that occurred during a 2.5-min period were counted and expressed as number per min. Blinks were counted every 7.5 min. Blinks were counted using a hand-held tally counter. If the eyes were not visible to the observer for at least 2.0 of the 2.5-min period, the count was discarded. The correlation between the observations of two raters using this method was consistently greater than 0.97, calculated by Pearson product moment correlation.

The drugs used were (+)-PHNO (Merck, Sharp and Dohme, West Point, PA), (+)-SCH 23390 HCl (Research Biochemicals Inc., Natick, MA), remoxipride (Astra Läkemedel AB, Södertälje, Sweden) and dihydrexidine, which was synthesized as described by Brewster *et al.* (1990). All drugs were administered acutely by i.m. injection and the same five monkeys each participated in all drug studies reported here. The  $D_1$  agonist, dihydrexidine, was tested at doses of 0.3, 1 and 2 mg/kg, whereas the  $D_2$  agonist, PHNO, was tested at doses of 0.001 and 0.01 mg/kg. The  $D_1$  antagonist, SCH 23390, was administered at doses of 0.01 and 0.3 mg/kg and the  $D_2$  antagonist, remoxipride, at a dose of 1 mg/kg. The highest dose of dihydrexidine (2 mg/kg) was given 8 months before the other drugs as part of a preliminary study on blink rate. However, at this earlier time the effects of saline and PHNO were also tested, so a comparison between the response to these treatments over 8 months was possible. Due to the limited availability of dihydrexidine, the 2 mg/kg dose could not be repeated.

With the time when agonists (or saline) were injected defined as 0 min, observations began at -75 min, antagonists (or saline) were injected at -45 min and observations continued until at least +75 min. The actions of the two antagonists used ( $D_1$  SCH 23390 and  $D_2$  remoxipride) are known to persist for at least 2 h (Schulz *et al.*, 1985; Martin *et al.*, 1984). In the antagonism studies the treatments were pseudo-randomized (balanced for sequence), and the observer was blind to the drug combination (antagonist/agonist) administered.

Drug-induced differences in blink rate were determined using multifactor repeated measures analyses of variance after appropriate tests for variance homogeneity and distribution. When significant interactions were found in the full multifactor model, the main effects of treatment (dose) or time were tested separately, or planned comparisons were made based upon prior tests as follows, according to Winer (1974). The base-line period was reanalyzed alone to test for differences across treatments or doses during the repeated base-line measures. The peak effect of the agonist drugs was determined from the main effect of time and this point was tested across treatments (dose) by analysis of variance with multiple comparisons using the Duncan's procedure at  $P < .05$ .

## Results

The main effect of time was significant in the dihydrexidine dose-response experiment ( $F = 29.02$ ;  $df = 15,76$ ;  $P < .0001$ ) with both the 7.5- and 15-min time points significantly different from each other and from all other points (Duncan's,  $P < .05$ ). Dihydrexidine (0.3, 1 or 2 mg/kg) produced a significant effect on spontaneous blink rate. After a significant interaction between treatment by time ( $F = 5.68$ ,  $df = 42,228$ ;  $P < .0001$ ) was found, planned main effects comparisons were carried out. Peak differences at 7.5 min were significant ( $F = 6.7$ ;  $df = 3,3$ ;  $P < .004$ ) for each dose tested (as determined by Duncan's Multiple Range test,  $P < .05$ ). Dihydrexidine at 0.3 and 1.0 mg/kg elicited a dose-dependent increase in blink rate at 7.5 min, although 2.0 mg/kg produced a smaller increase in blink rate than the 1.0 mg/kg dose (fig. 1). Saline injections did not alter blink rate from the preinjection value ( $F = 0.06$ ,  $df = 3,16$ ;  $P = \text{N.S.}$ ).

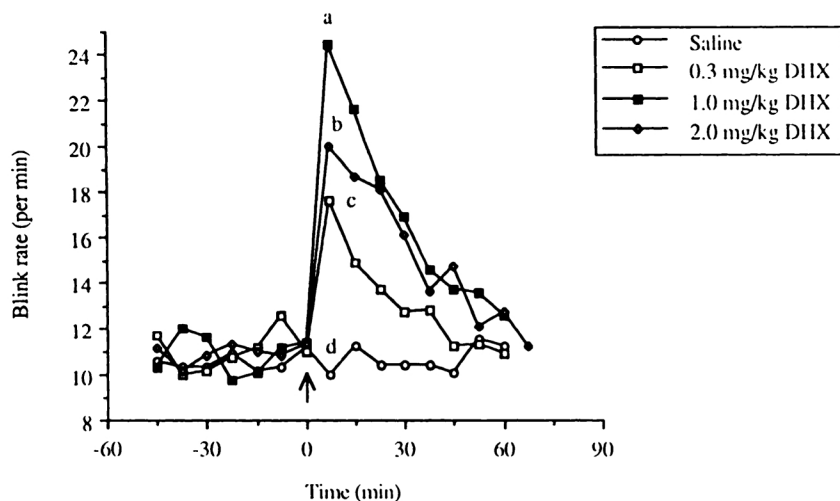
The blink rate response to 0.3 mg/kg dihydrexidine was completely prevented by prior administration of SCH 23390 (0.01 mg/kg), but not by remoxipride (1 mg/kg). The treatment by time interaction was significant ( $F = 3.49$ ;  $df = 50,87$ ;  $P < .0001$ ) and some differences at the 7.5-min peak were also significant ( $F = 8.12$ ;  $df = 3,3$ ;  $P < .002$ ), as determined by Duncan's Multiple Range test,  $P < .05$  (fig. 2). There were no differences in blink rate in the base-line period between the trials ( $F = 0.34$ ;  $df = 3,55$ ;  $\text{N.S.}$ ).

Neither SCH 23390 (0.01 mg/kg) alone, nor remoxipride (1 mg/kg) alone, altered blink rate compared with saline ( $F = 0.33$ ,  $df = 3,57$ ;  $\text{N.S.}$ ) (figs. 2 and 4). However, treatment with a higher dose of SCH 23390 (0.3 mg/kg) resulted in a marked and rapid decrease in blink rate (treatment by time ( $F = 17.54$ ;  $df = 10,29$ ;  $P < .0001$ )) (fig. 3).

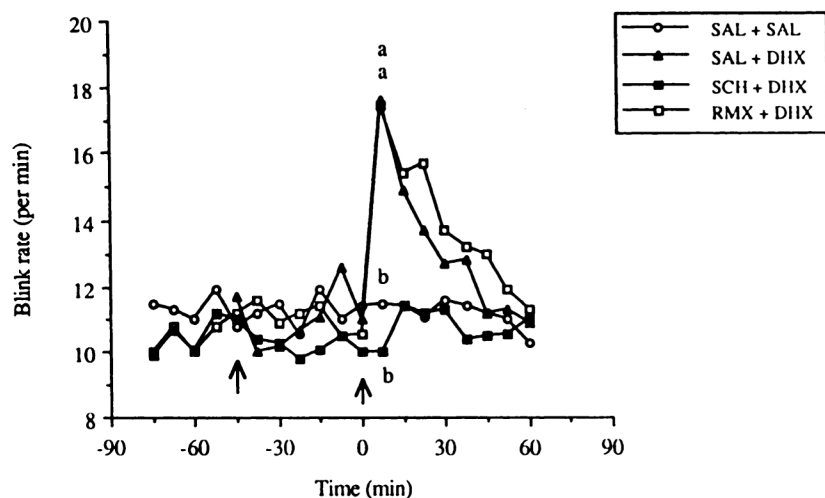
The main effect of time in the PHNO experiments was significant ( $F = 5.95$ ;  $df = 18,59$ ;  $P < .0001$ ), and the peak response at 7.5 min was significantly different from all other time points (Duncan's,  $P < .05$ ). PHNO (0.001 and 0.01 mg/kg) treatment of the monkeys produced a dose-dependent elevation of blink rate (fig. 4) (dose by time ( $F = 4.0$ ;  $df = 26,58$ ;  $P < .0001$ )). The effect at 7.5 min was significantly different ( $F = 7.53$ ;  $df = 2,2$ ;  $P < .01$ ), as elucidated by Duncan's Multiple Range test,  $P < .05$ ). No significant differences in blink rate existed before drug treatment ( $F = 0.29$ ;  $df = 2,36$ ;  $P = \text{N.S.}$ ).

The effect of PHNO (0.001 mg/kg) on blink rate was pre-

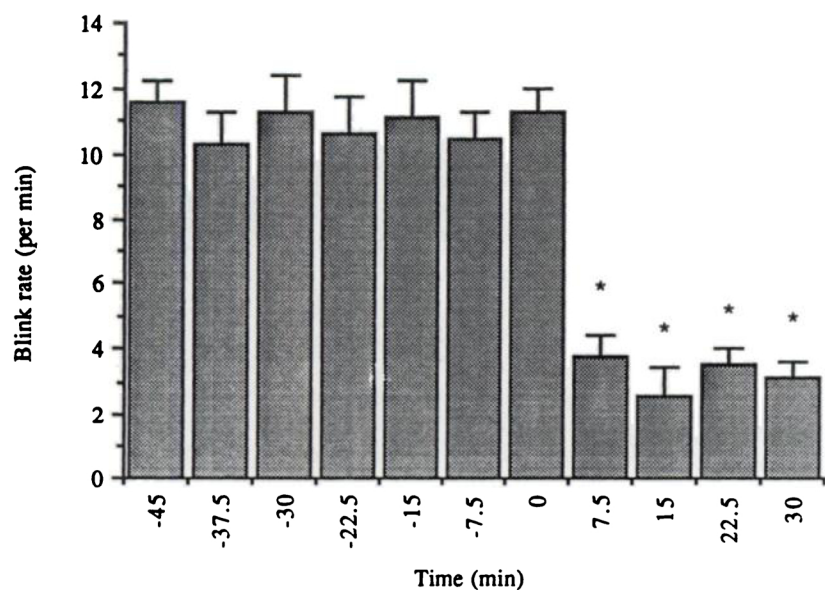




**Fig. 1.** Dose-response effect of dihydrexidine on blink rate in the African green monkey ( $n = 5$ ). Dihydrexidine (DHX) was injected (i.m.) at time 0 (arrow). At the time of peak effect (7.5 min), the blink rates in all four trials were significantly different from each other and are therefore marked with a different letter (a,b,c,d) based on Duncan's test ( $P < .05$ ) and the analyses of variance.



**Fig. 2.** Effect of  $D_1$  and  $D_2$  antagonists on the dihydrexidine increase in blink rate ( $n = 5$ ). The  $D_1$  antagonist, SCH 23390 (SCH, 0.01 mg/kg) or the  $D_2$  antagonist, remoxipride (RMX, 1 mg/kg) or saline (SAL) was injected (i.m.) at time -45 min (arrow). Dihydrexidine (0.3 mg/kg, i.m.) or SAL was injected at time zero (arrow). Means with different letters are significantly different from each other ( $n = 5$ ).

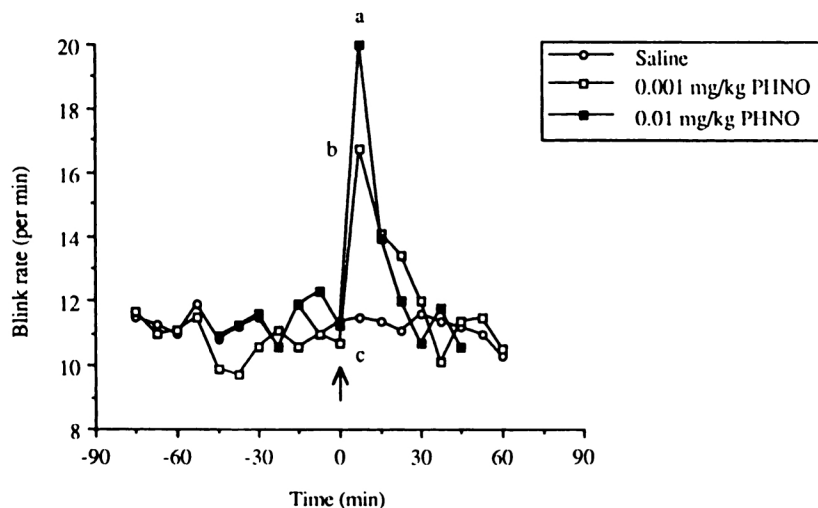


**Fig. 3.** Effect of SCH 23390 (0.3 mg/kg) on blink rate in the African green monkey ( $n = 5$ ). Drug-injected (i.m.) at time zero (arrow). Blink rates after SCH 23390 administration are significantly lower than before treatment.

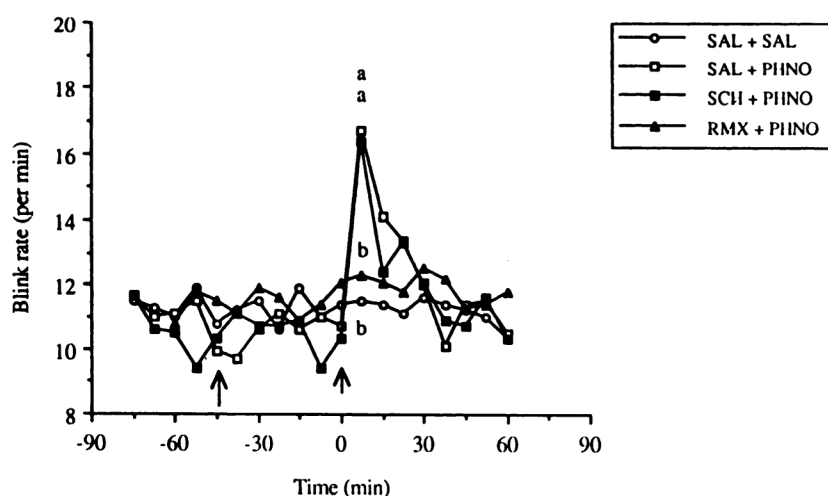
vented by pretreatment with remoxipride (1 mg/kg), but not by pretreatment with SCH 23390 (0.01 mg/kg) (fig. 5) (dose by time ( $F = 1.81$ ;  $df = 52,89$ ;  $P < .002$ )). Significant differences were found at the 7.5-min peak ( $(F = 4.29$ ;  $df = 3,3$ ;  $P = .02$ ), with specific differences determined by Duncan's Multiple Range test,  $P < .05$ ). The base-line period before drug admin-

istration was not significantly different across the PHNO antagonism experiments ( $F = 0.33$ ;  $df = 3,57$ ; N.S.).

The mean blink rate in the period before drug administration was not significantly different across any of the experiments reported here (range of means  $\pm$  S.E.;  $10.85-11.1 \pm 1.29-1.51$  min<sup>-1</sup>).



**Fig. 4.** Dose-response effect of PHNO on blink rate in the African green monkey ( $n = 5$ ). (+)-PHNO injected (i.m.) at time zero (arrow). At the time of peak effect (7.5 min), the blink rates in all trials were significantly different from each other and are therefore marked with a different letter (a,b,c).



**Fig. 5.** Effect of  $D_1$  and  $D_2$  antagonists on the PHNO-induced increase in blink rate ( $n = 5$ ). The  $D_1$  antagonist, SCH 23390 (SCH, 0.01 mg/kg, i.m.), or the  $D_2$  antagonist, remoxipride (RMX, 1 mg/kg, i.m.), or saline (SAL) was injected at time -45 min (arrow). PHNO (0.001 mg/kg, i.m.) or saline (SAL) was injected at time zero (arrow). Means with different letters are significantly different from each other ( $n = 5$ ).

Because the monkeys used in the present study had received saline and PHNO (0.01 and 0.001 mg/kg) in a previous investigation of the regulation of blink rate conducted 8 months earlier, the response of the animals to saline and PHNO on the two occasions was compared. These analyses showed that there was no significant difference in the blink rate response to saline ( $F = 0.67$ ,  $df = 1,8$ ; N.S.), to 0.01 mg/kg PHNO ( $F = 0.28$ ,  $df = 1,8$ ; N.S.) or to 0.001 mg/kg PHNO ( $F = 0.08$ ,  $df = 1,8$ ; N.S.) over 8 months.

## Discussion

These data strongly suggest that  $D_1$  dopamine receptors, as well as  $D_2$  receptors, play a major role in the regulation of spontaneous blink rate in the African green monkey. Thus, acute administration of either a  $D_1$ - or a  $D_2$ -selective dopamine agonist increased blink rate, and this effect could be prevented by administration only of the antagonists for the specific receptor subclass. Although it has been accepted that  $D_2$  receptors play an important role in the modulation of blink rate, the present data are the first to show a clear role for  $D_1$  receptors. These data also demonstrate independent mediation of a single behavior by both  $D_1$  and  $D_2$  receptor subtypes.

Dihydroxidine, the  $D_1$  agonist used in these studies, is the first drug to be bioavailable and have full efficacy at the  $D_1$  receptor. Because dihydroxidine has only a 10-fold  $D_1/D_2$  selec-

tivity for striatal dopamine receptors (Lovenberg *et al.*, 1989; Mottola *et al.*, 1990), it is critical to resolve whether the observed effects were due to  $D_1$  activation. The pharmacological studies we have described clearly illustrate the role of  $D_1$  receptors.

Either dihydroxidine (0.3 mg/kg) or the  $D_2$  agonist PHNO (0.001 mg/kg) resulted in a similar increase in blink rate. The effect of dihydroxidine (0.3 mg/kg) on spontaneous blink rate was not altered by pretreatment with remoxipride (1 mg/kg), a selective dopamine  $D_2$  agonist (Ögren *et al.*, 1984). The same dose of remoxipride (1 mg/kg), however, completely blocked the increase in spontaneous blink rate that resulted from administration of a submaximal dose (0.001 mg/kg) of PHNO, a selective dopamine  $D_2$  agonist (Martin *et al.*, 1984). This indicates that the failure of remoxipride to prevent the dihydroxidine-induced elevation of blink rate was *not* due to the administration of an ineffective dose of remoxipride. Neither 0.01 mg/kg SCH 23390 nor 1 mg/kg remoxipride administered alone altered blink rate. Administration of a higher dose of SCH 23390, however, resulted in a large decrease in blink rate, which is consistent with the maintenance of blink rate by  $D_1$ , in addition to  $D_2$  (Lawrence and Redmond, 1991), dopaminergic tone.

In addition to this direct evidence, studies in rats are also of relevance. In the rat, dihydroxidine produces behavior charac-

teristic of D<sub>1</sub> receptor activation at doses up to 3 mg/kg (Darney *et al.*, 1990, 1991). Effective drug doses in primates are often less than in rodents, and the dose of dihydrexidine chosen (0.3 mg/kg) for the antagonist studies was one that caused a submaximal increase in blink rate. Thus, the use of a low dose of dihydrexidine ensured that preferential occupation of D<sub>1</sub> receptors would occur *in vivo*.

Moreover, it is known that dihydrexidine is selective for dopamine receptors. A screen against 40 other receptor types showed a lack of potency (*i.e.*, IC<sub>50</sub> greater than 10  $\mu$ M), except for weak affinity at  $\alpha$ -2 adrenergic receptors (IC<sub>50</sub> approximately 300 nM, compared to 10 nM for D<sub>1</sub> receptors; D. M. Mottola; W. K. Brewster, L. L. Cook, D. E. Nichols, R. B. Mailman, submitted. Lovenberg *et al.*, 1989).

Unlike remoxipride, SCH 23390 (0.01 mg/kg), a selective dopamine D<sub>1</sub> antagonist (Iorio *et al.*, 1983), completely blocked the effect of dihydrexidine on blink rate. SCH 23390 (0.01 mg/kg) did not affect the PHNO-induced change in blink rate, indicating that the effect of SCH 23390 in the dihydrexidine study was not due to an interaction with dopamine D<sub>2</sub> receptors. Thus, a low dose of a D<sub>1</sub> agonist increased blink rate, and this effect was prevented by a D<sub>1</sub>, but not a D<sub>2</sub>, antagonist. On the other hand, blink rate was increased by a low dose of a D<sub>2</sub> agonist, and this effect was blocked by a D<sub>2</sub>, but not D<sub>1</sub>, antagonist.

Although administration of 0.03 or 1 mg/kg dihydrexidine resulted in rapid and dose-dependent increases in blink rate, a dose of 2 mg/kg dihydrexidine was less effective than 1 mg/kg in increasing blink rate. One explanation for the reduced effect of this dose of dihydrexidine was that it was tested 8 months before the present experiment. It should be noted, however, that there was no difference in blink rate response over the same 8-month period to injection of either saline or PHNO (0.01 mg/kg or 0.001 mg/kg) in the same five animals. This demonstrates that the rate of spontaneous blinking is very stable over time in the monkey.

There are several other possible explanations for the observation that 2 mg/kg dihydrexidine caused a lesser response than did 1 mg/kg. The higher dose may have induced behaviors associated with decreased blink rates (*i.e.*, behavioral competition; Darney *et al.*, 1991). Alternatively, the higher dose of dihydrexidine may have sensitized relevant receptors to later doses of the agonist, although such "priming" has not been shown to persist for as long as 8 months (Morelli *et al.*, 1989). Another argument against the occurrence of priming in these studies is that the sequence of administration of dihydrexidine doses (0.3, 1.0 mg/kg) had no discernible effect on blink response. It is also possible that values above 20 blinks/min may represent a ceiling for dopamine-induced effects. Further studies will be required to distinguish between these possibilities.

Studies in rodents have provided evidence for different types of interactions between D<sub>1</sub> and D<sub>2</sub> receptors (Waddington and O'Boyle, 1989; Clark and White, 1987). A cooperative/synergistic interaction between D<sub>1</sub> and D<sub>2</sub> receptors occurs in the regulation of typical unconditioned motor responses and conditioned behaviors, such that those stimulated by a specific agonist are reversed by an antagonist of either class. Interestingly, after 6-hydroxydopamine lesions, this situation is altered and response to D<sub>1</sub> or D<sub>2</sub> agonists are sensitive only to their respective antagonist. On the other hand, in the regulation of certain atypical behaviors (*e.g.*, vacuous chewing), the direction of D<sub>1</sub>/D<sub>2</sub> interactions is inverse/oppositional, such that a be-

havior induced by selective D<sub>1</sub> stimulation is potentiated by a reduction in D<sub>2</sub> activity and inhibited by an increase in D<sub>2</sub> activity. In drug discrimination paradigms, however, D<sub>1</sub> and D<sub>2</sub> receptor systems appear to act in a functionally independent manner to regulate responding, such that cues established by selective D<sub>1</sub> and D<sub>2</sub> agonists can be independently manipulated by the appropriate antagonist (Kamien *et al.*, 1987; Arnt, 1988; Waddington and O'Boyle, 1989). Thus, D<sub>1</sub> and D<sub>2</sub> receptor systems appear to function independently in relation to blink rate and drug discrimination in the intact animal, or unconditioned motor behaviors after a lesion of the dopaminergic mesostriatal pathway.

This line of evidence raises the question of the anatomical localization of dopamine receptors involved in blink rate regulation. The reduced blink rate in Parkinson's disease is consistent with the involvement of the nigrostriatal dopamine pathway. It should be noted, however, that other transmitter deficits occur in Parkinson's disease, including damage to dopaminergic projections to limbic and cortical regions (Yahr and Bergmann, 1987). Of course, it is possible that the D<sub>1</sub> and D<sub>2</sub> receptors that regulate blink rate reside in different brain regions. The possibility of species-dependent differences in D<sub>1</sub>/D<sub>2</sub> interactions should also be considered, although the very low blink rate observed in rodents (Blount, 1928) may prevent experiments on blink rate in lower species. Although there is a paucity of data on D<sub>1</sub>/D<sub>2</sub> interactions in the primate, evidence to date suggests that D<sub>1</sub>/D<sub>2</sub> effects in primates may, at least in some cases, be different, even opposite, from those in rodents (see Waddington and O'Boyle, 1989). It will be important now to test whether D<sub>1</sub>/D<sub>2</sub> interactions can be observed in the regulation of other behaviors in primates.

The demonstration of D<sub>1</sub> receptor modulation of blink rate appears, at first, to contradict an earlier anecdotal account that the selective D<sub>1</sub> agonist, SKF 38393, did not alter blink rate in monkeys (cited in Karson, 1988). This is probably due, however, to the fact that SKF 38393, unlike dihydrexidine, is only a partial agonist. An absence of an effect of SKF 38393 on blink rate favored the hypothesis that nonselective dopamine agonists and antagonists altered blink rate by effects solely at D<sub>2</sub> receptors. It now seems likely that changes in blink rate observed after the administration of nonselective dopamine agonists or antagonists (Karson, 1988; Lewis *et al.*, 1990; Lawrence and Redmond, 1991) may also involve D<sub>1</sub>-mediated effects.

Blink rate is reduced in Parkinson's disease and in related dopamine deficiency syndromes. An L-dopa-induced increase in production of dopamine (which will interact with both D<sub>1</sub> and D<sub>2</sub> classes of receptor) in the parkinsonian subject is reflected in an increase in blink rate. Thus, measurement of blink rate may offer a quantifiable, noninvasive measure to assess dopamine-mediated recovery (*e.g.*, after a transplant or implant) in parkinsonian patients or in primate models of Parkinson's disease. An additional advantage of blink rate measurement over other indices of parkinsonian disability is that it does not compete with other behaviors. Thus, blink rate, but not balance, can be rated in the presence of akinesia or freezing episodes.

Because this report describes the first use of a full D<sub>1</sub> agonist in primates, it is worth noting that no apparent adverse behavioral effects were noted in acute doses up to 2 mg/kg. Dihydrexidine appears to be a selective D<sub>1</sub> agonist in primates at doses of approximately 0.3 mg/kg, which may be of use in other studies aimed at elucidating D<sub>1</sub> receptor-mediated functions. In

fact, we have recently demonstrated (Taylor *et al.*, 1991) that dihydrexidine (0.3 or 0.45 mg/kg) produces an elevation in spontaneous blink rate in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated parkinsonian monkeys and that the change in blink rate is correlated with an attenuation in motor deficits. Dihydrexidine, or analogs of dihydrexidine with full D<sub>1</sub> efficacy, may prove to be a novel treatment strategy for Parkinson's disease. The recent appreciation of a role for D<sub>1</sub> receptors in dopamine-mediated functions may redirect research on novel antipsychotic and antiparkinsonian drugs, which has been centered on drugs with selectivity and potency at the D<sub>2</sub> receptor. It is possible that the measurement of blink rate in monkeys may provide a convenient *in vivo* preparation to screen the potency and determine the D<sub>1</sub>/D<sub>2</sub> selectivity of dopamine receptor agonists or antagonists in primates.

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