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# MPTP Lesions and Dopaminergic Drugs Alter Eye Blink Rate in African Green Monkeys

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LAWRENCE, M. S. AND D. E. REDMOND, JR. *MPTP lesions and dopaminergic drugs alter eye blink rate in African green monkeys*. PHARMACOL BIOCHEM BEHAV **38**(4) 869–874, 1991.—Eye blink rates were studied in African green monkeys following relatively specific destruction of substantia nigra and its dopamine projections with the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Monkeys treated with MPTP had a significantly lower blink rate than controls over a period from two to five and a half months after treatment. Furthermore, the degree of parkinsonism expressed in treated animals was inversely correlated with blink rate. Pharmacologic studies further supported the role of dopamine receptors in the regulation of blink rate. PHNO (4-propyl-9-hydroxynaphoxazine), a potent and highly specific $D_2$ agonist, effective in alleviating parkinsonism, caused a significant transient increase in blink rate, while sulpiride, a $D_2$ antagonist, caused a decrease and blocked the effect of PHNO. Apomorphine and haloperidol, although less specific, had potent and predictable effects based on their interactions with dopamine systems. Blink rate may provide a nonintrusive measure of central dopamine activity that would help to evaluate the progress of Parkinson's disease or treatments which attempt to restore dopamine function.

Dopamine MPTP Monkeys Blink rate Brain lesions PHNO Haloperidol Apomorphine Sulpiride Ketamine

BASED on the observation that altered spontaneous eye blink rates are characteristic of some pathological states in which a dopamine abnormality is implicated, it has been hypothesized that blink rate reflects central dopamine activity (31). In dopamine deficient patients suffering from Parkinson's disease (14), blink rates are reduced (10, 29, 32). Conversely, in schizophrenia, a condition attributed to elevated dopaminergic activity, blink rates are increased (19, 23, 32). There are no experimental data to indicate precisely the anatomical localization of this postulated dopaminergic regulation of blink rate. Although loss of dopamine-containing cells from the substantia nigra is considered a characteristic feature of Parkinson's disease (9), deficits in a number of areas and other neurotransmitter systems are known to be involved in its pathophysiology (15). There are no reports of the effects on blink rate of neurotoxin induced lesions of the dopaminergic neurons originating in the substantia nigra.

Data on the pharmacological manipulation of blink rates in rhesus monkeys, however, support the role of dopamine, specifically $D_2$ receptors (16,22). Transient increases in blink rate after apomorphine are blocked by the $D_2$-receptor antagonist sulpiride, but also by the benzodiazepine, diazepam. Atropine increases and physostigmine decreases blink rate, further raising the possibility of other systems affecting blink rate directly, or indirectly, acting through dopamine receptors (16). Acute administration of dopamine antagonists, such as haloperidol, reduces blink rates (16) and chronic administration of antagonists sensitizes receptors to low dose effects of apomorphine (21). But the $D_2$ antagonist, sulpiride, was not reported to reduce blink rates by itself.

While these pharmacological effects are supportive of a role for dopamine in the regulation of blink rates, they provide no information about specific brain sites of action and they raise the possibility that relationships between blink rates and the severity of parkinsonism in patients are confounded by previous or continuing medication treatments (16,20). Dyskinetic patients receiving L-DOPA and various $D_2$ agonists had significantly higher blink rates than nondyskinetic patients, and in these patients, there was no effect of severity of disease. Nondyskinetic patients did show some effect of severity, based on three categories of Hoehn and Yahr stage (12,20), but failed to show the presumed normalizing effect of concurrently administered DA agonists or L-DOPA treatment on blink rate. In another study, largely medication-free patients did show effects of severity of disease, when divided into dichotomous groups, and two patients showed increased blink rates after improvement by medication (18). Two patients, in the same study, were noted to have received the neurotoxin MPTP as a possible etiology of their disease, but data from these patients

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were not reported separately (18). Such data might indicate more about the precise localization of the dopamine-mediated effects on blink rate.

Dopamine may not be the only neurotransmitter system affecting spontaneous blink rates. In addition to the pharmacological data cited above, studies in humans under a variety of conditions suggest that blink rate is dependent on emotional and cognitive states. Reading and simple memory operations depress blink rate (10, 13, 28), whereas anger and excitement increase blink rate (29). Elevations in blink rate have also been found under tense incentive-driven testing situations (24) and during periods of muscular exertion (11). Ponder and Kennedy excluded the importance of environmental stimuli communicated through ocular input under most conditions. Humidity, illumination, corneal anesthesia, or signals transmitted through the second, third, fourth, fifth, and sixth cranial nerves have no effect on normal blink rate in humans (29). But an increase in blink rate caused by cigarette smoke is blocked by anesthetizing the eye, suggesting that blink rate is responsive to signals of irritation of the cornea (29). More recently blink rate has been found to be elevated in Sjögren's syndrome patients, who suffer from a rapid drying of the corneal tear film (30), again suggesting that corneal irritation can play a role in blink rate regulation under unusual circumstances. In healthy subjects the mean rate at which dry spots in the corneal tear film develop is 26.8 seconds (27). Thus the blink rate necessary to prevent corneal drying (2 or 3 per minute) is far below the average blink rate in normal human subjects of 23 blinks per minute (16), suggesting that other factors regulate blinking at this much higher level.

The most important regulator of spontaneous normal blink rate, of the various factors mentioned, appears to be central dopaminergic activity. Previous studies implicate $D_2$ receptors and suggest that blink rates might be used as an index of central dopamine activity. To determine the possible anatomical and receptor localization of these effects, we studied blink rates in African green monkeys after treatment with the neurotoxin, MPTP. We attempted to quantitate the relationship between blink rate and degree of parkinsonism induced by this treatment, as well as the effects of other behaviors and/or emotional states that might confound the results. Finally, we studied various dopamine agonists and antagonists, including the highly specific $D_2$ agonist, PHNO, and the $D_2$ antagonist, sulpiride, in order to confirm and characterize further the role of $D_2$ receptors involved in the regulation of blink rate.

## METHOD

Blinks were defined as a spontaneous apposition of the upper and lower eyelid lasting no longer than 0.5 seconds as estimated by the observer. At each time point sampled, blinks were counted with a tally counter during a 2.5-minute period. A stop watch was used to keep track of the amount of time during which the monkey's eyes were visible to the observer within the 2.5-minute counting period. If during this 2.5-minute period the subject's eyes were visible for less than 90 seconds, the entire count was discarded. Blink rates are reported as the number of blinks per minute. All blink rates were measured by one observer, but simultaneous counts by two observers were done to determine interrater reliability.

A cumulative dose of 2.0 mg/kg of MPTP (Research Biochemicals Inc., Natick, MA) was administered intramuscularly over a period of 5 days to 11 mature young adult male *Cercopithecus aethiops sabaeus* from the island colony of St. Kitts, West Indies. An equivalent volume of saline was administered on the same schedule to 9 control monkeys. The blink rates and behaviors of these MPTP-treated and 9 control monkeys were measured from 2 to 5.5 months after MPTP treatment in a blinded study. Throughout the blink study period and for 5 months prior to the study period the monkeys were housed in the same cages and were accustomed to daily observation. The observer had no knowledge of which monkeys had received MPTP treatment. Blinks were counted as described either immediately before or after daily assessments of the monkey's behavioral status by time-sampled observations. The time-sampled observations consisted of five-minute periods during which the occurrence or absence of 18 ethologically defined discrete behaviors in 5-second intervals was recorded [one-zero sampling, according to Altmann (1)]. Ten other measures of the monkeys' movement, physical appearance, or response to stimuli, which are associated with parkinsonism, were rated on a subjective scale of 0 to 5, zero being normal (34). The behavioral status of the monkeys was quantified from sums of the raw behavioral scores, based upon previous factor analyses and empirical testing and verification of the validity of the factors. These factor scores include factors representing Anxiety, Arousal, Sedation, and "Quiet OK" behaviors. The Parkinsonian Score represents sums of behavioral scores of tremor, eyes closed, freezing, difficulty eating, food response, delay in initiation of responses, poverty of movement, response to threat, and time unable to stand (or "facedown").

Five healthy monkeys which were not involved in the MPTP study were subjected to DA agonist and antagonist administration. In this group, blinks were counted every 7.5 minutes from 45 minutes prior to drug administration and up to 2.5 hours afterward. PHNO (0.01, 0.001 mg/kg IM, Merck Sharp and Dohme, West Point, PA), apomorphine (0.2, 0.1 mg/kg SC, Sigma, St. Louis, MO), haloperidol (1.0 mg/kg IM, McNeil Pharmaceutical, Spring House, PA), sulpiride (100 mg/kg orally, Sigma, St. Louis, MO), ketamine (5 or 10 mg/kg IM, Aveco, Fort Dodge, IA) or 0.9% sodium chloride solution (saline) were administered. In some experiments, there were combinations of these drugs administered, with appropriate controls. The experiments were scheduled such that no drug was evaluated within four days of previous treatment and all experiments occurred between 12:01 p.m. and 3:00 p.m. to avoid the possible complications of diurnal activity rhythms. Several of the drug effects were compared with the same experiment in which saline was administered as a control procedure.

The significance of differences between the MPTP-treated and control monkeys was determined using a one-way analysis of variance. The stability of blink rates in normals and in the MPTP-treated monkeys was tested using an analysis of variance and linear regression. Statistical tests of the drug studies were done using repeated measures analyses of variance, with Duncan's multiple range test to determine differences between individual time points. Interrater reliability correlation and correlations between behaviors and blink rates were done using Spearman's rank correlation test (35).

## RESULTS

### *Blink Rate in Healthy Monkeys*

We estimate the mean blink of adult male *Cercopithecus aethiops sabaeus* to be 11.7 blinks per minute. This figure is based on the observation of the 9 healthy control monkeys in the MPTP study, each of which was observed undisturbed in its home cage. While blink rates varied considerably between individuals, there was no significant change in the blink rate of individual monkeys over a 2.5-month period. The stability of the blink rates of 6 individual normal monkeys over time [$F(1,154)=0.45$,

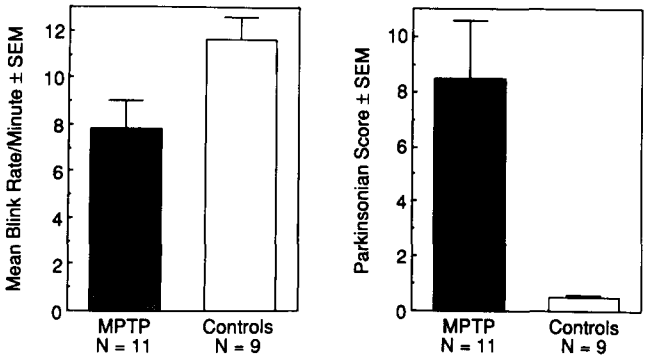


FIG. 1. The mean blink rates of 11 MPTP-treated monkeys were compared with those of 9 untreated monkeys. Blink rates were counted during a period from 2 months to 5.5 months after MPTP treatment. Differences in blink rates between the two groups were significant, $F(1,18) = 12.3$, $p<0.01$, as were differences in Parkinsonian Score, $F(1,18) = 11.4$, $p<0.01$.

$p$=NS, ANOVA regression of day on blink rate] and the high interrater reliability measures suggest that the counting period of 90 to 120 seconds which we employed was sufficient to quantitate blink rate under these conditions. The blink counting technique of stop watch and hand tally counters yielded a highly significant interrater correlation between 2 observers independently counting the same monkey at the same time ($r = .975$, $p<0.01$, $N = 30$).

*Neurotoxic Destruction of Dopamine Systems*

An MPTP treatment of 2.0 mg/kg given intramuscularly in divided doses over a period of 5 days resulted in varying degrees of parkinsonism among the treated animals, although as a group they became only mildly parkinsonian (see Fig. 1). Blink rate was significantly reduced in the MPTP-treated monkeys in comparison with the controls, $F(1,18) = 12.3$, $p<0.003$. There was no significant change in blink rate with time in four MPTP-treated monkeys observed on 26 days over a ten-week period of observation [$F(1,108) = 0.35$, $p$=NS, ANOVA regression of date on blink rate]. These monkeys had never been treated with antiparkinsonian medications or with neuroleptics, and they were on no other concurrent treatments.

In all of the MPTP-treated and control monkeys analyzed together, blink rate was inversely correlated with the severity of parkinsonism induced, as quantified by the Parkinsonian Score ($R = -.80$, $N = 20$, $p<0.001$). As expected, blink rate was also correlated with the raw behavioral scores related to motor ability which contribute to the Parkinsonian score (see Table 1). Of the various individual behaviors, poverty of movement correlated most highly with blink rate alone, followed by freeze and tremor. Sedation, which also contributes to the overall Parkinsonian Score, was significantly inversely correlated with blink rate at about the same significance level. The correlations were not due to group differences alone but were highest in the MPTP-treated monkeys [Parkinsonian Score was inversely correlated with blink rate ($R = -.88$, $N = 11$, $p<0.001$); see Fig. 2]. These correlations were not significant in the controls calculated alone ($R = -.05$, $N = 9$, $p$=NS).

The "normal" spontaneous behaviors quantified in these animals also showed some relationships with blink rate. Arousal was positively correlated with blink rate in the MPTP group, but not in the controls. This was not due to differences in the expression of these behaviors by the two groups, since both groups exhibited these behaviors a similar proportion of the time (Table 1). Anxiety and Quiet OK behaviors were uncorrelated with blink rate in each group separately but overall showed significant correlations, possibly due to differences in the expression of the behaviors by each group.

TABLE 1

CORRELATION COEFFICIENTS (R) BETWEEN BEHAVIORAL MEASURES AND BLINK RATE IN A GROUP OF 11 MPTP-TREATED AND 9 CONTROL MONKEYS

| | All N=20 | MPTP N=11 | | Control N=9 | |
|---|---|---|---|---|---|
| | R | R | Mean | R | Mean |
| Factor Analyzed Summary Scores | | | | | |
| Anxiety | .61* | .48 | 8.0 | −.22 | 14.1 |
| Arousal | .62* | .82* | 1.8 | .43 | 2.6 |
| Quiet OK | .64* | .64 | 3.9 | −.03 | 10.9 |
| Sedation | −.79* | −.86* | 11.0 | −.17 | 1.33 |
| Components of the Parkinsonian Score | | | | | |
| Freeze | −.85* | −.89* | 10.9 | −.17 | 1.24 |
| Difficulty eating | −.58* | −.64 | 0.45 | | 0 |
| Food response | −.52 | −.45 | 0.39 | | 0 |
| Delay in initiating responses | −.66* | −.64 | 0.54 | | 0 |
| Poverty of movement | −.86* | −.86* | 1.15 | −.55 | 0.02 |
| Response to threat | −.53 | −.45 | 0.44 | | 0 |
| Tremor | −.75* | −.59 | 3.17 | −.26 | 0.18 |
| Parkinsonian Score | −.80* | −.88* | 8.51 | −.05 | 0.42 |

*R values were significant ($p<0.01$).

*Dopamine Agonists and Antagonists*

Blink rate did not depart from the stable baseline following the injection of saline. Apomorphine caused a transient dose-dependent increase in blink rate. Both 0.1 and 0.2 mg/kg apomorphine caused a sharp dose-dependent increase in blinks which plateaued for 30 minutes and returned to baseline within 75 minutes after injection (see Fig. 3). At 0.01 mg/kg PHNO also caused an increase in blink rate. The elevation in blink rate steadily returned to baseline within 60 minutes after an initial peak at 7.5 minutes (see Fig. 4). PHNO had a similar but reduced effect at 0.001

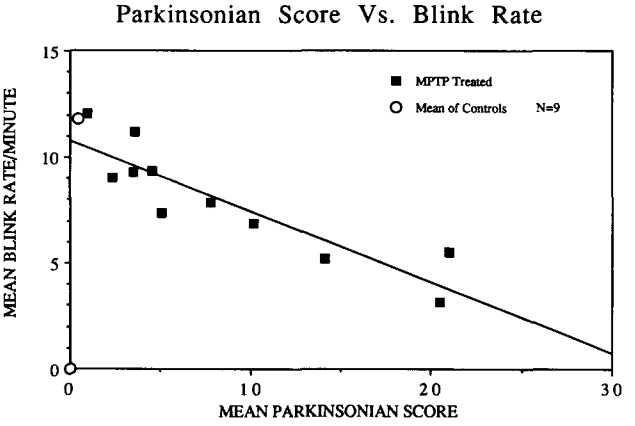


FIG. 2. The mean parkinsonian score for each MPTP-treated monkey is plotted against its mean blink rate, with the linear regression for the MPTP-treated monkeys shown. The circle shows the mean parkinsonian score for all 9 controls plotted against their mean blink rate.

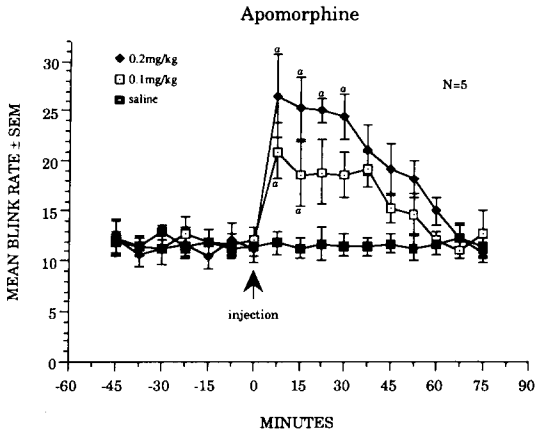


FIG. 3. Five monkeys were injected with apomorphine (0.1, 0.2 mg/kg) or saline at time point zero in three separate experiments. An ANOVA showed a significant dose × time interaction, $F(32,202)=3.64$, $p<0.01$. Points labeled α were significantly different from all other time points within that dose by Duncan's multiple range test. The three trials were significantly different from each other, $F(2,202)=47.93$, $p<0.01$, based on the main effect of dose and Duncan's multiple range test ($p<0.05$). Blink rate is reported as blinks per minute.

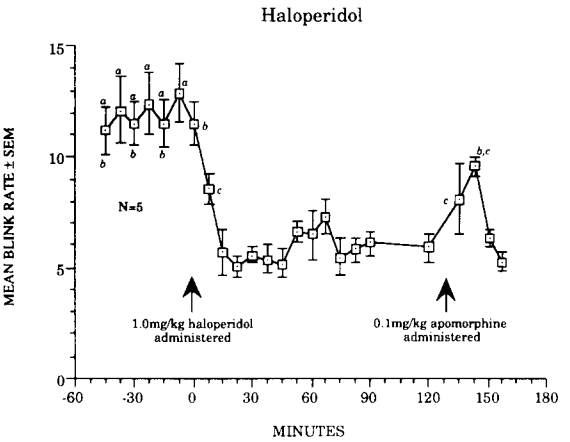


FIG. 5. Haloperidol (1.0 mg/kg) administered at time point zero decreased blink rate at least for 120 minutes. Apomorphine (0.1 mg/kg), administered at 127.5 minutes, appeared to reverse this decrease briefly. A one-way ANOVA showed the effect of time to be significant, $F(23,87)=14.85$, $p<0.01$. Points labelled with the same letter were not significantly different from each other and were different from all unlabelled points. One monkey did not receive apomorphine and was dropped from the analysis after 75 minutes. Blink rate is reported as blinks per minute.

mg/kg. Haloperidol (1.0 mg/kg IM) reduced the blink rate to half the baseline level within 15 minutes and maintained that level throughout the two hour observation period (see Fig. 5). This reduction in blink rate was transiently reversed by 0.1 mg/kg apomorphine administered 127.5 minutes after the haloperidol injection. In an experiment to determine the effect of the $D_2$ antagonist, sulpiride, on blink rates and the possible blockade of the effects of PHNO, blinks were counted beginning five hours after oral pretreatment with 100 mg/kg sulpiride. A low dose of ketamine (5 mg/kg) was required to allow oral administration of the sulpiride by nasogastric tube. Pretreatment with 5 mg/kg ketamine alone was not significantly different from saline after five hours. Pretreatment with ketamine also did not block the elevation in blink rate which followed the injection of 0.001 mg/kg PHNO [$F(12,52)=-2.66$, $p<0.01$, main effect of time from analysis of variance]. Pretreatment with sulpiride caused a significant reduction in blink rate in comparison with ketamine alone or saline control data [main effect of drug treatment, $F(3,224)=47$, $p<0.01$] and blocked the effect of 0.001 mg/kg PHNO (see Fig. 6).

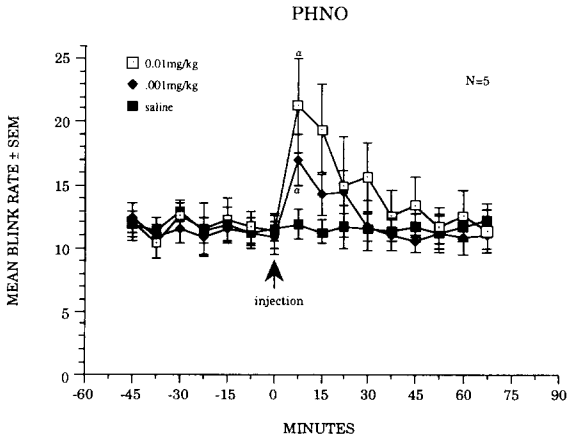


FIG. 4. Five monkeys were injected with PHNO (0.01, 0.001 mg/kg) or saline at time point zero in three separate experiments. The lower dose of PHNO, which demonstrated a robust effect, was used in subsequent blocking experiments with sulpiride (see Fig. 6). ANOVA showed a significant interaction between dose and time, $F(30,183)=3.79$, $p<0.01$. The 7.5-minute time point for the PHNO doses (labelled α) were significantly different from all other time points within that dose by Duncan's multiple range test. Overall, the doses were significantly different [main effect of dose, $F(2,183)=21.14$, $p<0.01$] with the peak effects different from saline (Duncan's test $p<0.05$). Blink rate is reported as blinks per minute.

## DISCUSSION

The mean blink rate of 11.7 blinks per minute is slightly lower than previous measurements of 13.6 blinks per minute in "West Indian monkeys," probably the same species used in the present study (2). The slight discrepancy may reflect the considerable variation in blink rate between individual monkeys or observation techniques or the fact that our monkeys were more thoroughly conditioned to observation. We found that blink rates of individual healthy monkeys, however, were very stable over time. Since blink rates can be counted reliably and do remain stable over long periods, changes in blink rate observed after brain lesions or pharmacological treatments may reflect changes in the neuroanatomical substrates and receptors involved in blink rate regulation if other behavioral and environmental factors are controlled experimentally.

This report is the first to document alterations in blink rate due to an experimentally induced lesion in the brain. Previous data have suggested dopamine involvement in blink rate regulation based upon the suspected involvement of dopamine in a number of disorders such as Parkinson's disease and schizophrenia (31,32) and upon pharmacologic effects (16). For these reasons, cell loss induced by the neurotoxin, MPTP, is of particular interest because it is relatively confined to well documented sites in specific dopaminergic regions, especially in monkeys that are not severely parkinsonian. In the African green monkey, MPTP produces destruction of DA-containing cells and decreases in dopamine concentrations and increases in the HVA/dopamine ratio in the retrorubral area (A8), the substantia nigra (A9), and the ventral

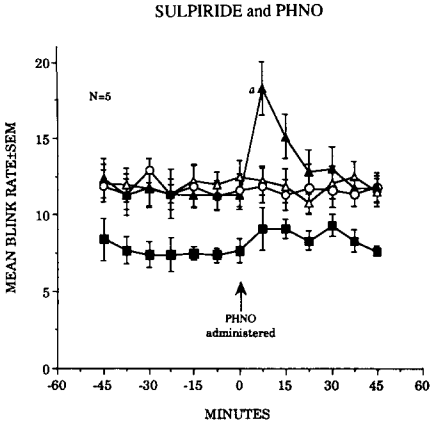


FIG. 6. PHNO administered at 0 minutes caused an increase in blink rate (solid triangles) while pretreatment with sulpiride blocked the increase induced by PHNO alone (solid squares). Blinks were counted starting at five hours after nasogastric administration of sulpiride (100 mg/kg). Sulpiride pretreatment required a low dose of ketamine to facilitate handling. As a control procedure, pretreatment with 5 mg/kg of ketamine alone (open triangles) had no effect on baseline blink rate after five hours compared with saline control (open circles) and did not block the increase in blink rate following PHNO (0.001 mg/kg) (solid triangles). Blink rates were decreased after pretreatment with sulpiride (solid squares) compared with ketamine alone or with saline and all three of these were different from the ketamine + PHNO treatment [analysis of variance showed a significant main effect of treatment group, $F(3,224)=46$, $p<0.01$, with between group differences by Duncan's test ($p<0.05$). Blink rate is reported as mean blinks per minute. The point labeled $\alpha$ was significantly different from all other time points within that treatment by Duncan's multiple range test ($p<0.05$).

tegmental area (A10 dopamine cell group) (4–7). These cells project to the striatum and other telencephalic regions (3, 8, 26, 33). In monkeys which are mildly parkinsonian (to the same degree as those in the present study) these deficits are even more specifically confined to dopamine systems in or near the substantia nigra (5,8). Since destruction of these systems by MPTP has a long-lasting effect on blink rates, it seems likely that the locus of dopamine influence on blink rates resides in one of these regions.

The cell destruction caused by MPTP and the behavioral deficits which result from this cell loss are very similar to those found in idiopathic Parkinson's disease. A decrease in blink rate is another similarity in the symptomatology of MPTP-induced parkinsonism and idiopathic Parkinson's disease. Blink rate has been correlated with the severity of idiopathic Parkinson's disease (16, 18, 20), but only one of the groups studied was composed of medication-free patients, and in that group some of the patients were not medication naive (18). Thus active or previous medication status might have influenced the result of those studies, especially since changes in receptor sensitivity following drug treatments that alter blink rate have been reported (21). By investigating blink rates in monkeys with an MPTP-induced parkinsonism, we were able to look at the relationship between blink rate and the severity of parkinsonian signs in unmedicated subjects under uniform environmental and treatment conditions. The varying degrees of parkinsonism which resulted from different individual sensitivities to MPTP also allowed us to compare blink rates between subjects which exhibited a range of impairment.

The strong correlation between blink rate and Parkinsonian Score appears not to depend upon other transient behavioral states such as anxiety which have been demonstrated to affect blink rate in humans. Elevated blink rates have been found to occur in humans during periods of arousal and tension (24,29) and in all animals together significant correlations were found with the factors for anxiety and arousal. However, anxiety was not statistically correlated with blink rate within the treatment groups. As expected, most behavioral components of the parkinsonian summary score, such as poverty of movement and freezing, correlated statistically with blink rate in the same direction as the overall score. Arousal and sedation also are statistically correlated, in opposite directions, with blink rate. Observations of individual animals suggest that other measures of parkinsonism remain associated with low blink rates when "sedation" is not present. Overall, these relationships, combined with the absolute differences in blink rates induced by damage to dopamine systems from MPTP treatment, suggest that both the associated behaviors and blink rate are regulated by dopaminergic systems.

Pharmacologic manipulations in normal monkeys further supported this conclusion. We found a dose-related increase in blink rate following apomorphine administration, which peaked within 7.5 minutes. Higher doses of apomorphine have been reported to elevate blink rates in rhesus monkeys with a maximal effect at 30 minutes (22). The strong effect of apomorphine generally implicates dopamine receptors in blink rate regulation. The sustained depression of blink rate elicited by haloperidol, and its transient reversal by apomorphine in our study further supports this conclusion. It is possible that the reported effects of the benzodiazepine diazepam and cholinergic agents such as atropine and physostigmine on blink rate may be acting indirectly through the dopamine system (16). However, the possible actions of other neurotransmitter systems on blink rate require much more investigation before such a mechanism can be accepted.

We sought to clarify the role of the dopamine $D_2$ receptor in the regulation of blink rate by administering the highly specific $D_2$ receptor agonist, PHNO, and the $D_2$ receptor antagonist, sulpiride. PHNO and sulpiride had opposite pronounced effects on blink rate, with PHNO causing an increase and sulpiride causing a decrease compared with baseline and control conditions. Doses of sulpiride that reduced blink rate also effectively blocked the increase in blink rate that normally follows a low dose of PHNO, further clearly supporting the involvement of $D_2$ receptors in the action of these drugs. Others have also reported that sulpiride partially blocks the elevation of blink rate caused by dopamine agonists, but none have previously documented a significant reduction in blink rate following sulpiride administration alone (16). It seems likely that the lower doses of sulpiride which effectively block the action of $D_2$ agonists in some brain areas are themselves inadequate to alter basal DA activity levels in the involved regions after systemic administration. The higher doses necessary to alter basal DA activity in the regions which affect blink rate may be explained by differential sensitivity of subgroups of DA neurons to sulpiride, as demonstrated by in vivo microdialysis (25).

Karson et al. reported that SKF38393 (a partial $D_1$ agonist) had no effect on blink rate, suggesting that $D_1$ receptors do not play a role in blink rate regulation (17). However, in view of the preliminary nature of the data and the availability of even more selective and full $D_1$ receptor agonists and antagonists, further studies are warranted before ruling out a role for $D_1$ receptors.

The reliability with which blink rate is measured and its link to dopamine activity suggests that blink rate may be a useful indicator of central dopamine activity. In light of the sensitivity of blink rate to the destruction of dopamine systems by MPTP and the strong effect of antiparkinsonian $D_2$ receptor agonists on blink rate regulation, blink rate may be especially valuable for monitoring the progress of Parkinson's disease or possible restorative treatments such as neural transplantation.

ACKNOWLEDGEMENTS

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