The Effect of Apomorphine on Blink Kinematics in Subhuman Primates with and without Facial Nerve Palsy

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Purpose. The purpose of this study was to document the effect of acutely delivered apomorphine, a dopamine receptor agonist with both D1 and D2 properties, on blink rate and the amplitude–velocity characteristics of eyelid kinematics in a group of nonhuman primates.

Methods. Three cynomolgus and two rhesus macaques underwent baseline recordings for eyelid kinematics, using the Robinson search coil technique. Next, each animal received a 0.15-mg/kg subcutaneous injection of apomorphine. Recordings were taken at 45 and 90 minutes, respectively, after injection. Blink rates per minute were obtained, and main sequence relationships were calculated for every animal. The data were pooled for each eyelid, excluding one monkey who was affected by facial nerve palsy and was analyzed separately.

Results. Monkeys with normal facial musculature and normal baseline blink rates showed consistently longer, faster blinks after apomorphine. The main sequence relationship, although tending to be lower, was not statistically different from baseline. One monkey, with prior facial nerve palsy and a very steep amplitude versus peak velocity relationship, showed normalization of the main sequence slope after apomorphine at both 45 and 90 minutes after injection.

Conclusions. Apomorphine consistently lowers blink rate and changed blink metrics in normal monkeys and, more dramatically, in a monkey with facial nerve palsy. These findings add credence to models in which dopamine deficiency plays a role in the modulation of blink kinematics. (*Invest Ophthalmol Vis Sci.* 2002;43:2933–2938)

Previous studies in a variety of areas have suggested that dopaminergic regulation plays a role in eyelid movement control.[1–3] Dopaminergic manipulation has resulted in changes in blink rate and in reflex blink control.[4,5] Patients with Parkinson disease have decreased blink rates and also show abnormally short reflex blink recovery cycles. Clinically, they may show reflex blepharospasm.[6,7] Patients with benign essential blepharospasm (BEB) show an increased blink rate associated with rapid reflex blink recovery cycle and a low velocity–amplitude relationship. Thus, they have both an overlap and differences with the patients in the Parkinson disease group.[8] The mainstay of therapy in BEB is repeated injections with botulinum toxin, because centrally active medications are generally not sufficiently beneficial. However, a thorough investigation into the effects of newer D1 and D2 agonists and antagonists on the act of spontaneous blinking has not been undertaken. Apomorphine, a dopamine receptor agonist with both D1 and D2, but predominantly D2 properties, has been shown to normalize the reflex blink recovery cycle in patients with BEB, whereas levodopa has failed to do so.[2]

Given the encouraging preliminary findings on the use of apomorphine as a potential therapeutic agent in BEB, we sought to evaluate its effect on blink kinematics in normal nonhuman primates (NHPs) and in an NHP with a previously acquired facial nerve palsy, a model known to upregulate the velocity–amplitude relationship of blinks.

Methods

All methods involving experimental animals adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Animal Subjects

Eyelid movements were recorded and analyzed in five NHPs (three cynomolgus and two rhesus macaques). The Institutional Animal Care and Use Committee at the University of Kentucky approved the animal use protocol. Each animal was untreated before the administration of apomorphine for this study. Pole- and collar-trained NHPs were conditioned to sit confined in a primate chair while watching television—specifically, action cartoons—for a duration of up to 2 hours, by use of a positive reinforcement reward system (i.e., infant food and juice). The time frame for shaping this behavior was adjusted to the individual animal's tolerance and training aptitude.

Procedure

The NHP was placed in the center of a 4-ft Robinson search coil system (CNC Engineering, Seattle, WA). The animal's head was fixed with a noninvasive custom-made head-holder, fashioned from Plexiglas and rigid Styrofoam. This head-holder was attached to the primate's chair and secured the animal's head by slightly pressing the sides and top of the head for immobilization. Fine Teflon-coated copper wire coils (160 mg, 50 turns, 4 mm in outer diameter) were taped to the center of each upper eyelid, immediately adjacent to the eyelashes. Search coils did not obstruct normal eyelid movements.

Each animal underwent baseline recordings for eyelid kinematics, by the Robinson search coil technique,[9] as described in our previous studies. After baseline recordings, each animal received a 0.15-mg/kg subcutaneous injection of apomorphine (Don Gash, PhD, University of Kentucky Department of Anatomy and Neurobiology, personal communication, 2000). Recordings were taken at 45 and 90 minutes after injection.

Data Collection and Analysis

Eyelid position signals were amplified, filtered (500-Hz cutoff), digitized, and sampled at 1000 Hz per channel. They were analog–digital converted with 16-bit resolution and a 5-μs conversion time, with a peripheral component interconnect (PCI) board (DAS-1602; Measurement Computing Corp., Middleboro, MA) and stored for off-line analysis. Spontaneous blinks were collected for each time point by using real-time data-collection software (TEMPO; Reflective Computing, St. Louis, MO). To ensure that the eyelid gaze began in the same position

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TABLE 1. Spontaneous Blink Rates in Nonhuman Primates after Administration of Apomorphine

Animal Group	Baseline	45 Minutes	90 Minutes
Normal*	10.15 ± 2.78	11.42 ± 1.26	7.8 ± 1.49
FNP	11.5	9.33	16.3

FNP, facial nerve palsy.

* Mean ± SE for normal animals based on $n = 3$ because of missing data.

each time before a blink, a threshold was programmed into the data-collection software so that blink data collection began only when the animal looked straight ahead. This threshold was set before data collection for all recordings.

Blink rates (blinks per minute) were obtained by video taping the animals for 5 minutes at each data-recording session for later analysis. Onset and end of down-phase and up-phase of blinks were manually marked for analysis on computer. A minimum of 19 blinks per normal animal and 20 blinks for the animal with facial nerve palsy were analyzed during each recording interval. The eyelid kinematics investigated included, down- and up-phase duration, amplitude, and peak velocity. Eyelid values were combined and pooled for analysis, except for the data in one cynomolgus monkey with a preexisting facial nerve palsy of unknown origin. This animal was studied and its data presented individually. Statistical analysis cannot be performed on data from a single animal. We plan to obtain statistics on a larger number of animals with facial nerve palsy in subsequent studies.

Main-sequence relationships (peak velocity plotted against amplitude) were calculated for every animal. The effects of apomorphine were evaluated by repeated-measures ANOVA for each blink parameter. Post hoc analysis was based on the Fisher least-significant difference procedure for pair-wise comparisons. The factors included in the analysis were blinks nested within postinjection interval, the interval itself (baseline, post–45-minute and post–90-minute), and animal identification number (this factor was included to account for the relationship among observations from the same animal in the repeated-measures design), for each kinematic property.

RESULTS

Amplitude, duration, and peak velocity were measured and analyzed independently, and in addition, the predictable relationship between amplitude and peak velocity (the main sequence relationship) was calculated and plotted. In our previous studies, the main sequence has been a useful measure in distinguishing differences between groups or subjects.[8,10–17] With our present study, we set out to see how the D2 agonist, apomorphine affects the blink reflex and blink main-sequence relationship.

Effect of Apomorphine on Blink Rate

As shown in Table 1, in response to apomorphine injections, monkeys with normal facial musculature and normal blink rates showed an increase in blink rate from baseline to the 45-minute postinjection time point. There was also a decrease from the baseline blink rate measured at the 90-minute time point, as has been described previously.[18,19] The monkey with preexisting facial nerve palsy exhibited a decrease in blink rate from baseline at the 45-minute postinjection time point. Furthermore, it exhibited an effect opposite that of the normal group at the 90-minute postinjection time point—that is, the blink rate increased.

Effect of Apomorphine on Down-Phase Blink Metrics

Normal Subjects. Apomorphine induced changes in normal animals are summarized in Table 2 and are described in the following sections.

Duration. Post hoc analysis revealed that a longer blink down-phase duration was recorded 45 minutes after the injection, compared with both baseline ($P < 0.0001$) and 90 minutes after the injection ($P < 0.0001$). The baseline and post–90-minute interval durations were not significantly different ($P < 0.2353$).

Amplitude. Apomorphine caused a statistically significant increase in blink down-phase amplitude at the 90-minute postinjection time point compared with both baseline ($P < 0.0043$) and the 45-minute postinjection time point ($P < 0.0039$). The 45-minute interval and baseline amplitudes were not significantly different ($P = 0.9757$).

Peak Velocity. Apomorphine caused a statistically significant increase in the peak velocity of the blink down-phase at the 90-minute postinjection time point, compared with baseline ($P = 0.0006$) and at the 45-minute postinjection time point ($P = 0.0073$). There was no significant difference in between baseline velocities and those recorded at 45 minutes postinjection ($P = 0.4213$).

Animal with Facial Nerve Palsy. One cynomolgus monkey in the study, which had been caught in the wild, was affected by facial nerve palsy (origin unknown). Data from this animal were analyzed separately from those of the rest of the study group. Changes in blink metrics for this monkey due to apomorphine are summarized in Table 3 and are described in the following sections. Note that in this animal only kinematics from the nonparetic side were discussed, because the paretic blinks were so small that analysis was considered to be unreliable.

Duration. The duration of the down-phase blinks in the right (nonparetic) eyelid of this monkey was much shorter (29.00 ms) than those of the normal monkeys (48.25 ms) These values increased in duration from baseline to the time point 45 minutes after injection and remained elevated at 90 minutes after injection.

Amplitude. At baseline, this monkey showed a decrease in blink amplitude in the nonparetic eyelid, (18.51 deg/sec) compared with normal monkeys (21.21 deg/sec). After administration of apomorphine, amplitude initially decreased, as measured at the 45-minute interval, but by the 90-minute interval,

TABLE 2. Summary of Down-Phase Kinematic Properties of Spontaneous Blinks in Normal Nonhuman Primates after Administration of Apomorphine

Recording Group	Duration (ms)	Amplitude (deg/sec)	Velocity (deg/sec^2)	MSS
Baseline	48.25 ± 2.26	21.21 ± 1.05	1013.00 ± 58.22	50.41
45 Minutes	74.39 ± 5.97	21.17 ± 0.66	1053.75 ± 40.34	48.10
90 Minutes	54.14 ± 3.04	24.71 ± 0.91	1190.96 ± 40.87	32.19

Mean ± SE of blink kinematics of each recording group is reported (except main sequence slope, MSS).

TABLE 3. Summary of Down-Phase Kinematic Properties of Spontaneous Blinks in a Nonhuman Primate with Facial Nerve Palsy after Administration of Apomorphine

Recording Group	Duration (ms)	Amplitude (deg/sec)	Velocity (deg/sec^2)	MSS
Right eyelid (nonparetic)				
Baseline	29.00 ± 1.46	18.51 ± 1.07	1283.66 ± 70.06	59.75
45 Minutes	53.75 ± 6.12	15.90 ± 1.78	867.67 ± 81.85	40.32
90 Minutes	52.60 ± 3.10	22.49 ± 1.60	1055.22 ± 56.23	31.31
Left eyelid (paretic)				
Baseline	36.10 ± 4.22	1.75 ± 4.22	98.14 ± 7.26	19.47
45 Minutes	88.10 ± 10.64	4.57 ± 0.74	131.84 ± 12.96	13.73
90 Minutes	44.80 ± 5.78	3.59 ± 1.27	147.06 ± 40.26	30.97

* Mean ± SE of blink kinematics of each recording group is reported (except main sequence slope, MSS).

the average amplitude had increased to a level similar to that in the normal monkeys.

Peak Velocity. The average peak blink velocity in the nonparetic eyelid at baseline (1283.66 deg/sec^2) was higher than that of the normal monkeys (1013.00 deg/sec^2). After administration of apomorphine, the peak velocity in this animal decreased below initial baseline, as well as the peak velocities recorded in the normal subjects. Peak velocity then rose, so that at the 90-minute interval velocity was similar to those of the normal animals.

Effect of Apomorphine on Main Sequence

As shown in Figure 1 and Table 2, in monkeys with normal facial musculature and normal blink rates, the down-phase main sequence slope decreased slightly at 45 minutes after injection (48.09) and then decreased even further 90 minutes after injection (32.19), compared with baseline values (50.41). However, this change was not statistically significant (P = 0.1308). Statistical information cannot be provided for a single animal, but it was interesting to find that the monkey with preexisting facial nerve palsy had a rather steep amplitude versus peak velocity relationship in the unaffected eyelid at baseline (59.75) and a very shallow relationship in the affected eye (19.47). Yet after apomorphine, the data showed normalization of the main-sequence slope for each eyelid at 90 minutes after injection (Fig. 2, Table 3).

DISCUSSION

To define the origin of BEB and subsequently devise better treatment protocols for this disease, a better understanding of the anatomic and neurochemical substrate for the disease is needed. There are several lines of evidence to suggest that dopaminergic pathways play a role in eyelid motor control and, more specifically, blepharospasm. Parkinson disease is the most thoroughly investigated movement disorder with a dopaminergic origin. These patients often demonstrate clinical reflex blepharospasm, and have reduced habituation of the R2 component of the blink reflex after supraorbital stimulation.[20] An animal model of blepharospasm has been produced by destruction of dopamine-containing neurons in rodents injected with 6-hydroxydopamine (6HD).[1] Although the site of the abnormality has not yet been found in human BEB,[21] a number of brain lesions have been identified as causing blepharospasm in selected cases, including lesions of the basal ganglia, upper brain stem and thalamus, and the pontine area.[22–29] Recently a positron emission tomography (PET) study in patients with BEB showed decreased [18F]-spiperone binding in the putamen, indicating a selective D2-like receptor abnormality.[30]

Our understanding of the neurophysiology of D1 and D2 receptor behavior in blink control or in motor control at large

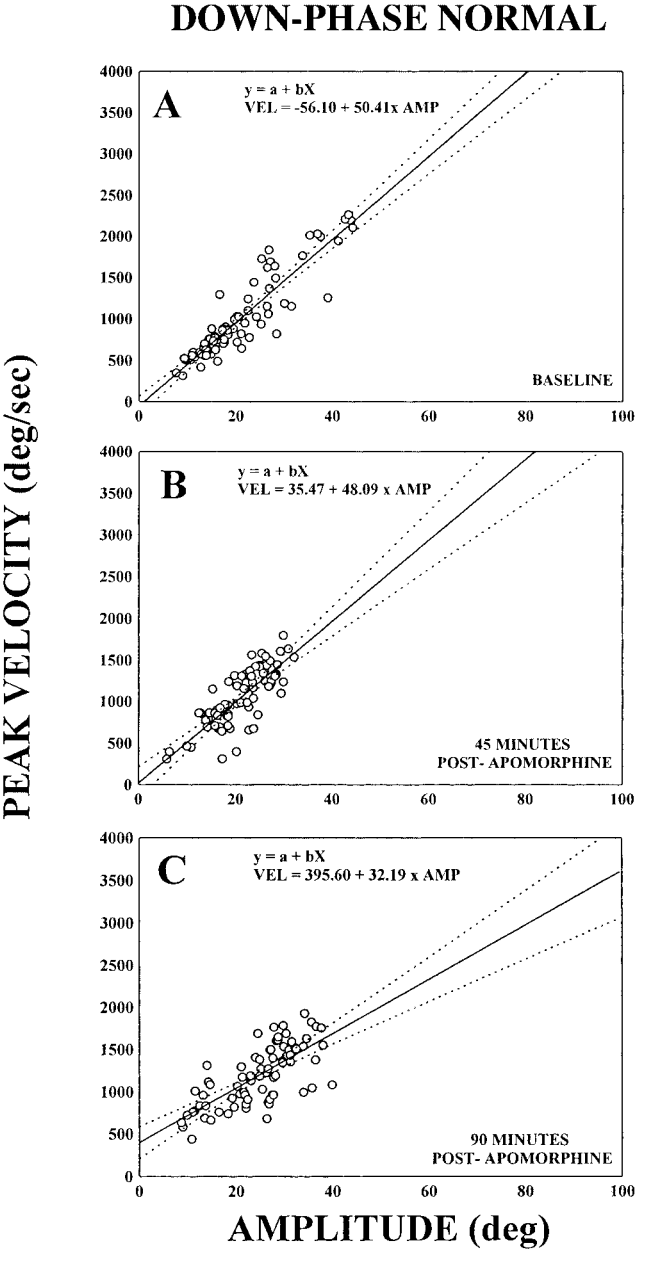

FIGURE 1. Monkeys with normal facial musculature and normal blink rates showed a predominant lowering of main-sequence slope from (**A**) baseline to (**B**) 45 minutes, to (**C**) 90 minutes after administration of apomorphine. *Dashed lines*: range containing 95% of the blinks for each group of normal monkeys; *solid line*: best fit linear regression line; n = 76 for each graph for normal monkeys.

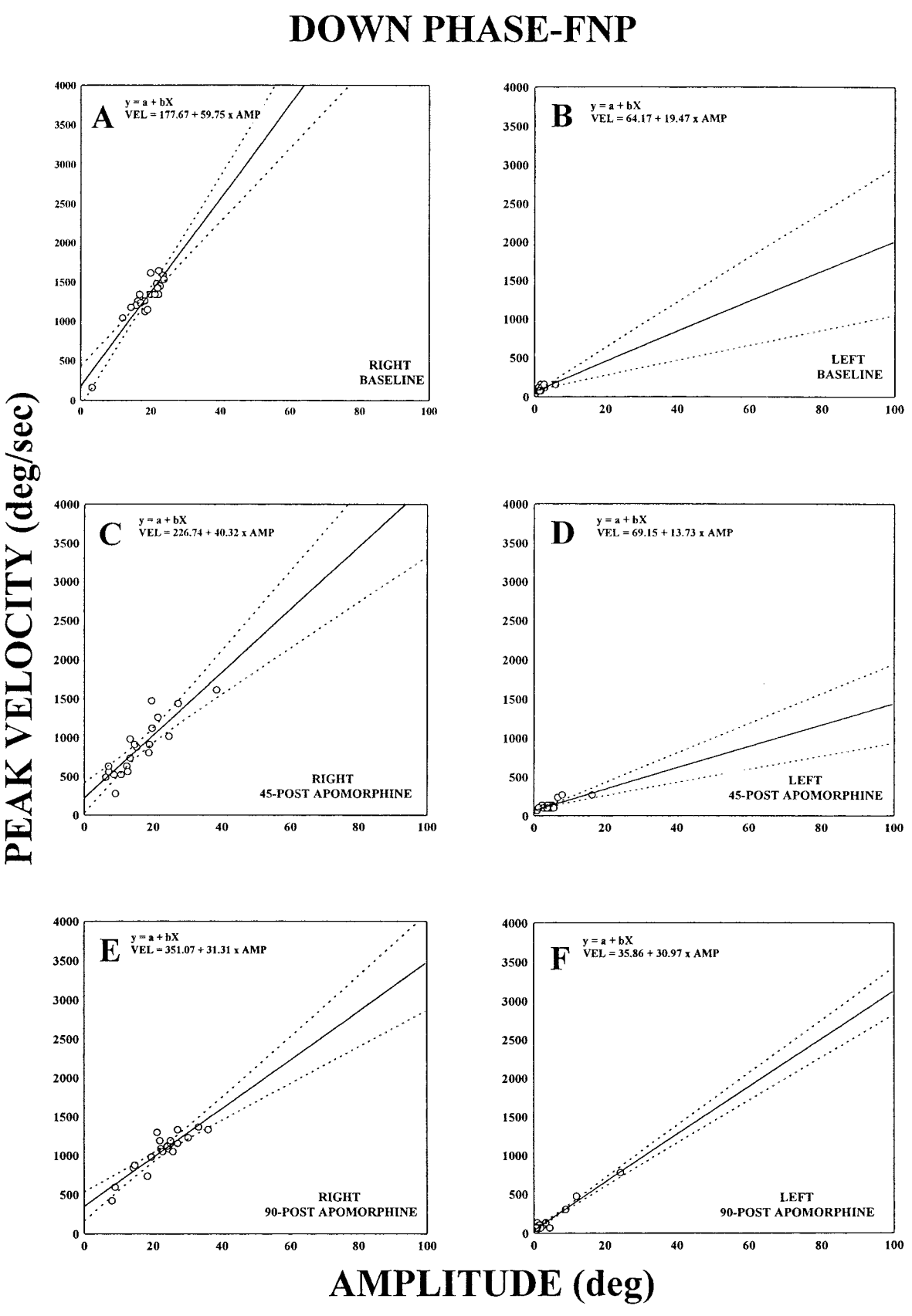

FIGURE 2. One monkey with preexisting facial nerve palsy (FNP) and steep amplitude versus peak velocity relationship in the nonparetic (right) eyelid at baseline (**A**, **B**) showed normalization of the main sequence slope in the right eye 45 minutes after administration of apomorphine (**C**, **D**) and in both eyes 90 minutes after injection (**E**, **F**). *Dashed lines*: range containing 95% of the blinks for each group of normal monkeys; *solid line*: best fit linear regression line; $n = 20$ for each graph for the facial nerve palsied animal.

is still evolving. Levodopa, the first-line drug in the management of Parkinson disease, does not normalize the blink reflex recovery cycle in blepharospasm,[2] and attempts to use levodopa as a therapeutic agent in BEB have been disappointing.[3,31] Apomorphine, a predominantly D2 agonist, restores a more normal blink reflex recovery cycle,[2] and has been described as being of benefit in some patients with BEB.[32] The coincidence that apomorphine acts to increase blink rate in normal and Parkinsonian monkeys[4,5] helps to normalize the blink reflex recovery cycle in humans with BEB,[2] suggests that the effects of dopaminergic manipulation on the neural control of blinking may be complex. It seems to shift the regulation one way for one parameter (increasing blink rate) and the other way for a different parameter (normalizing reflex recovery cycle).

We undertook the present study of the effects of apomorphine on a number of blink metrics, blink rate, and main sequence relationship, to establish a background for the study of D1and D2 drugs in pathologic conditions. Specifically, we quantified its effects in both NHPs and in an NHP with spontaneous blink upregulation due to unilateral facial nerve palsy. The latter was examined to provide preliminary data on the effects of apomorphine on blink plasticity. In previous investigations, we have shown a bilateral upregulation of the main sequence slope for blink down-phase in response to unilateral facial nerve palsy. Other investigators have shown increased reflex blink sensitivity in the form of decreased blink reflex recovery cycle to double stimulation.[15,33] These studies established the capability of blink modulatory mechanisms to adaptively respond to a peripheral need for greater eye closure, both in the form of decreased threshold for the firing of facial motor neurons, and also an increased number of neurons firing in a given blink.

Thus, these studies and the present data suggest that facial paralysis or paresis can lead to changes in the blinks of the uninvolved eyelid.[14,15] These findings may have relevance in BEB. We have also described an entity in humans termed Bell palsy–induced blepharospasm. Central inhibitory mechanisms normally serve to regulate both normal blink reflex excitability and the extent of any adaptive response. Consequently, most patients with Bell palsy do not have eyelid spasms because of the normalizing effect of these central inhibitory networks. However, a subclinical loss of inhibitory neurotransmitter may reduce the ability of susceptible individuals to respond appropriately to an upregulation stimulus, setting in motion the uncontrolled blink excitability and motoneuron recruitment that manifests as frequent blinking and eyelid spasms in blepharospasm.[14,15]

Clearly, basal ganglia circuits influence blinks, for treatment of monkeys with 1-methyl-1,4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin specific for dopaminergic neurons in the substantia nigra, dramatically lowers blink rate.[5] However, the specific mechanism by which apomorphine or other dopamine receptor agonists influence blink excitability and motoneuron recruitment is unclear. Classic basal ganglia modeling holds that a D2 agonist acting through the indirect pathway could normalize thalamic input to the cortex.[34] However, the idea of a differential D1 and D2 effect on the direct and indirect striatopallidal pathways, respectively, is not supported by new studies showing colocalization of D1 and D2 receptors on most striatal neurons.[35] Furthermore, both D1 and D2 receptor agonists produce a rapid and dose-dependent increase in blink rate when given to NHPs. This drug-induced change in blink rate is blocked by prior administration of the receptor type-specific antagonist.[4] As shown by the present findings, blink rate is only one of many blink kinematic phenomena that may be under neuromodulatory control by dopaminergic basal ganglia circuits.

In the present study we found small changes in spontaneous blink metrics in normal NHPs after the administration of apomorphine. Down-phase duration, amplitude, and peak velocity were all increased at either 45 or 90 minutes. The main sequence slope had a consistent, although not statistically significant, trend to lower values in normal animals. The combination of increase in the three metrics (duration, amplitude, and peak velocity) with nearly normal main sequence slope indicates that administration of apomorphine in normal animals induced a bias toward larger blinks that had relatively normal component relationships. In the past, we have found that disease states often affect these blink metrics differentially, producing a change in the main-sequence slope. Our results in the present study indicate that, in normal NHPs, the metrics are symmetrically shifted upward after administration of apomorphine, with no significant alteration in main sequence. These larger but normally proportioned blinks represent a relatively simple alteration in neural control, as might be seen in a hypervigilant state known to occur with administration of apomorphine in cynomolgus monkeys with MPTP-induced lesion[36] and in rodents.[37]

In the animal with facial nerve palsy and an upregulated main-sequence slope, a very different scenario was encountered. The baseline main sequence slope was dramatically steeper on the nonparetic side in this animal, as we have previously described in humans with facial nerve palsy.[13] In the nonparetic eye, effects after administration of apomorphine in this animal included, decreased main-sequence slope to normal levels at 45 and 90 minutes and decreased peak velocity. In the paretic eye, the slope and velocity increased toward baseline levels. We interpret these findings as a possible normalization of facial motoneuron recruitment in a situation of abnormally high activation. This finding could have some analogy to the normalization of reflex blink recovery cycle induced by apomorphine in patients with BEB. Although it is likely that distinct supranuclear centers subserve reflex and spontaneous blink, there may be shared basal ganglia, brain stem, and cerebellar modulatory pathways. It may be that these shared pathways are affected by apomorphine.

The effects observed in the monkey with facial nerve palsy must be considered preliminary results, because only a single animal was studied. Future investigations will be conducted to confirm or refute the finding and to investigate the effect of apomorphine administered before experimentally induced facial paralysis.

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