Midbrain 6-hydroxydopamine lesions modulate blink reflex excitability

Michele A. Basso¹, Robert E. Strecker¹,², Craig Evinger³

¹ Department of Psychology, SUNY at Stony Brook, Stony Brook, NY 11794-2500, USA
² Department of Psychiatry and Behavioral Sciences, SUNY at Stony Brook, Stony Brook, NY 11794-2500, USA
³ Department of Neurobiology Behavior and Ophthalmology, SUNY at Stony Brook, Stony Brook, NY 11794-2500, USA

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Abstract. The blink reflex abnormalities present in the 6 hydroxydopamine (6-OHDA) lesioned rat model of parkinsonism mimicked those of the human with Parkinson's disease. In alert rats, we monitored the long and short latency components of the orbicularis oculi electromyographic (OOemg) response evoked by electrical stimulation of the supraorbital branch of the trigeminal nerve (SO). Two paradigms, habituation and double pulse, provided a measure of blink reflex excitability. In normal rats, repeated stimulation of the SO produced habituation of the R2 component of the blink. In the double pulse paradigm, presentation of two identical SO stimuli resulted in a reduced or suppressed OOemg response to the second stimulus relative to the first. In rats with complete, unilateral lesions of midbrain dopamine neurons, repeated SO stimulation produced facilitation rather than habituation of the R2 component of the blink reflex. This facilitation occurred only with the eyelid contralateral to the lesion. In the double pulse paradigm, the lesioned rats showed increased excitability rather than suppression. This effect occurred bilaterally, although the increased excitability was strongest contralateral to the lesion. Rats with partial lesions of midbrain dopamine neurons exhibited qualitatively similar, but less pronounced blink reflex abnormalities. The R1 component of the blink reflex was unaffected by either the complete or partial lesions. Thus, modification of the blink reflex by 6-OHDA lesions provides a reproducible parkinsonian-like symptom which is amenable to investigations of increases in reflex excitability.

Key words: Basal ganglia – Parkinson's disease – Dopamine – Substantia nigra – Rat

Introduction

Stimulation of the supraorbital branch of the trigeminal nerve (SO) evokes two responses in the orbicularis oculi, the eye lid closing muscle. The first response (R1) has a short latency, and involves two or three synapses. The second response (R2) has a longer latency and involves several synapses in the spinal trigeminal nucleus and reticular formation (Ongerboer de Visser 1983). It is possible to measure the excitability in these two pathways quantitatively. Presenting two identical supraorbital nerve stimuli with a short interstimulus interval normally evokes a response to the second stimulus that is smaller than the response to the first. By comparing the magnitude of the second response to the magnitude of the first response, the double pulse paradigm provides a quantitative measure of excitability for both the long and short latency neural circuits. Another way to quantify blink circuit excitability is by determining the amount of habituation that occurs in response to repeated SO stimulation. The ease of measurement and quantification, as well as its reliability, make the blink reflex a powerful tool for investigating control of reflex function by central structures such as the basal ganglia. Moreover, the demonstration that changes in the blink reflex correlate with the degree of clinical disability in Parkinson's disease (Matsumoto et al. 1992) affirms the importance of blink reflex measurements.

Extrapyramidal disorders dramatically modify the blink reflex (Pearce et al. 1968; Messina et al. 1972; Kimura 1973a; Boiardi et al. 1975; Esteban and Gimenez-Roldan 1975; Caraceni et al. 1976; Esteban et al. 1981; Dengler et al. 1982; Beradelli et al. 1985; Bollen et al. 1986; Caliguri and Abbs 1987; Agostino et al. 1988). For example, the blink reflex is hypoexcitable (Caraceni et al. 1976) and habituation is more rapid than normal in Huntington's disease (Esteban and Gimenez-Roldan 1975). In contrast, the blink reflex is hyperexcitable and resistant to habituation in patients with Parkinson's disease. (Penders and Delwaide 1971; Kimuma 1973a; Kimura 1973b; Esteban and Gimenez-Roldan 1975; Kimura 1983). Since treatment of Parkinson's disease with L-DOPA reduces blink reflex abnormalities, dopamine appears to play a role in regulating blink reflex excitability (Messina et al. 1972).

Correspondence to: C. Evinger
Pharmacological manipulations support the hypothesis that dopaminergic mechanisms modulate blink reflex excitability. Chronic administration of haloperidol, a dopamine receptor blocker, increases the amplitude of the R1 component of the blink reflex (Raffaele et al. 1988). Apomorphine, a dopamine receptor agonist, reduces blink amplitude and increases the latency of the R2 component (Evinger et al. 1992). In addition, nicotine, which causes dopamine release in the striatum, increases R2 latency and decreases the amplitude of the R2 component of the blink reflex (Evinger 1989; Evinger et al. 1993).

The present investigation characterized blink reflex abnormalities in the 6-hydroxydopamine (6-OHDA) lesioned rat model of Parkinson's disease. A previous study showed a qualitative reduction in blink reflex habituation with 6-OHDA lesions (Shallert et al. 1989). Our study demonstrated the laterality of this effect, as well as provided a quantitative measure of the changes occurring in the long and short latency blink circuits. These data allow a direct comparison of the rat model with humans with Parkinson's disease and provide a quantitative model for the investigation of basal ganglia modulation of reflexes. We found that midbrain 6-OHDA lesions produced blink reflex abnormalities virtually identical to those of humans with Parkinson's disease. Thus, changes in the blink reflex provide a reproducible parkinsonian-like symptom in the rat model amenable to studies of the mechanisms producing excitability in basal ganglia disorders and testing the efficacy of new treatment paradigms.

**Materials and methods**

**Subjects**

Seven Sprague-Dawley rats weighing between 200 and 500 g served as subjects in this study. Five animals had complete, unilateral lesions and two had partial lesions of the substantia nigra (SN) and ventral tegmental area (VTA) resulting from 6-OHDA injection. All procedures in this experiment strictly adhered to federal, state, and university guidelines concerning the use of animals in research.

**Lesions**

Under general anesthesia (equithesin, 1 ml/100 g body wt) and using aseptic techniques, we produced unilateral destruction of the right ascending midbrain dopamine system with intracerebral injections of 6-OHDA (Brundin et al. 1988). We employed two stereotaxic injections of 6-OHDA (3 μg/μl in 20% ascorbic acid) into the right mesotelencephalic dopamine pathways. In the first, we injected 7.5 μg 6-OHDA into the substantia nigra pars compacta (SNc). The coordinates used were 4.4 mm caudal to bregma, 1.2 mm lateral to the midline, and 7.4 mm ventral to the dural surface with the toothbar set at 2.4 mm below the interaural line. In the second, we injected 6 μg 6-OHDA into the medial forebrain bundle. The coordinates for this injection were 4.0 mm caudal to bregma, 0.8 mm lateral to the midline, and 8.0 mm ventral to the dural surface with the toothbar set at 3.4 mm above the interaural line.

To enable the recording of blink reflex responses prior to 6-OHDA lesions, two rats were implanted with guide cannulae aimed at the SNc and the medial forebrain bundle. The cannulae were 26-gauge stainless steel tubing embedded in a dental acrylic base attached to the skull. After collecting prelesion data on reflex blinks, the rats were anesthetized and the 6-OHDA was injected through the cannulae. The cannulae were occluded with stylets before and after the lesion.

**Motor asymmetry**

At least ten days post lesion, all animals were tested for motor asymmetries by measuring amphetamine-induced rotation. Animals with unilateral 6-OHDA lesions exhibit rotational locomotion in response to amphetamine. Unilateral lesions of the ascending dopamine system create an imbalance which is amplified by injections of amphetamine. Hence, the increase in locomotion behavior that is seen with amphetamine is unidirectional, toward the side of the lesion (Ungerstedt and Arbuthnott 1970). Injections of d-amphetamine sulfate (5 mg/kg, i.p.) were administered and the animals were placed in rotation bowls. Beginning at 10 min post injection, the number of full 360° turns was counted for 1 min by a trained observer every 10 min of the 60 min test session. The net number of turns toward the lesion per minute for the entire test session was calculated by subtracting the number of contraversive turns from the number of ipsiversive turns.

**Chronic recording preparation**

Following a 3-day recovery from 6-OHDA lesions or cannula implants, rats were prepared for chronic recording of the blink reflex. Under general anesthesia (ketamine 90 mg/kg and xylazine 10 mg/kg) and using aseptic techniques, the SO was exposed and encased in Teflon tubing containing a pair of stimulating electrodes. Electromyographic recordings of orbicularis oculi muscle activity were made through a pair of Teflon-coated stainless steel wires [0.0045 in. (0.11 mm) coated diameter] implanted into the lateral margins of the eyelid. All wires were led subcutaneously to a dental acrylic base on the top of the skull, which was secured by three or four 3/16-in. (4.8-mm) self-tapping screws. The rats recovered from this surgery rapidly and exhibited normal eyelid movements.

For each animal, stimulating parameters were determined by adjusting the intensity and duration of the electrical pulse to the supraorbital nerve electrode and evaluating the EMG response of the orbicularis oculi muscle (OOemg). The stimulation parameters were adjusted to produce clear R1 and R2 components of the blink reflex. After initially setting the parameters, these were kept constant for each animal throughout all testing sessions. Typically, these stimulating intensities evoked an identical blink over the entire testing period, which usually was up to 4 weeks (Fig. 3). Many factors can influence the magnitude of the blink reflex. For example, increasing the level of excitement augments blink reflex amplitude, while warning that a blink-evoking stimulus will occur decreases the blink magnitude. We avoided such confounding factors by testing the rats under identical conditions every day. Since the rats underwent many days of testing, the laboratory was neither novel nor exciting. Since we had long intervals between SO stimuli (> 15 s), the rats never habituated to the SO stimulus, except with habituation testing. Moreover, long-term habituation of the blink reflex to SO stimulation does not occur even under optimal conditions (A. S. Powers and C. Evinger, unpublished observations). Thus, changes in blink reflex excitability observed in this experiment cannot be attributed to changes in the stimulation or recording conditions. For the seven rats, the SO stimulus intensities ranged from 1.5 to 3.0 mA and the stimulus durations ranged from 60 to 120 μs.

**Habituation and excitability paradigms**

**Habituation paradigm.** Two stimulation paradigms were used to quantify the excitability of the blink reflex. Habituation of the blink
reflex was tested by presenting animals with a series of five blocks of ten identical electric pulses to the supraorbital nerve. The interval between the pulses was either 1000 or 1500 ms. The interval between the blocks was either 1 or 2 min.

**Double pulse paradigm.** Blink reflex excitability was assessed by presenting two electric pulses, equal in intensity and duration, to the supraorbital branch of the trigeminal nerve. The interstimulus interval (ISI) was randomly varied among the intervals 50, 100, 200.
400, 600, and 800 ms. To avoid habituation, the time between stimulus pairs was variable around 15 s.

Tyrosine hydroxylase immunohistochemistry

Under deep anesthesia, animals were intracardially perfused with a warm solution of 6% dextran in phosphate buffer (PB), pH 7.4, followed by 1 l cold 4% paraformaldehyde solution (pH 7.4) in PB. Brains were post fixed in 4% paraformaldehyde for 2–4 h and then immersed in a 30% sucrose solution also in PB (pH 7.4) until the brains sank.

Frozen sections, 40 μm thick, were cut and preincubated in 1% normal goat serum diluted in 0.3% triton-X in PB (PBSTG). The tissue was rinsed in phosphate buffered saline and incubated overnight at 4°C in primary antibody against tyrosine hydroxylase raised in rabbit (Eugene Tech) and diluted 1: 5000 in PBSTG. After incubation, the tissue was rinsed in PBS and then incubated in secondary antibody, dilution 1: 200, for 2 h. The avidin-biotin method was used for visualization and diaminobenzidine was the chromagen.

Data acquisition and analysis

EMG signals were stored on a computer (3000 Hz, 12 bit A/D resolution) and analyzed off line using an interactive computer program that calculated amplitudes and latencies for the EMG records.

A statistical analysis of the habituation data was performed using two, 2 x 10 mixed factorial ANOVAs. One compared the habituation of the Ooemg contralateral to the lesion with the combination of the ipsilateral Ooemg and the prelesion Ooemg responses, while the other compared habituation of the ipsilateral Ooemg with the combination of the contralateral Ooemg and the prelesion Ooemg responses. This was the non-repeated measure. This method was dictated by the fact that normal, prelesion data were available for two animals. The comparison of interest in this analysis was between the contralateral side and the ipsilateral, prelesion combination because the effects of unilateral 6-OHDA lesions primarily affect the contralateral side of the body. Three animals contributed at least 15 blinks to each of the ten trials; a total of at least 150 blinks per animal.

A statistical analysis of the double pulse data was performed using a one-way, repeated measures ANOVA. The data were collapsed across ISI and the comparison was between the contralateral, ipsilateral, and prelesion Ooemg responses. We expected no significant effect of ISI; therefore, we chose to collapse across ISI in order to use all of the data in the analysis rather than data from a single ISI. This was done for both the R1 and the R2 components. Each of the four animals contributed at least 30 blinks for each of the six ISIs to the analysis, a total of at least 180 blinks per animal.

Results

Dopaminergic denervation was assessed behaviorally by amphetamine-induced rotation 10 days post lesion, and anatomically by tyrosine hydroxylase (TH) immunohistochemistry of the substantia nigra and ventral tegmental area. Based on histological and behavioral criteria, animals formed two distinct groups. The first group consisted of five animals which had nearly complete, unilateral dopamine lesions as evidenced by the presence of at least seven net rotations per minute induced by amphetamine and the near absence of TH-immunoreactive neurons on the lesioned side (Fig. 1). The mean number of rotations per minute for all the completely lesioned animals was 10.6 (standard deviation, SD, 4.29). The second group of two animals with incomplete lesions failed to rotate and had substantial numbers of TH-positive immunostained cells (Fig. 2) on the lesioned side of the midbrain. The total number of cells counted from three sections (420 μm apart) of an incompletely lesioned animal on the lesioned side was 1266. The total number of cells on the lesioned side of the same three sections was 965. Even though the incomplete lesions produced a less than 30% reduction in TH-positive midbrain cells, these modest lesions clearly modified the blink reflex.

Blink reflex

The blink reflex evoked by supraorbital stimulation consists of a short latency, R1 component followed by a
longer latency, R2 component of OOemg muscle activity ipsilateral to the stimulus (Fig. 3). The virtually identical OOemg response across days demonstrated the reliability of the blink reflex. The mean R1 latency was 5.46 ms (standard error, SE, 0.12; n = 45 blinks from three animals) and this component was normally larger than the R2 component. The average R2 latency was 16.63 ms (SE 0.40; n = 45 blinks from three animals). Since reflex blinks are not consensual in the rat (Evinger et al. 1993), it was possible to treat the two eyelids independently so that a single animal could serve as its own control. This was particularly useful when assessing reflex excitability and habituation in rats with unilateral brain manipulations as in the present study.

Completely lesioned animals

Blink reflex excitability and habituation were tested before lesions in two animals, and between 20 and 50 days post lesion. Complete lesions had a profound effect on both the habituation and the excitability of the blink reflex.

Habituation. The R1 component of the rat blink reflex normally exhibits only modest habituation. The lesion did not alter this pattern (Fig. 4A). There were no significant differences among the ipsilateral, contralateral, or prelesion R1 OOemg responses (ANOVA: $F_{1,19} = 1.761$, $P$ n.s. for the contralateral vs ipsilateral, prelesion combination; ANOVA: $F_{1,19} = 2.228$, $P$ n.s. for the ipsilateral vs the contralateral, prelesion combination).

The R2 component of the rat blink reflex normally habituates to approximately 50% of its first trial response by the third trial (Fig. 4B). Following the 6-OHDA lesion, reflex blinks elicited by SO stimulation ipsilateral to the lesion were not statistically different from prelesion blinks, while the blinks evoked by SO stimulation contralateral to the lesion showed marked facilitation. There was a significant difference between the contralateral R2 response and all other R2 responses, (ANOVA: $F_{1,18} = 5.498$, $P < 0.05$).

Double pulse. In normal rats, both components of the blink reflex to the second of two identical electrical stimuli of the supraorbital branch of the trigeminal nerve were less than the OOemg activity in response to the first stimulus (Fig. 3). The R1 component however, showed less suppression than the R2 component (Fig. 6, open bars). In contrast, rats with unilateral 6-OHDA lesions exhibited a marked increase of the R2 blink reflex excitability in response to SO stimulation on the side contralateral to the lesion (Figs. 5, 6B). The R2 component of the blink reflex evoked by stimulation of the SO ipsilateral to the lesion also showed a modest but clear increase in excitability (Fig. 6B, ANOVA: $F_{2,42} = 24.4$, $P < 0.001$). Post hoc $t$-tests showed that all comparisons - ipsilateral versus contralateral, ipsilateral versus normal and contralateral versus normal - differed significantly from each other ($P < 0.05$). Nevertheless, the lesion did not modify suppression of the R1 component of the blink reflex (Fig. 6A; ANOVA: $F_{2,58} = 0.8$ $P$ n.s.).

Incompletely lesioned animals

With less than a 30% reduction in TH neurons, two animals exhibited modifications of the blink reflex that were quantitatively less than those of the five animals with complete lesions, but were qualitatively similar. The R2
Fig. 4A, B. The results of habituation testing in completely lesioned rats. A Mean relative R1 response to ten consecutive stimuli. B Mean relative R2 response to the same 10 stimuli. The OOemg magnitude is normalized to the first trial. Filled triangles are responses from the side contralateral to the lesion, open triangles are responses from the side ipsilateral to the lesion, and open squares are responses from normal (prelesioned) animals. Each data point represents the mean of 45 blinks, at least 15 blinks from each of the three animals. Bars (sometimes partly or completely masked by the symbols) are standard errors of the mean.

Fig. 5. OOemg response to double pulse stimulation of the SO ipsilateral and contralateral to a complete 6-OHDA lesion. Each trace is the average of ten trials.
component of the blink reflex elicited by SO stimulation contralateral to the lesion failed to habituate (Fig. 7A). Likewise, the R2 component of the blink reflex exhibited increased excitability (Fig. 7B). This failure to habituate and the increase in excitability, never achieved the levels seen in completely lesioned animals (compare Fig. 7 and Fig. 5). As with the complete lesions, partial lesions of dopamine neurons in the midbrain did not affect the R1 component of the blink reflex.

Discussion

The failure of blink reflex habituation in the 6-OHDA lesioned rat model of Parkinson's disease mimicked that seen in humans with Parkinson's disease (Pearce et al. 1968; Messina et al. 1972; Kimura 1973a; Esteban and Gimenez-Roldan 1975; Dengler et al. 1982; Beradelli et al. 1985; Bollen et al. 1986; Caliguri and Abbas 1987). Rats with bilateral dopamine lesions have previously been shown to lack blink reflex habituation in response to glabellar taps (Shallert et al. 1989). We further demonstrated that, as is true for parkinsonian patients, only the long latency, R2 component of the OOemg failed to habituate and even exhibited facilitation in the completely lesioned rats. Moreover, this modification in blink reflex habituation occurred only on the side contralateral to the lesion. Even in the partially lesioned animals, the R2 component contralateral to the lesion failed to habituate.

6-OHDA lesions disrupted the suppression of the R2 OOemg response to the second of two identical electric pulses delivered to the supraorbital branch of the trigeminal nerve. Complete 6-OHDA lesions not only eliminated suppression but produced a 700% increase in R2 component excitability. While the excitability increase was largest contralateral to the lesion, the side ipsilateral also showed a clear increase. Parkinson's disease in humans does not usually cause excitability changes of this magnitude. For example, a 300 ms ISI results in 80% suppression of the R2 in normal humans but only a 20% sup-
pression in patients (Kimura 1973a). This is a 60% increase in excitability. Our partially lesioned rats exhibited excitability increases between 60% and 300%. These levels more closely approximate those seen in humans with Parkinson's disease. This observation confirms our other results indicating that the complete, unilateral dopamine lesion typically used in the rat model is actually an exaggeration of certain aspects of Parkinson's disease (Gray et al. 1991). The complete 6-OHDA lesion may correspond to patients with Parkinson's disease who are unresponsive to l-DOPA drug therapy, e.g., those with late-stage Parkinson's disease. Indeed, both contralateral forepaw deficits (Gray et al. 1991) and blink reflex excitability (Basso and Evinger, unpublished observations) seen in completely lesioned rats are unresponsive to drugs such as l-DOPA and apomorphine. The dopamine depletions in the partially lesioned rats, while enough to modify the blink reflex, were insufficient to produce amphetamine induced rotation. This result demonstrated that the changes in blink reflex habituation and excitability are significantly more sensitive measures of dopamine depletion than rotational behavior and thus provide a useful model that mimics a clinical symptom of Parkinson's disease.

The mechanisms through which dopamine and the basal ganglia modulate reflex excitability are unclear. The present study, as well as others demonstrate that reductions in basal ganglia DA cause an increase in excitability of the blink reflex (e.g., Boiardi et al. 1975; Raffaele et al. 1988) and many other cranial and spinal reflexes (e.g., Lee et al. 1983; Fuhr et al. 1992). In contrast, increases in basal ganglia DA cause a decrease in blink reflex excitability (Evinger et al. 1993). The present results suggest that dopaminergic systems within the basal ganglia influence the blink reflex by reducing the inhibitory drive normally acting on the blink reflex. Consistent with this idea, Parkinson's disease produces a decrease in spinal cutaneous reflex inhibition without altering excitatory components (Fuhr et al. 1992). It is possible that by suppressing reflexes in regions not involved or inappro-
priate for a planned voluntary movement, the basal gan-
glia ensure the appropriate execution of voluntary move-
ments (Mink and Thach 1991). For example, voluntary
arm movements decreases blink reflex excitability in
normal humans (Sanes 1984). In contrast, Parkinson's pa-
tients with reflex hyperexcitability have difficulty acquir-
ing visual targets with combined eye and head moves-
ments, because the vestibulococular reflex (VOR), which
is normally suppressed during this head rotation, moves
the eyes away from the target (White et al. 1988). Perhaps
the dopamine-deprived basal ganglia failed to suppress
the VOR during voluntary gaze shifts. Thus, investiga-
tions of the circuits and mechanisms through which the
basal ganglia modulate the blink reflex may shed light on
the organization of voluntary movement.

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