

Nigrostriatal Lesion and Dopamine Agonists Affect Firing Patterns of Rodent Entopeduncular Nucleus Neurons

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Ruskin, David N., Debra A. Bergstrom, and Judith R. Walters. Nigrostriatal lesion and dopamine agonists affect firing patterns of rodent entopeduncular nucleus neurons. *J Neurophysiol* 88: 487–496, 2002; 10.1152/jn.00844.2001. Altered activity of the entopeduncular nucleus, the rodent homologue of the globus pallidus internal segment in primates, is thought to mediate behavioral consequences of midbrain dopamine depletion in rodents. Few studies, however, have examined dopaminergic modulation of spiking activity in this nucleus. This study characterizes changes in entopeduncular neuronal activity after nigrostriatal dopaminergic lesion and the effects of systemic treatment with selective D₁ (SKF 38393) and D₂ (quinpirole) agonists in lesioned rats. Extracellular single-unit recordings were performed in awake immobilized rats, either in neurologically intact animals ($n = 42$) or in animals that had received unilateral 6-hydroxydopamine infusion into the medial forebrain bundle several weeks previously ($n = 35$). Nigrostriatal lesion altered baseline activity of entopeduncular neurons in several ways. Interspike interval distributions had significantly decreased modes and significantly increased coefficient of variation, skewness and kurtosis; yet interspike interval mean (the inverse of firing rate) was not affected. Also, spectral analysis of autocorrelograms indicated that lesion significantly reduced the incidence of regular-spiking neurons and increased the incidence of neurons with 4–18 Hz oscillations. Dopamine agonist treatment reversed some lesion-induced effects: quinpirole reversed changes in interspike interval distribution mode and coefficient of variation, while combined quinpirole and SKF 38393 blocked the appearance of 4–18 Hz oscillations. However, no agonist treatment normalized all aspects of entopeduncular activity. Additionally, inhibition of firing rates by D₁ or combined D₁/D₂ receptor activation indicated that dopamine agonists affected the overall level of entopeduncular activity in a manner similar to that found in the substantia nigra pars reticulata and globus pallidus internal segment after dopamine neuron lesion. These data demonstrate that lesion of the nigrostriatal tract leads to modifications of several aspects of firing pattern in the rodent entopeduncular nucleus and so expand on similar findings in the rodent substantia nigra pars reticulata and in the globus pallidus internal segment in humans and nonhuman primates. The results support the view that dysfunction in the basal ganglia after midbrain dopamine neuron loss relates more consistently to abnormal activity patterns than to net changes in firing rate in the basal ganglia output nuclei, while overall decreases in firing rate in these structures may play a more important role in adverse motor reactions to dopamine agonist treatments.

INTRODUCTION

Idiopathic Parkinson's disease is a condition of unknown etiology involving loss of the dopamine (DA) neurons of the

midbrain, which richly innervate the striatum, a major component of the basal ganglia. Loss of these midbrain neurons leads to serious deficits in motor function, including bradykinesia, rigidity, and limb tremor. Although treatable in initial stages with systemic DA replacement therapy, such treatments lose their efficacy over time and eventually induce involuntary dyskinesias. It is thought that motor dysfunctions associated with both parkinsonism and therapy-induced dyskinesias relate to abnormal basal ganglia neuronal activity, particularly in the basal ganglia output structures: the globus pallidus internal segment (GPi) of primates [and its rodent homologue, the entopeduncular nucleus (EPN)] and the substantia nigra pars reticulata (SNpr). Electrophysiological studies have provided support for dysfunctional activity in many basal ganglia nuclei after DA neuron loss. While some of these studies have found DA cell-loss-induced changes in firing rate, a somewhat more consistent finding in Parkinson's disease patients and in primate parkinsonian models is the presence of abnormal firing patterns. These firing patterns can involve such features as increased bursting (Filion 1979; Miller and DeLong 1987), shifts in interspike interval (ISI) histogram shape (Wichmann et al. 1999), and abnormal oscillatory activity (Bergman et al. 1994; Filion 1979). This latter phenomenon has been relatable to limb tremor in some studies (Bergman et al. 1994; Hurtado et al. 1999; Hutchison et al. 1997b; Raz et al. 2000). These observations (reviewed in Obeso et al. 2000; Vitek and Giroux 2000; Walters et al. 2001) give rise to the consideration that changes in firing pattern, rather than tonic firing rate, might be of primary importance in mediating the functional effects of DA on forebrain activity and motor behavior.

The involvement of the GPi in Parkinson's disease is supported by the successful alleviation of both bradykinesia and DA replacement-therapy-induced dyskinesia by lesioning or high-frequency electrical stimulation of this nucleus (Olanow et al. 2000). Also, anatomical evidence suggests that the GPi/EPN is likely to be of particular interest for investigation of the central substrates of parkinsonian symptoms. For instance, the GPi/EPN appears to relate to limb movement, while the SNpr relates to head and eye movement (DeLong and Georgopolous 1979), and it been proposed that the SNpr is more associative, while the GPi/EPN is more purely motor (Joel and Weiner 1994). The rodent model of Parkinson's disease is a practical

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vehicle for further and more extensive investigation of the effects of DA cell loss on firing pattern in the GPi/EPN and the ability of DA agonist treatment to reverse these changes. Electrophysiological studies of the effects of DA depletion in rodents, however, have rarely examined the EPN (Robledo and Feger 1991).

The present study reports results from recordings of EPN neurons in neurologically intact rats and in rats with lesions of the nigrostriatal DAergic pathway to assess the effects of DA depletion on EPN neuron firing rate and several aspects of firing pattern, including ISI histogram characteristics, oscillatory activity in several frequency ranges, and bursting. In addition, this study characterizes the effects of agonists selective for the D₁ and D₂ DA receptor subtypes (alone and in combination) on EPN activity in DA-depleted rodents.

METHODS

Nigrostriatal lesions

Male Sprague-Dawley rats (Taconic Farms) weighing 200–275 g at the time of surgery were used. Rats were anesthetized with chloral hydrate (400 mg/kg ip) and placed in a stereotaxic apparatus (Kopf) with the incisor bar set at –3.5 mm. A hole was drilled in the skull above the appropriate coordinates, and a 25-gauge injection cannula lowered to the left medial forebrain bundle: 4.4 mm rostral to the lambdoid suture, 1.2 mm lateral to the sagittal suture, and 8.3 mm ventral to the dura mater. Six micrograms of 6-OHDA HBr (weighed as the salt; Research Biochemicals) in 3 μ l of 0.9% saline containing 0.1% ascorbic acid were infused via the cannula over 3 min. The cannula was left in place for 5 min after the infusion. Rats were injected with desmethylmipramine (15 mg/kg ip; Research Biochemicals) 30 min prior to the intracerebral infusion to protect noradrenergic neurons. The diet of lesioned rats was supplemented with fruit as needed to maintain weight. Three to 4 wk after surgery, rats were screened for lesion efficacy by injection of apomorphine (0.05 mg/kg sc). Only rats that strongly rotated 15–25 min after apomorphine injection (minimum of 5 rpm) were used for electrophysiology. Rotation after treatment with this dose of apomorphine indicates DA loss in the striatum of at least 90% (Hudson et al. 1993) and our high-performance liquid chromatography (HPLC) studies demonstrated that striatal DA levels on the lesioned side in rotation-screened animals were 1–3% of those on the unlesioned side (Carlson et al. 1990). EPN recordings began 1 wk after screening.

Electrophysiology

Extracellular single-unit activity was recorded in the rodent EPN in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health) and with the approval of the National Institute of Neurological Disorders and Stroke Animal Care and Use Committee. In previous studies of basal ganglia activity, we have found that the effects of DA agonists on spiking activity were greatly reduced by general anesthesia (Allers et al. 2000; Bergstrom et al. 1984; Kreiss et al. 1996; Ruskin et al. 1999a, 2001). In the present study, therefore, recordings were performed in awake, immobilized rats as previously described (Ruskin et al. 1999a). Briefly, all surgical procedures (tracheotomy, scalp incision, skull drilling) were performed with rats under halothane anesthesia. To prevent discomfort, all surgical sites and pressure points were infiltrated with the long-acting local anesthetic mepivacaine, and ear bar tips and the exteriors of tracheal cannulas were coated with 2% lidocaine gel. Corneal drying was prevented with LacriLube. Rats were tracheotomized, and a 13- or 14-gauge cannula was inserted into the trachea. Rats were placed into a stereotaxic apparatus, the scalp deflected, and a hole was drilled in the skull over the appropriate area. After surgical procedures

were finished, halothane anesthesia was discontinued, rats were paralyzed with gallamine triethiodide (16 mg/kg iv) injected through a tail vein, and artificial respiration immediately begun via the tracheal cannula with a rodent ventilator (model 683, Harvard Apparatus). Artificial respiration rates were adjusted to maintain exhaled CO₂ between 3.4 and 4.5%. Supplements of gallamine were given as needed. Body temperature was maintained at 36–38° with a heating pad. Studies in a parallel group of paralyzed rats demonstrated that heart rate and blood pressure were within normal physiological ranges, suggesting that the immobilized, artificially ventilated state did not produce significant amounts of stress (unpublished observations).

Glass microelectrodes were filled with 2 M NaCl solution containing 1% Pontamine sky blue, broken back under microscopic control until tip resistance measured between 2.5 and 6 M Ω , and lowered stereotaxically to the following coordinates (in mm): 2.6–2.8 posterior to the coronal suture, 2.6–2.8 lateral from the sagittal suture, and 6.8–8.0 ventral to the dura mater. All recordings were made in the left hemisphere, which was the lesioned hemisphere in lesioned rats. Fine vertical control of microelectrode placement was achieved with micromanipulators (MO-8, Narashige). Single-unit activity was amplified (Axoclamp 2A, used in bridge mode), band-pass filtered between 250 and 5,000 Hz, and monitored on-line with a digital oscilloscope (Hewlett-Packard) and audio monitor (Grass). Spikes were identified with a voltage/window discriminator and recorded by Spike2 software (Cambridge Electronic Design). All recorded EPN units had biphasic (\pm) or triphasic ($\pm/+$) waveforms. Five to ten min of baseline activity were recorded before DA agonists or vehicle (distilled water) were injected via a tail vein. After injection, units were recorded for at least 10 min. For combined agonist treatment, D₁ agonist was injected 10 min after D₂ agonist. One unit was recorded per rat. DA agonists were obtained from Research Biochemicals. These drugs were dissolved in distilled water and injected at 0.5 ml/kg. After data collection, Pontamine sky blue was iontophoresed by 15 min of constant current injection (–20 μ V). Brains were immersion-fixed in formalin at least 24 h. Fifty-micrometer sections were taken on a freezing microtome, and mounted on subbed slides for histological examination. Only units confirmed as being within the EPN by location of dye deposit and/or electrolytic lesion were analyzed.

Data analysis

For analysis of ISI characteristics, ISI histograms were constructed from baseline epochs. Histograms had 2 ms bins and extended to intervals of 600 ms. No data segment used for ISI analysis or burst analysis had less than 2,000 spikes. Characteristics of ISI histograms (mean, median, mode, coefficient of variation, skewness, kurtosis) did not have normal population distributions in most cases and so were analyzed with nonparametric Mann-Whitney *U* or Wilcoxon tests. Mode was defined as the ISI value corresponding to the peak of the ISI histogram. Skewness provided a measure of the symmetry of the distribution of the ISIs around the mean. Kurtosis reflected the peakedness of the ISI histogram. Population data for ISI distribution characteristics were illustrated with median/box-and-whisker plots. Bursting was analyzed with a method that compares the shape of the discharge density histogram (constructed with intervals equal to the mean ISI) to a Poisson distribution with a mean of one (Kaneoke and Vitek 1996); firing pattern was considered to be bursty if the histogram significantly differed from the Poisson distribution and bursts occurred at a rate of at least two per 1,000 spikes.

Oscillatory characteristics of spiking activity were examined with the Lomb periodogram (Kaneoke and Vitek 1996). This method provides a measure of statistical significance for spectral features: spectra are tested against the null hypothesis that binned spiking activity had a random Gaussian distribution. Spectra of random Gaussian signals are characterized by an exponential distribution of spectral power (Horne and Baliunas 1986; Scargle 1982), i.e., the

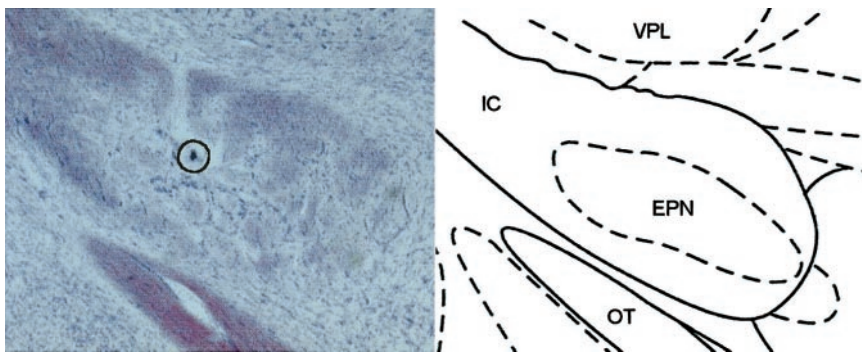


FIG. 1. Representative example of postrecording histology. The section was treated with Cresyl Violet. The stained somata of entopeduncular nucleus (EPN) neurons are delineated by background staining of the internal capsule (IC). Pontamine sky blue iontophoresed from the recording electrode is visible as an opaque spot (circled, left) in the dorsal EPN. OT, optic tract; VPL, ventroposterolateral nucleus of the thalamus. Adapted from Paxinos and Watson (1997).

probability of finding points in the spectrum decreases exponentially along the power axis. Spectra derived from data were compared with this exponential distribution, and the null hypothesis was rejected at the $P = 0.01$ level. The Lomb periodogram specifically analyzes signals for periodic oscillations; fluctuations that are not sufficiently periodic (i.e., regular) do not produce significant peaks in a Lomb spectrum. Only significant spectral peaks were considered in the present study. Oscillations in the 4–100 Hz range were characterized with the Lomb periodogram performed on autocorrelograms (3-ms bins, 750-ms lag, generated from 180 s of data). Neurons were classified as “regular spiking” during a given epoch if the strongest spectral peak in the 4–100 Hz range was within 25% of the mean firing frequency within that epoch. The occurrence of spectral peaks between 4 and 18 Hz was also examined, based on prior studies indicating increased activity in this range after midbrain DA neuron lesion (see DISCUSSION). A slower range of oscillatory activity in the basal ganglia of awake rats correlated with ventilation (Allers et al. 2000; Ruskin et al. 1999a, 2001). This type of oscillation was characterized by examining the 0.5–2.0 Hz frequency range with the Lomb periodogram performed on binned spiking activity (200-ms bins, 180 s of data) (Ruskin et al. 1999c). Treatment-induced changes in the incidence of various activity patterns were analyzed with Fisher exact tests.

RESULTS

Single units that were histologically verified after recording as being in the EPN were typically identifiable during the recording sessions by several criteria. These units were located ventral to the characteristically bursty neurons of the ventral thalamic nuclei and thalamic reticular nucleus. In each electrode passage, after passing the most ventral thalamic unit on that particular track, 100–200 μm of silence would be encountered as the electrode passed through the dorsal aspect of the internal capsule until tonically active units in the EPN were encountered. A typical electrode placement is illustrated in Fig. 1. EPN neurons had high baseline firing rates (rates less than 10 Hz were uncommon) and were judged with the use of the audio monitor as usually being much less bursty than the more dorsal thalamic neurons. EPN neurons also had short spike waveform durations, which were equivalent in intact and nigrostriatal-lesioned animals: 0.83 ± 0.03 and 0.82 ± 0.03 (SE) ms, respectively; waveform duration was measured from the beginning of the initial positive wave to the end of the following negative wave.

Effects of nigrostriatal lesion on tonic activity

Baseline firing rates of EPN neurons had similar means in intact rats [29.0 ± 1.6 Hz, $n = 42$] and in nigrostriatal-lesioned rats, ipsilateral to the lesion (29.7 ± 2.2 Hz, $n = 35$). However,

detailed analyses of the properties of ISIs from both conditions showed that while nigrostriatal lesion did not significantly alter ISI mean or median, this treatment did significantly change the shape of baseline ISI histograms (Fig. 2). ISI histograms after lesion had a relative increase in the number of short ISIs, and an emergence of a rightward tail of long ISIs, which were relatively rare in intact animals (Fig. 2A). These two effects combined to produce a decrease in ISI mode, an increase in the ISI coefficient of variation (CV), and increases in skewness (indicating a more asymmetrical ISI distribution) and kurtosis

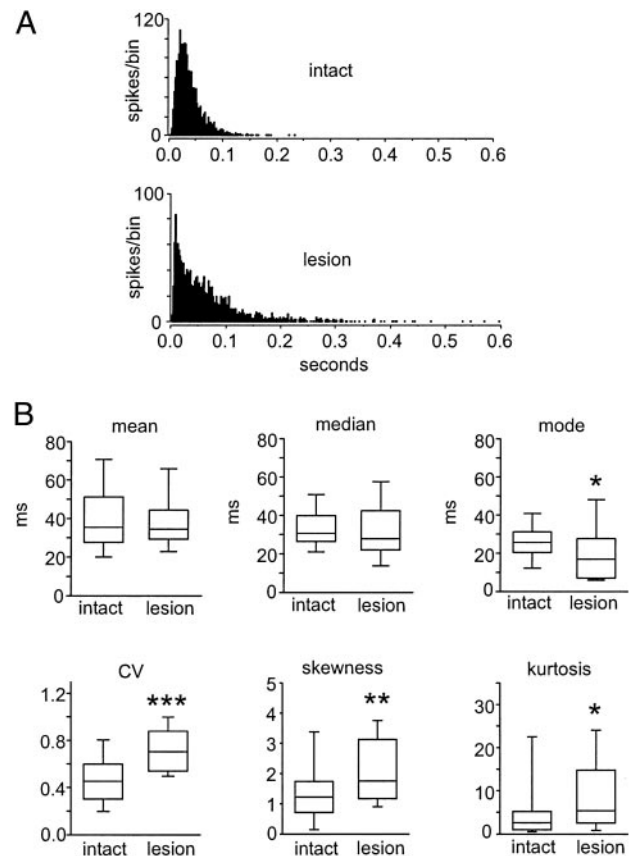


FIG. 2. Effects of nigrostriatal lesion on EPN interspike interval distributions. A: interspike interval (ISI) histograms of typical neurons from neurologically intact rats and from nigrostriatal-lesioned rats. Note the reduced mode and increased number of longer intervals of the lesioned-hemisphere unit. B: population statistics of lesion effect on ISI distributions. Center line indicates the median, box indicates the 25–75% range, whiskers indicate the 10–90% range. The lesion-induced increases in skewness and kurtosis indicate a leftward shift of the distribution peak and an increased sharpness of that peak, respectively. $n = 42$ intact rats; $n = 35$ lesioned rats. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

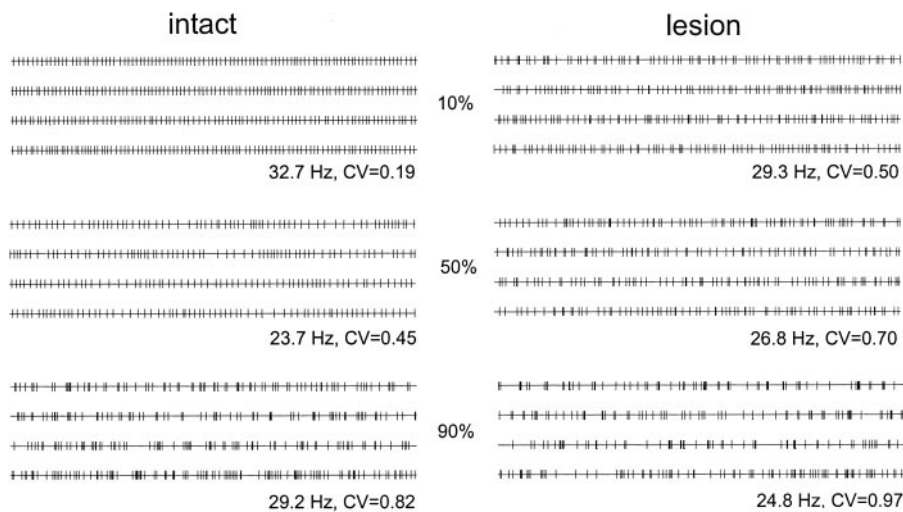


FIG. 3. Examples of EPN spiking activity from intact and nigrostriatal-lesioned animals. Rasters are 3 s wide (12 s total length) and are organized *top-to-bottom* according to increasing percentile rank for ISI coefficient of variation (CV). Firing rate and CV are given *below* each raster. CV is higher in neurons from lesioned animals at each percentile rank. Of these examples, spectral analysis of autocorrelograms indicated that the top “intact” example met the criterion for regular spiking (with a 32.8 Hz oscillation), while oscillations in the 4–18 Hz band (in this instance, a 10.8 Hz oscillation) were found in the bottom “lesion” example.

(indicating a more sharp-peaked ISI distribution; Fig. 2B). Spike rasters in Fig. 3 illustrate the increase in ISI CV after lesion. This increase in ISI CV did not, however, indicate an increase in bursting, which was rarely found in intact or lesion baselines (Table 1).

Effects of nigrostriatal lesion on firing pattern were also evident when autocorrelograms of baseline activity were examined for significant oscillations in several frequency ranges. In intact rats, a substantial proportion (24%) of neurons had oscillatory activity at a frequency near the mean firing frequency, indicating regular spiking (Table 1, Fig. 4). The mean frequency of these oscillations was 28.0 ± 3.4 Hz. As expected, the ISI distributions of regular-spiking neurons had significantly lower CV and skewness than other neurons (Fig. 5; see also example in Fig. 3). After nigrostriatal lesion, regular spiking was found in only one neuron (Table 1). Moreover, 29% of EPN neurons after lesion demonstrated oscillations in the 4–18 Hz range (average frequency: 13.0 ± 1.1 Hz), while only 7% of neurons from neurologically intact rats had oscillations in this range (Table 1, Fig. 4). Oscillatory activity within the 4–18 Hz range was only occasionally a result of regular-spiking activity of neurons that were firing within this range; rather, the net firing rate of the unit was usually well above 18 Hz (Fig. 4). Some EPN neurons had oscillations in the 0.5–2.0 Hz range that appear to be related to ventilation (Allers et al. 2000; Ruskin et al. 1999a, 2001). These oscillations were present in baseline of 21% of neurons in intact rats, and had a mean frequency of 1.13 ± 0.11 Hz, corresponding

closely to the rate of ventilation. Ipsilateral to nigrostriatal lesion, no neurons had baseline oscillations in this 0.5–2.0 Hz range, a significant decrease in incidence ($P < 0.01$).

Dopamine agonist effects in lesioned rats

DA agonist treatments reversed some effects of nigrostriatal lesion on EPN firing pattern. The D_2 agonist quinpirole and the D_1 agonist SKF 38393 were administered at doses previously shown to produce contraversive rotation when injected intravenously in freely moving nigrostriatal-lesioned rats (Ruskin et al. 1999b, and unpublished data) (for instance, quinpirole at 0.10 mg/kg intravenous produced a mean of 59 contraversive rotations over the 20 min after injection). Quinpirole (tested at 0.10 and 0.26 mg/kg) failed to consistently affect ISI mean or median (Fig. 6A) but did significantly reverse two effects of nigrostriatal lesion, increasing ISI mode and decreasing ISI CV (Fig. 6A). These effects are visible in the two representative examples in Fig. 6B: mode shifts rightward after quinpirole injection, and there is a loss of long ISIs (contributing to a reduction in CV).

SKF 38393 at a dose of 3.4 mg/kg (but not at 1.3 mg/kg) significantly increased ISI mean, median, and mode without affecting ISI CV (Fig. 6A). These changes in ISI mean, median, and mode are indicative of the overall reduction in spiking activity of EPN neurons after this dose of SKF 38393.

Two agonist combinations were also tested. Quinpirole at 0.10 or 0.26 mg/kg was combined with the low (1.3 mg/kg)

TABLE 1. The incidence of baseline spiking patterns of entopeduncular nucleus neurons

| | Intact Basal, % | Lesion Basal, % | Lesion Vehicle, % | Lesion SKF 38393, % | Lesion Quinpirole, % | Lesion Quinpirole + SKF 38393, % |
|---------------------|-----------------|-----------------|-------------------|---------------------|----------------------|----------------------------------|
| Regular spiking | 24 | 3** | 0 | 0 | 0 | 0 |
| 4–18 Hz oscillation | 7 | 29* | 43 | 14 | 13 | 0† |
| Bursting | 7 | 11 | 0 | 7 | 13 | 38† |
| <i>n</i> | 42 | 35 | 7 | 14 | 15 | 13 |

Percentages of neurons in various conditions demonstrating regular spiking, 4–18 Hz oscillations or bursting. * $P < 0.05$, ** $P < 0.02$ intact basal versus lesion basal; † $P < 0.05$ lesion basal versus lesion agonist (Fisher tests). Two doses were tested for each agonist or agonist combination; results for the above parameters did not differ with differing doses and so the groups are combined for simplicity (SKF 38393: 1.3 or 3.4 mg/kg; quinpirole: 0.1 or 0.26 mg/kg; quinpirole + SKF 38393: 0.1 mg/kg + 1.3 mg/kg, or 0.26 mg/kg + 1.3 mg/kg). Bursting neurons are defined by at least 2 bursts per 1,000 spikes. With a more stringent definition (6 or more bursts per 1,000 spikes), the incidence of bursting neurons remained similar (for example: 5% intact basal, 9% lesion basal). Neurons that were completely silenced after DA agonist injection (1 after SKF 38393, 3.4 mg/kg; 2 after quinpirole + SKF 38393, 0.1 mg/kg + 1.3 mg/kg) are not included in this analysis.

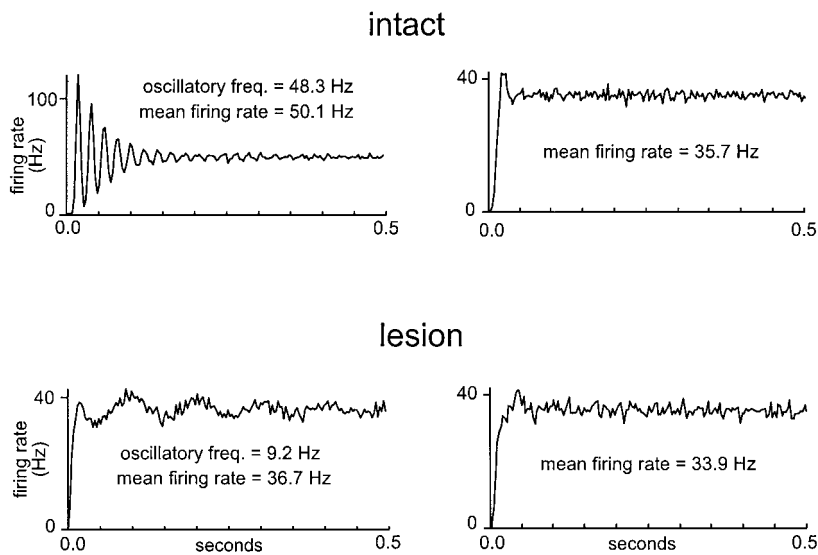


FIG. 4. Illustrations of 2 types of EPN oscillatory spiking patterns. The presence of statistically significant oscillations was determined by spectral analysis of the autocorrelograms. *Top*: data from intact animals. Example autocorrelograms illustrate the presence (*left*) or absence (*right*) of regular spiking. Note the similarity of the firing frequency and oscillatory frequency in the example at *left*. This type of activity was rarely found after nigrostriatal lesion. *Bottom*: data from nigrostriatal-lesioned animals. Example autocorrelograms illustrate the presence (*left*) or absence (*right*) of 4–18 Hz oscillations. At *left*, note that the oscillatory frequency (9 Hz) is well below the firing frequency. This type of activity was found most commonly in lesioned animals.

dose of SKF 38393. The combined agonists affected ISI histogram characteristics similarly to SKF 38393 at 3.4 mg/kg, causing increases in ISI mean, median, and mode concomitant with an overall reduction in spiking activity (Fig. 6A). ISI CV was not significantly changed. Combined quinpirole + SKF 38393 also was the only treatment to significantly change the incidence of bursting (Table 1). No DA agonist treatment (combined or alone) significantly changed ISI skewness or kurtosis (not shown).

The increased incidence of 4–18 Hz oscillations in nigrostriatal-lesion baseline activity was reversed only by the combination of quinpirole and SKF 38393 (Table 1), while the lesion-induced decrease in regular-spiking was not reversed by

any DA agonist treatment. Although not found in baseline activity of any neuron in lesioned rats, ventilator-related (0.5–2.0 Hz) oscillations appeared in three neurons after DA agonist injection (mean frequency: 1.12 ± 0.02 Hz). The agonists injected in these cases were SKF 38393 (3.4 mg/kg, 1 neuron) and SKF 38393 + quinpirole (1.3 mg/kg + 0.10 mg/kg, 2 neurons).

Vehicle injection had no significant effect on ISI histogram characteristics (Fig. 6A) or the incidence of any measured oscillatory activity (Table 1).

DISCUSSION

The present study characterized a number of novel effects of both 6-hydroxydopamine-induced nigrostriatal lesion and systemic DA agonist injection on EPN activity. Single-unit recordings from EPN neurons showed that several parameters of the firing pattern of EPN neurons are altered following dopamine cell lesion, in the absence of any change in firing rate. Subsequent injection of D₁ and D₂ DA agonists produced further alterations in EPN firing pattern and/or firing rate, according to drug and dose. DA agonist treatments had a normalizing effect on some aspects of abnormal EPN firing patterns, although none produced complete normalization. Also, some induced additional abnormalities, such as the overall rate inhibition and emergence of bursting after combined D₁/D₂ agonist injection. In conjunction with rodent SNpr studies, which have consistently found that nigrostriatal lesion altered firing pattern but produced inconsistent results regarding firing rate, these data suggest that the behavioral consequences of nigrostriatal lesion are caused by abnormalities in firing pattern rather than simple overactivity in the basal ganglia output nuclei. Recent studies have also demonstrated altered baseline EPN activity in another movement disorder, dystonia (Bennay et al. 2001; Gernert et al. 2000).

ISI distribution characteristics

Nigrostriatal lesion significantly changed distribution of ISIs in baseline, decreasing ISI mode and increasing ISI variability,

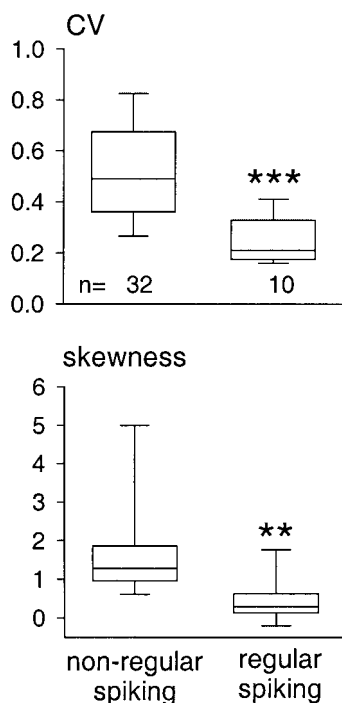


FIG. 5. Regular-spiking neurons (found almost exclusively in neurologically intact rats) had lower ISI CV and skewness than other neurons, indicating relatively tight and Gaussian-shaped ISI distribution. All data from baseline epochs in intact rats. Conventions as in Fig. 2.

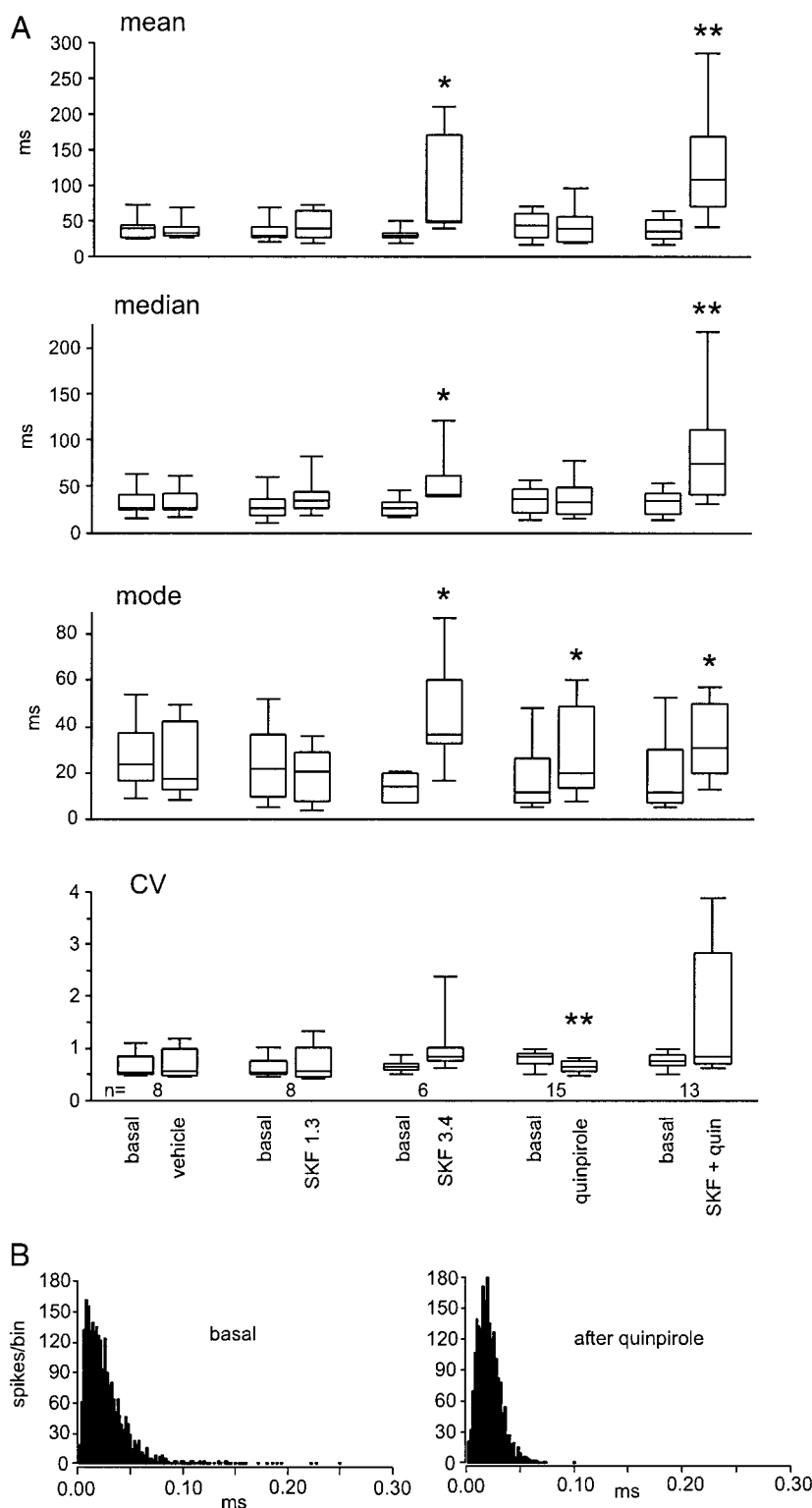


FIG. 6. Effects of DA agonist treatment on ISI distributions in nigrostriatal-lesioned rats. *A*: postagonist ISI characteristics are shown with the baseline ISI characteristics for those same neurons; statistics are paired comparisons. ISI effects did not differ between quinpirole at 0.10 or 0.26 mg/kg or between either of these doses combined with 1.3 mg/kg SKF 38393; these groups are therefore combined. As explained in the legend to Table 1, units that were completely silenced after DA agonist injection are not included in this analysis. Conventions as in Fig. 2. *B*: ISI histograms from a neuron before and after quinpirole injection (0.10 mg/kg). Note the increase in distribution mode and the loss of long ISIs due to quinpirole treatment.

skewness and kurtosis. These changes are largely related to a relative preponderance of short ISIs and the emergence of atypically long ISIs. ISI mean, however, was not decreased by lesion, indicating that the loss of DA did not produce a net increase in EPN firing rates. A net increase in spiking activity in the EPN and SNpr after reduced DAergic transmission is predicted by some basal ganglia models; however, studies of the SNpr from different laboratories have varied in their find-

ings on this point (for instance, Burbaud et al. 1995; MacLeod et al. 1990; Rohlf's et al. 1997). Most similarly to the present study, Wichmann et al. (1999) reported reduced ISI median and increased ISI skewness in GPi activity after injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) without a significant change in net firing rate. These types of changes in the shape of ISI distributions are likely to have occurred in studies in which net firing rate was found to significantly

increase only in subsets of GPi neurons after MPTP (Bergman et al. 1994).

The lesion-induced increase in ISI CV might be interpreted as increased bursting. However, our specific measure of bursting behavior, based on properties of the discharge density histogram (Kaneoke and Vitek 1996) indicated no increase in bursting after lesion, and little bursting in either intact or lesioned rats. We previously reported similarly low levels of bursting in the rodent SNpr ipsilateral to nigrostriatal lesion (Ruskin et al. 1999b). If bursting is defined as a type of temporal ordering of short and long ISIs, specifically, by "clumps" of short ISIs separated by long ISIs, then an increase in CV does not necessarily indicate an increase in bursting because even in cases with high CV the temporal order of short and long ISIs could be random.

Treatment with DA agonists normalized some lesion-induced changes in ISI distribution. D₂ agonist, in particular, increased ISI mode (but not mean) and decreased ISI variability, but no drug treatment reduced ISI skewness or kurtosis. D₁ agonist and combined D₁/D₂ agonists also increased ISI mode, but in these cases, ISI mean and median were also increased, indicating that these treatments produced a net drop in the amount of spiking activity and so cannot be considered to normalize ISI distributions. Net inhibitions after injection of D₁ or combined D₁/D₂ agonists are also found in the SNpr (Ruskin et al. 1999b; Waszczak et al. 1984; Weick and Walters 1987a,b), although D₁ agonists appear to more potently affect the EPN because 3.4 mg/kg SKF 38393 consistently inhibits EPN neurons (present results) but has variable effects on SNpr neurons (Ruskin et al. 1999b; Weick and Walters 1987a,b). Studies of DA agonist effects on GPi firing rates in parkinsonian humans and primates have almost exclusively used the mixed D₁/D₂ agonist apomorphine or the DA precursor l-3,4-dihydroxyphenylalanine (l-DOPA). While the primates and Parkinson's disease patients in these studies have typically received chronic DA agonist treatment, and the rodents in the present study were treated acutely, the parallels regarding DA agonist control of firing rate are compelling. At sufficient doses, apomorphine and l-DOPA consistently reduce GPi firing rates in Parkinson's patients (Hutchison et al. 1997a; Levy et al. 2001; Lozano et al. 2000; Merello et al. 1999; Stefani et al. 1997) and DA-deafferented monkeys (Boraud et al. 1998, 2001; Filion 1979; Filion et al. 1991; Papa et al. 1999) and so are similar to our findings in the rodent EPN with combined D₁/D₂ agonist treatment. Also, the present data agree with Boraud et al. (2001)'s report, which found GPi rate inhibitions in MPTP-treated monkeys caused by the D₁ agonist SKF 38393. There is some evidence that robust inhibition of the GPi in MPTP-treated primates is associated with DA agonist-induced dyskinesias (Boraud et al. 2001; Papa et al. 1999), suggesting that, in primate or rodent, doses of DA agonists which produce such inhibitions of the basal ganglia output nuclei are not optimal for reversing the behavioral effects of midbrain DA depletion.

DA agonist-induced motor activation has been thought to be mediated by net inhibition of the EPN and SNpr, and it is true that, in rats with unilateral nigrostriatal lesions, a number of DA agonists at particular doses can produce both rotation and reduce EPN or SNpr firing rates ipsilateral to the lesion. The present results with the D₂ agonist quinpirole illustrate one of the several exceptions to this rule. Quinpirole injection at

rotation-inducing doses did not significantly increase ISI mean, i.e., decrease the average firing rate. Changes in ISI mean varied from neuron to neuron, including increases, decreases, and no change. D₂ agonist-induced rotation is therefore not mediated by an overall inhibition of the EPN. A similar dissociation of rotation and EPN/SNpr inhibition is also found with D₁ receptor activation. Low intravenous doses of several D₁ agonists induce rotation, without producing a population inhibition in SNpr or EPN neurons (Ruskin et al. 1999b). As an example, 1.3-mg/kg SKF 38393 intravenously induces significant contraversive rotation but causes varied firing rate changes in both the SNpr or EPN (Ruskin et al. 1999b and present results). Higher doses of D₁ agonists become effective in inhibiting overall activity in these nuclei (and still induce rotation) (Ruskin et al. 1999b and present results). Therefore although strong unilateral inhibition of the EPN or SNpr is sufficient to cause rotation (for example, Scheel-Krüger et al. 1977), it is not necessary. In the absence of robust inhibition, it seems likely that DA agonist-induced rotational behavior (and possibly DA-related motor activation generally) either relates to the decreased firing rates of a specific minority of EPN/SNpr neurons or relates instead to changes in firing patterns in these nuclei. Mixed EPN/SNpr firing rate responses in relation to movements are predicted in some recent models of basal ganglia function (Mink 1996; Redgrave et al. 1999).

Oscillatory activity

Nigrostriatal lesion significantly changed several types of oscillatory activity present in the EPN, particularly causing an emergence of 4–18 Hz oscillations, a loss of higher frequency oscillations indicating regular spiking, and a loss of 0.5–2.0 Hz oscillations. Oscillatory activity in the 0.5–2.0 Hz range has previously been noted in spike trains from subsets of neurons in the EPN and other basal ganglia nuclei, including the GP, SNpr, and subthalamic nucleus (Allers et al. 2000; Magill et al. 2000, 2001; Ruskin et al. 1999a, 2001; Tseng et al. 2001). In this preparation, oscillations in this range in these structures are correlated in frequency with the rate of respiration (Allers et al. 2000; Ruskin et al. 1999a, 2001), seemingly reflecting a tendency of a subset of basal ganglia neurons to fire in concert with some aspect of respiration. In the present study, this type of activity disappeared from the EPN after nigrostriatal lesion. Other studies have examined the effect of DA cell lesion on oscillatory activity in this frequency range in the subthalamic nucleus (Allers et al. 2000) in awake rats, and in the GP, SNpr, and subthalamic nucleus in anesthetized preparations (Magill et al. 2001; Tseng et al. 2001). In contrast to the present observations, in many of these studies nigrostriatal lesion induced an increase in 0.5–2.0 Hz oscillatory activity. However, these results, in concert with findings that DA agonists modulate very slow (less than 0.5 Hz) oscillations in the basal ganglia (Allers et al. 2000; Ruskin et al. 1999a, 2001), are consistent with the idea that changes in DA receptor activity can influence oscillatory activity across a wide range of frequencies in the basal ganglia.

Among the most interesting of the changes noted in the present study were the emergence of 4–18 Hz oscillations in EPN spike trains and the loss of higher frequency oscillations indicating regular spiking following nigrostriatal lesion. Notably, these effects were specific to the lesioned hemisphere:

preliminary recordings from the EPN of the intact side of unilaterally-lesioned rats indicate that 4–18 Hz oscillations and regular spiking were present in 11 and 22% of neurons, respectively (unpublished data), percentages essentially identical to those found in intact rats (compare with Table 1). The emergence of 4–18 Hz activity in the lesioned hemisphere parallels findings in the GP of Parkinson's disease patients (Hurtado et al. 1999; Hutchison et al. 1997b) and MPTP-lesioned primates (Bergman et al. 1994, 1998; Filion and Tremblay 1991; Nini et al. 1995; Raz et al. 2000). Treatment with combined D₁ + D₂ agonist (but not either agonist alone) completely blocked the appearance of 4–18 Hz activity in lesioned rats. This normalizing effect parallels an example of apomorphine-induced reduction in this type of oscillatory activity in the GPi of MPTP-treated primates (Fig. 3A in Filion et al. 1991).

Multi-unit recording studies in primates have shown that 4–18 Hz range basal ganglia oscillations after DA deafferentation are highly correlated between neurons, indicating an abnormal level of interdependence (Bergman et al. 1998; Hurtado et al. 1999; Nini et al. 1995), and oscillatory activity in this range has been proposed to be the central generator for limb tremor in humans and nonhuman primates. Although infrequently examined in nonprimate species, jaw, head, and body tremor does occur after unilateral or bilateral DAergic lesion in rats (Buonomici et al. 1986; Butcher et al. 1973; Finn et al. 1997; Jolicoeur et al. 1991; Lindner et al. 1999), paralleling the increased incidence of 4–18 Hz EPN oscillations. Recordings in the present study, however, were performed during neuromuscular blockade so that muscular tremor was necessarily absent. The presence of lesion-associated activity in this tremor-related frequency range under conditions in which peripheral feedback (such as from muscle stretch receptors) was absent further supports the idea that loss of DA changes the properties of oscillation generators in the basal ganglia (McAuley and Marsden 2000).

The loss of regular spiking after lesion is reflected in the changes observed in EPN ISI distributions because regular-spiking EPN neurons had low ISI skewness and CV, and lesion significantly increased both these measures. Our unpublished observations indicate a very similar lesion effect in the SNpr on the incidence of regular spiking (percentages identical to those in Table 1, $P < 0.02$, intact $n = 37$, lesion $n = 33$), supporting similar findings from other laboratories (Burbaud et al. 1995; Murer et al. 1997). In the current investigation, no DA agonist treatment was able to reinstate regular spiking in the EPN probably because none of these treatments completely normalized ISI distributions. In primates, l-DOPA injection does not reverse the MPTP-induced drop in the percentage of regular spiking neurons in the GPi (Boraud et al. 1998). Similarly, in studies of rodent SNpr (Burbaud et al. 1995; Murer et al. 1997), subthalamic nucleus lesion (which, like DA replacement therapy, attempts to compensate for midbrain DA cell loss) did not increase the incidence of regular-spiking neurons, although other changes in SNpr activity were normalized [and in spite of the fact that subthalamic nucleus lesion in otherwise intact rats does increase regular spiking in the SNpr (Ryan and Sanders 1993)]. The failure of these treatments suggests that the presence of regular-spiking activity in the basal

ganglia output nuclei may be one of the most sensitive physiological indicators of an intact, normally-functioning nigrostriatal pathway. Overall, no DA agonist treatment in the present study fully normalized EPN activity in lesioned rats. A more complete normalization might be possible with a careful titration of agonist doses, for instance, to levels that are antiparkinsonian but do not induce rotation (Olsson et al. 1995; Schallert et al. 1983). Also, the additional abnormalities produced by some DA agonist treatments might, in some cases, be due to these exogenous drugs acting at DA receptors outside the basal ganglia. How chronic loss of DA triggers alterations in firing patterns of EPN neurons, manifested in this rodent preparation by loss of regular-spiking activity, increased incidence of 4–18 Hz oscillatory behavior, and changes in ISI distribution, remains a critical question central to understanding the symptomatology of Parkinson's disease.

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