Multisecond Oscillations in Firing Rate in the Basal Ganglia: Robust Modulation by Dopamine Receptor Activation and Anesthesia

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Ruskin, David N., Debra A. Bergstrom, Yoshiki Kaneoke, Bindu N. Patel, Michael J. Twery, and Judith R. Walters. Multisecond oscillations in firing rate in the basal ganglia: robust modulation by dopamine receptor activation and anesthesia. J. Neurophysiol. 81: 2046–2055, 1999. Studies of CNS electrophysiology have suggested an important role for oscillatory neuronal activity in sensory perception, sensorimotor integration, and movement timing. In extracellular single-unit recording studies in awake, immobilized rats, we have found that many tonically active neurons in the entopeduncular nucleus (n = 15), globus pallidus (n = 31), and substantia nigra pars reticulata (n = 31) have slow oscillations in firing rate in the seconds-to-minutes range. Basal oscillation amplitude ranged up to ±50% of the mean firing rate. Spectral analysis was performed on spike trains to determine whether these multisecond oscillations were significantly periodic. Significant activity in power spectra (in the 2- to 60-s range of periods) from basal spike trains was found for 56% of neurons in these three nuclei. Spectral peaks corresponded to oscillations with mean periods of ~30 s in each nucleus. Multisecond baseline oscillations were also found in 21% of substantia nigra dopaminergic neurons. The dopamine agonist apomorphine (0.32 mg/kg iv, n = 10–15) profoundly affected multisecond oscillations, increasing oscillatory frequency (means of spectral peak periods were reduced to ~15 s) and increasing the regularity of the oscillations. Apomorphine effects on oscillations in firing rate were more consistent from unit to unit than were their effects on mean firing rates in the entopeduncular nucleus and substantia nigra. Apomorphine modulation of multisecond periodic oscillations was reversed by either D1 or D2 antagonists and was mimicked by the combination of selective D1 (SKF 81297) and D2 (quipiprole) agonists. Seventeen percent of neurons had additional baseline periodic activity in a faster range (0.4–2.0 s) related to ventilation. Multisecond periodicities were rarely found in neurons in anesthetized rats (n = 29), suggesting that this phenomenon is sensitive to overall reductions in central activity. The data demonstrate significant structure in basal ganglia neuron spiking activity at unexpectedly long time scales, as well as a novel effect of dopamine on firing pattern in this slow temporal domain. The modulation of multisecond periodicities in firing rate by dopaminergic agonists suggests the involvement of these patterns in behaviors and cognitive processes that are affected by dopamine. Periodic firing rate oscillations in basal ganglia output nuclei should strongly affect the firing patterns of target neurons and are likely involved in coordinating neural activity responsible for motor sequences. Modulation of slow, periodic oscillations in firing rate may be an important mechanism by which dopamine influences motor and cognitive processes in normal and dysfunctional states.

INTRODUCTION

The tonic level of dopamine (DA) receptor stimulation in the brain has a profound influence on motor, cognitive, and affective function in animals and man. Increased levels of DA receptor stimulation induce hyperactivity and stereotypic behavior and may underlie the pathophysiology of schizophrenia and Tourette's syndrome. Decreased DA receptor stimulation resulting from nigrostriatal degeneration in Parkinson's disease or administration of DA receptor antagonists is associated with hypoactivity and catalepsy. The effects of DA receptor stimulation on motor activity are typically ascribed to effects on tonic firing rates in basal ganglia nuclei. Systemic treatment of neurologically intact, awake animals with DAergic agonists causes a variety of firing rate changes in the substantia nigra pars reticulata (SNPR), entopeduncular nucleus (EPN), and globus pallidus (GP) (Bergstrom et al. 1982; Walters et al. 1987; Waszczak et al. 1984). However, many of these rate changes do not conform to the predictions of current basal ganglia models. For instance, the mixed D1/D2 agonist apomorphine causes a range of firing rate increases and decreases in the SNPR of normal rats (Waszczak et al. 1984), yet many models predict that DA agonists should cause net rate decreases in this nucleus, as well as in the EPN (Albin et al. 1989; DeLong 1990; Scheel-Krüger 1986).

In recent years, there has been a growing interest in the behavioral relevance of firing pattern, particularly oscillatory pattern (Engel et al. 1997). Oscillations in neuronal activity in awake animals are common in motor areas of cerebral cortex and thalamus (MacKay 1997). Oscillations in motor and sensory regions of the brain have been hypothesized to coordinate activity in distributed populations of neurons to organize motor sequences and form sensory percepts. In the basal ganglia, there have been several reports of oscillatory patterns (with frequencies >1 Hz) in firing rate in awake animals and humans (Feingold et al. 1996; Nini et al. 1995; Wilson et al. 1977). For example, in parkinsonian patients and monkeys, neurons in the GP and subthalamic nucleus have oscillatory activity in the range of 4–10 Hz, which appears to relate to limb tremor (Bergman et al. 1996; Hutchison et al. 1997).

Studies of oscillatory neuronal activity in awake subjects, however, do not often focus on phenomena with frequencies less than ~0.5–1 Hz. The present study describes novel, slow (<0.5 Hz) oscillations in baseline firing rate in the substantia nigra, GP, and EPN of awake, paralyzed, neurologically intact rats. A preliminary study from this laboratory indicated that
these oscillations were present in a large fraction of SNPR neurons (Twery et al. 1996). DA agonist-induced changes in the period and power of these multisecond periodicities in firing rate are investigated, as well as the effects of general anesthetics and D₁ and D₂ receptor blockade. Also, in addition to slow (<0.5 Hz) oscillations, some basal ganglia neurons have firing rate oscillations in a slightly faster range (Twery et al. 1996). This range roughly coincided with the ventilation rate, suggesting that it might represent periodic activity related to a periodic external stimulus. The present study directly examined the relationship of these two phenomena by simultaneously recording neuronal activity and ventilator action in a subset of animals.

METHODS

Sprague-Dawley rats weighing 250–400 g were used. Extracellular recordings of tonically active single units (with biphasic waveforms) were performed in artificially respired, locally anesthetized rats or in chloral hydrate (400 mg/kg) or urethan (1.2 g/kg) anesthetized rats as previously described (Bergstrom et al. 1984). All surgical procedures have been described previously (Bergstrom et al. 1984) and were conducted in accord with National Institutes of Health guidelines (Cohen et al. 1985). In the artificially respired, locally anesthetized preparation, rats were tracheotomized under halothane anesthesia, and the trachea was intubated with a cannula. To prevent discomfort of the animals, incision and pressure sites were thoroughly infiltrated with the long-acting local anesthetic mepivacaine HCl, anesthetic gel (2% lidocaine) was applied to the outside of the trachea cannula and the tips of the stereotaxic ear bars, and corneal drying was prevented with Lacri-Lube (Allergan Pharmaceuticals). After placement in a stereotaxic instrument and the completion of all surgical procedures, halothane anesthesia was discontinued, and rats were paralyzed with the injection of gallamine triethiodide (16 mg/kg) through a tail vein. Rats then were artificially ventilated at a rate adjusted to maintain expired CO₂ levels between 3.4 and 4.5%. Supplements of gallamine were given as needed. Body temperature was maintained 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 (D. A. Bergstrom, C. Helke, and J. R. Walters, unpublished observations).

Glass microelectrodes (2.5–6 MΩ, 2 M NaCl filling solution) were directed stereotaxically through drilled skull holes to the EPN, GP, or substantia nigra. Electrical signals were passed through an Axoclamp 2A amplifier in bridge mode, and amplified single-unit activity was isolated with a window discriminator and collected with Spike2 software (version 2.18, Cambridge Electronic Design). In the substantia nigra, both pars reticulata and DAergic pars compacta neurons were recorded; DAergic neurons were identified by their characteristic long-duration waveform and firing pattern. After a baseline recording period of at least 5 min, DA agonist or vehicle (water) was injected intravenously, and units were held another 10–15 min. Typically, a DA antagonist drug was then injected intravenously. Only one unit from each rat was recorded after agonist injection. Recordings were typically 25–35 min in length. At the end of recording, Pontamine Sky Blue was iontophoresed, and the recording site was later verified histologically. Apomorphine was obtained from Sigma; domperidone was obtained from Janssen Pharmaceutica; SCH 23390, eticlopride, SKF 61297, and quinpirole were obtained from Research Biochemicals Inc.

To study neuronal activity related to the process of artificial respiration, a switch was installed in the ventilator apparatus (Harvard, model 683), which produced a voltage pulse at the time of greatest piston extension, i.e., one pulse per ventilation cycle. In the majority of recordings, this voltage signal was recorded simultaneously with neuronal activity (in separate channels) by the data acquisition software (Spike2). The ventilator rate during any particular epoch could then be measured post hoc, and also the ventilator signal could be used as a trigger to construct poststimulus time histograms (PSTHs) of neuronal activity.

Data segments (180 s) were selected from baseline and postdrug times for analysis of firing rate periodicities. One segment was selected from each of baseline, postagonist and (when present) postantagonist epochs. Data segments (180 s) were selected so as to be representative of the activity of the entire epoch, and data segments after drug treatments were generally taken from the 5- to 10-min time range postinjection. Spike trains were smoothed by binning (nonoverlapping square bins). Visual inspection of spike trains smoothed at different binwidths indicated that the prominent periodic firing rate changes that typically occurred with periods in the range of 2–60 s were best seen with binwidths of <1 s, and so spike trains were smoothed with 500- or 200-ms bins in the current analysis. Smoothed spike trains were analyzed with the Lomb algorithm to characterize periodicities in the spike train, with the method of Kaneoke and Vitek (1996), which has been previously used to assess oscillatory activity in the basal ganglia (Boraud et al. 1998; Kaneoke and Vitek 1996). In the current analysis, the program was modified so that power spectra were taken from smoothed spike trains instead of smoothed autocorrelations. The Lomb algorithm was selected over the fast Fourier transform because of the ability of the Lomb algorithm to evaluate the statistical significance of spectral features (Scargle 1982), allowing classification of spike trains as either having or lacking significant power within a particular range of periods. Significant periodicities were examined within the range of 2–60 s (0.5–0.017 Hz) with 500-ms bins for analysis of multisecond oscillations, or within the range of 0.4–2 s (2.5–0.5 Hz) with 200-ms bins for analysis of ventilation-related oscillations. Periods longer than 60 s would exhibit less than three possible cycles within the 180-s spike train and so were not considered. Peaks in the periodogram power spectra were considered to be significant at P < 0.01 in comparison with independent Gaussian random values. Only 1 of 100 spectra of segments of random Gaussian noise would be expected to have peaks above the power level represented by the P = 0.01 line; hence peaks above this line are highly likely to indicate true periodic activity (Horne and Baliunas 1986; Press et al. 1992). Only significant spectral peaks are considered here, and relative power of spectral peaks is reported as the ratio of the spectral peak height to the height of the P = 0.01 significance line.

Drug-induced changes in the periods of spectral peaks were statistically analyzed in two ways. First, all significant spectral peaks were included in distribution tests: within a condition, the numbers of spectral peaks within defined ranges (2–10 s, 10–20 s, 20–30 s, ... ) from all spike trains were noted, and drug-induced changes in this distribution were analyzed with χ² tests. Second, for many spike trains much of the spectral power is concentrated into one peak, which was defined as the “main” peak, i.e., the tallest (most powerful) spectral peak within the studied range. Drug-induced changes in the period of main spectral peaks were analyzed with Student’s t-tests. Also, drug-induced changes in the power (height) of main spectral peaks were analyzed with Wilcoxon tests; cases in which there were no significant peaks were assigned a zero value in this test.

RESULTS

Basal oscillations

Visual inspection of the basal activity of basal ganglia neurons (15 EPN, 31 GP, and 31 SNPR) in awake rats demonstrated that the baseline firing rate in many of these neurons was not stationary, but rather fluctuated at long time scales. Examples of these basal variations are shown in Figs. 1 and 2.
These fluctuations had a large amplitude in some neurons. For instance, the basal firing rate of the neuron in Fig. 2C reached up to 156% and down to 58% of the mean firing rate. Lomb algorithm analysis revealed that these fluctuations were often periodic; significant periodicities (P, 0.01) in basal firing rate within the presently examined range of periods (2–60 s) were exhibited by many neurons in each nucleus (Table 1). In many cases, more than one significant spectral peak was found in a given spike train. Figure 3 (left column) illustrates basal periodicity data from all EPN neurons, and subsets of GP and SNPR neurons. In all three nuclei, peaks from basal spike train spectra were broadly distributed across the examined range of periods. When considering only the most powerful spectral peak for each spike train (the main spectral peak), means for main spectral peak period of basal spike trains were 30 s in each nucleus (Table 1).

Basal activity of 14 DA neurons of the substantia nigra pars compacta (SNPC) (identified by characteristic long extracellular waveforms as well as histology) was also recorded in awake rats. Although basal firing rates of these neurons were, as expected, much slower than in the other nuclei presently investigated, significant (but relatively low power) spectral peaks were still found in three of these cells, with similar periods as in the other nuclei (Table 1). These oscillations in DA neuron activity, however, were less obvious on visual inspection of the spike trains, probably due to their low power and also the slow overall firing rate of these cells.

**Effects of dopamine agonist and vehicle injection**

The mixed D1/D2 agonist apomorphine at 0.32 mg/kg iv (an intravenous dose that increased apparent arousal level and induced strong stereotypic sniffing in freely moving rats) modulated firing rate oscillations in virtually all tested neurons (15 EPN, 10 GP, and 10 SNPR) in awake rats in a manner that was readily visible on inspection of smoothed spike trains (Figs. 1 and 2, A–C). Apomorphine-induced effects appeared within 1–3 min after injection in most units and typically persisted until antagonist injection (Fig. 1) or the end of the recording. The oscillations in firing rate after apomorphine were often remarkably large in amplitude. For example, the postapomorphine oscillations in Fig. 2B range between 166 and 40% of the mean firing rate, whereas the postapomorphine oscillations in Fig. 2C range between 220 and 58% of the mean.

Spectral analysis revealed that the proportion of units with significant oscillatory activity increased after apomorphine in the EPN (from 67 to 87%), GP (from 44 to 90%), and SNPR (from 58 to 100%). Apomorphine also increased the rate of oscillations in each structure, leading to increased numbers of peaks in the 5- to 20-s period range, and decreased numbers of peaks in the 30- to 60-s period range (Fig. 3; P < 0.01 for all 3 structures). This increase in oscillation rate is also reflected in main spectral peaks, which are significantly shifted to shorter periods in all three structures (P < 0.001 in all cases; Fig. 4, examples in Fig. 2). Group means for main spectral peak
FIG. 2. Lomb periodogram power spectra and the spike trains from which they were derived, showing examples of basal and postdrug neuronal activity from awake rats (A–C) and anesthetized rats (D and E). Spike trains are smoothed with 500-ms bins and are shown scaled to their highest point (in Hz). Mean firing rate is given in the bottom left corner of each spike train plot. Ninety-second segments of the 180-s trains used for analysis are shown. Beneath spike trains are the corresponding power spectra, which are shown with a line signifying the $P = 0.01$ significance level; spectral peaks that cross this line indicate significant periodicities (Horne and Baliunas 1986; Kaneoke and Vitek 1996). Several cases have multiple significant peaks. Spectra for a neuron are scaled to the highest spectral peak for that neuron (except in D and E in which there are no significant spectral peaks).

Basal and post-dopamine (post-DA) agonist epochs are illustrated for each unit; some postantagonist epochs are also shown. A: EPN. B and E: globus pallidus (GP). C and D: SNPR. Of the 3 illustrated neurons recorded in awake rats, units A and C have significant baseline periodicities, and unit B does not. After apomorphine (0.32 mg/kg iv), all 3 units have strong periodicities. The smoothed spike trains from postapomorphine time segments demonstrate the periodic and repetitive nature of the rate oscillations. They are also indicative of the various shapes of the oscillations. In the 2 cases (A and C) where periodicities are present both before and after apomorphine, the drug increases the oscillation frequency. In these 3 neurons, DA antagonists given after apomorphine completely block periodic activity (A: $D_2$ antagonist eticlopride 0.2 mg/kg iv; B and C: $D_1$ antagonist SCH 23390 0.5 mg/kg iv). In D, a typical SNPR neuron from a chloral hydrate-anesthetized rat that has a baseline firing rate that is stationary on a time scale of many seconds. Apomorphine (and subsequent haloperidol, 0.2 mg/kg) has little effect. Power spectra from these spike trains reveal no significant periodicities. Similarly, in E a typical GP neuron from a urethan-anesthetized rat demonstrates a very stationary firing rate both in baseline and after injection of combined SKF 81297 and quinpirole (1.0 mg/kg iv each). There are no significant peaks in the accompanying power spectra.
of the selective D1 and D2 agonists, SKF 81297 and quinpirole, these cells for many minutes after injection. Apomorphine (0.32 mg/kg) was not tested in recordings of SNPR (data not shown). The high-amplitude oscillations in firing rate represent a more consistent population response than the changes in overall firing rate.

Effects of selective D1 and D2 antagonists

Apomorphine effects on periodic oscillations in firing rate were reversed in most cases by intravenous administration of the D1 antagonist SCH 23390 or the D2 antagonist eticlopride (examples in Figs. 1 and 2, A–C). After 0.5 mg/kg SCH 23390 (tested in 19 cases) or 0.2 mg/kg eticlopride (6 cases), relatively few neurons had significant periodicities. Combined data for SCH 23390 and eticlopride demonstrate decreases in the proportion of units with periodicities compared with 0.32 mg/kg apomorphine alone (EPN: 87 to 25%; GP: 90 to 25%; SNPR: 100 to 40%). For both antagonists, in those cases where any significant periodicities remained, the spectral peaks were typically of low power and/or long period (Fig. 3, right column). The combined data for SCH 23390 and eticlopride demonstrate significant antagonist-induced changes in the distribution of spectral peaks compared with 0.32 mg/kg apomorphine alone in the EPN and SNPR (P < 0.01), due mainly to a loss of spectral peaks in the 5- to 20-s range (Fig. 3). This effect did not reach statistical significance for the GP. SCH 23390 and eticlopride also caused similar reversals of the effects of combined SKF 81297 and quinpirole in the GP (Fig. 3).

To investigate the possible involvement of peripheral DA receptors in the effect of apomorphine, in a small number of cases the peripheral D2 antagonist domperidone (0.2 mg/kg) was injected ~10 min after apomorphine (0.32 mg/kg). In tested neurons (EPN, n = 2; GP, n = 2), domperidone had minimal effect on the amplitude or frequency of postapomorphine oscillations in firing rate (example in Fig. 1C).

Effects of general anesthetics

Nineteen SNPR neurons and 10 GP neurons were recorded from chloral hydrate– or urethane-anesthetized rats, respectively. Basal firing rates were significantly slower than those of neurons from awake rats (Table 1), although the ranges widely overlapped (data not shown). In contrast to neurons in awake rats, neurons in chloral hydrate- or urethane-anesthetized rats had basal firing rates that typically appeared stationary on time scales of many seconds, with few and minor variations (Fig. 2, D and E). Lomb algorithm analysis of baseline activity revealed that only 1 of these 29 neurons (a GP unit) had significant periodicities in basal firing rate in the 2- to 60-s range of periods, which represents significant decreases in the proportion of oscillatory neurons compared with awake rats (Table 1).

### Table 1. Baseline firing rates and periodicities in basal ganglia nuclei

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>n</th>
<th>Firing Rate, Hz</th>
<th>Period of Main Spectral Peak, s</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Awake, immobilized</td>
<td>Anesthetized</td>
</tr>
<tr>
<td>EPN</td>
<td>15</td>
<td>31.7 ± 3.0</td>
<td>10/15 (67)</td>
</tr>
<tr>
<td>GP</td>
<td>31</td>
<td>35.7 ± 2.8</td>
<td>16/31 (52)</td>
</tr>
<tr>
<td>SNPR</td>
<td>31</td>
<td>28.1 ± 2.0</td>
<td>17/31 (55)</td>
</tr>
<tr>
<td>SNPC (DAergic)</td>
<td>14</td>
<td>2.8 ± 0.4</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>GP (urethane)</td>
<td>10</td>
<td>20.6 ± 2.7*</td>
<td>1/10 (10)†</td>
</tr>
<tr>
<td>SNPR (CH)</td>
<td>19</td>
<td>19.6 ± 2.7*</td>
<td>0/19 (0)†</td>
</tr>
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</table>

Firing rate and main spectral peak period data are given as means ±SE; n is number of neurons; numbers in parentheses are percentages. Baseline data on all recorded neurons. Data for periodicities cover the range from 2 to 60 s. “Proportion with Periodicities” refers to the proportion of neurons having statistically significant periodic activity. The individual value is given for main spectral peak period for the one anesthetized GP unit that had significant periodic activity: EPN, entopeduncular nucleus; GP, globus pallidus; SNPR, substantia nigra pars reticulata; DA, dopamine; CH, chloral hydrate; NP, none present. * P < 0.05, † P < 0.03 compared with the same nucleus in awake rats, Student’s t-test and Fischer Exact test, respectively.

Periods of postapomorphine spike trains were 14–16 s (Fig. 4). In addition, apomorphine increased main spectral peak power (height) in the EPN (P < 0.01) and GP (P < 0.05), indicating greater regularity of the oscillations; this effect did not reach significance in the SNPR (data not shown). The high-amplitude oscillations in firing rate after apomorphine were also evident with autocorrelogram analysis of selected units, when appropriately long binwidth and lag times were used (data not shown). Apomorphine (0.32 mg/kg) was not tested in recordings of SNPC DAergic neurons, because this intravenous dose of apomorphine typically completely inhibits firing activity of these cells for many minutes after injection.

Similar effects were found after injection of a combination of the selective D1 and D2 agonists, SKF 81297 and quinpirole (1.0 mg/kg each, tested in the GP; n = 14). Oscillatory frequency was strongly increased after this treatment, as was reflected in a emergence of spectral peaks below 10 s (Fig. 3) and a significant (P < 0.001) reduction in main spectral peak period. In fact, this treatment shifted main spectral peak period to an even faster range (8.0 ± 0.6 s, mean ± SE) than did 0.32 mg/kg apomorphine.

Injection of vehicle (SNPR: n = 12; GP; n = 7) or of a lower dose of apomorphine (0.08 mg/kg iv; SNPR: n = 9) had no consistent effect on oscillations (data not shown). Neither treatment affected the proportion of units with significant periodic oscillations, and neither significantly changed the distribution of spectral peaks, or the period or power of the main spectral peaks. The emergence of power in the 5- to 20-s range that was found in the 0.32-mg/kg apomorphine groups was absent in both of these groups. Inspection of individual units revealed that vehicle or low-dose apomorphine injection had variable and small effects.

In addition to changing firing pattern, this dose of apomorphine also changed overall firing rate in most neurons (Fig. 5).
DA agonists were administered intravenously during the majority of anesthetized-animal recordings. In contrast to the data from locally anesthetized rats, apomorphine (0.32 mg/kg) given during chloral hydrate anesthesia failed to induce significant oscillatory activity in any neurons within the 2- to 60-s range (n = 10 SNPR neurons; Fig. 2D). Also, the combination of SKF 81297 and quinpirole (1.0 mg/kg each) was given to urethan-anesthetized rats, and significant oscillatory activity was found after this treatment in only 1 of 10 GP neurons (1 neuron had a significant spectral peak with a period of 57 s).

Oscillatory baseline activity related to ventilation

Spectra of smoothed baseline spike trains from a subpopulation of neurons (4/15 EPN, 2/24 GP, 6/31 SNPR; overall 17%) in awake rats had significant spectral peaks within the 0.4- to 2.0-s range of periods (almost all were between 0.8 and 1.1 s, coinciding with the range of typical ventilator rates). Spectral peaks in this faster range differed from typical longer period (2–60 s) peaks in that they appeared to be sharper (Fig. 6), and, in virtually all cases, there was only one spectral peak in this range, compared with the multiplicity of significant spectral peaks at the longer periods in many neurons.

A separate sample of GP neurons (including 7 of the units in rats receiving combined D₁ and D₂ agonist) were recorded during concomitant recording of ventilator action. Baseline spike trains from 6 of these 44 GP neurons (14%) had significant spectral peaks within the 0.4- to 2.0-s range of periods, and spectral peak periods and ventilator periods had essentially the same value (within 1%; Fig. 6), except in one case in which the spectral peak period (1.69 s) was double the ventilator period (0.85 s).

The relationship between artificial ventilation and these 0.4- to 2.0-s range periodicities was revealed not just by the similarity of periods of the two phenomena, but also by inspection of PSTHs of neuronal activity. In neurons with at least moderately strong spectral peaks in this range, PSTHs triggered on the ventilator signal demonstrated a regular variation in neuronal activity apparently related to the action of the ventilator (Fig. 6). In neurons with a lower power (but still significant) spectral peak in this range, there was typically no strong periodicity within a condition. Power of each spectral peak (y-axis) is relative to the power level of the P = 0.01 significance line, which is set equal to 1. Spectral peak periods (x-axis) are given in seconds. Numbers of neurons are shown on each graph. Left column: Basal data. Middle column: after 0.32 mg/kg iv apomorphine (top 3 rows) or SKF 81297 combined with quinpirole, 1.0 mg/kg iv each (bottom row). Right column: after DA receptor antagonist. Basal data for each nucleus show the wide interunit variability of oscillatory periods. In each nucleus, apomorphine causes a significant shift in spectral peak frequency distribution toward shorter periods. The combination of selective D₁ and D₂ agonists has a similar effect in the GP. Data for SCH 23390 (SCH; 0.5 mg/kg iv) and eticlopride (Etic; 0.2 mg/kg iv) were similar, and so are grouped. Injection of these antagonists after DA agonist causes a striking loss of powerful spectral peaks, particularly at shorter periods. The antagonist-induced change in spectral peak frequency distribution is significant for the EPN and SNPR, and one of the GP groups (bottom).

The smaller number of spectral peaks for the antagonist condition reflects both a drop in the number of oscillatory neurons for each nucleus (see text) and a lower n (not all neurons were tested with antagonist). ** P < 0.01 compared with basal; †† P < 0.01 compared with agonist alone, χ² tests.
DISCUSSION

The current spectral analyses of spike trains reveal slow periodic oscillations in firing activity in the EPN, GP, and substantia nigra. Although some of these firing rate periodicities (namely those with a frequency faster than 0.5 Hz) were found to be related to ventilation, those with longer periods are presumably generated by endogenous processes, and these processes are sensitive to general anesthesia and DA receptor activation. Previous studies of basal ganglia electrophysiology have reported periodic activity in faster frequency ranges (Bergman et al. 1994; Hutchison et al. 1997; Wilson et al. 1977). The present data show that basal ganglia firing activity can also have significant structure at the seconds-to-minutes scale, which is not commonly examined. Although slow changes in central activity are often associated with sleep or anesthesia, the present data demonstrate that slow periodic activity can also occur in the waking condition in the basal ganglia, and that the power of these oscillations and the proportion of units demonstrating oscillations actually increase in response to a drug treatment that increases arousal and induces strong stereotypic behavior in freely moving animals. Because strong apomorphine-induced periodicities in firing rate are observed in the two output nuclei of the basal ganglia, the SNPR and EPN, the present study suggests that multisecond firing rate oscillations are transmitted to targets of the SNPR and EPN, particularly during the behavioral activation caused by apomorphine.

Multisecond oscillations in baseline cerebral cortical activity during waking have been found in a number of species, including humans, with measurements of direct cortical potentials (Aladjalova 1957; Norton and Jewett 1965), electroencephalogram (Ehlers and Foote 1984; Keidel et al. 1990; Pfurtscheller 1976; Trimmel et al. 1990), and blood flow/oxygenation (Biswal et al. 1995; Cooper et al. 1966; Lowe et al. 1998) and appear to relate to slow periodicities in motor output and in state of vigilance or arousal (Ehlers and Foote 1984; Keidel et al. 1990). Like the presently described periodicities in the basal ganglia, these slow cerebral cortical oscillations are not present during deep anesthesia (Aladjalova 1964; Norton and Jewett 1965). Oscillations measured with these techniques reflect synchronous activity of large neuronal

FIG. 4. Apomorphine (apo; 0.32 mg/kg)–induced changes in main spectral peak period in the EPN, GP, and SNPR. The main peak is defined as the most powerful (tallest) of the significant spectral peaks in a spike train. \( n \) is the number of neurons in each group. Dots indicate data points; also shown are means \( \pm \) SE. Neurons without significant periodicity are indicated above each graph (“no osc.”). Apomorphine (0.32 mg/kg iv) significantly decreased main spectral peak period compared with baseline in all 3 structures. *** \( P < 0.001 \), Student’s \( t \)-test.

FIG. 5. Relationship of apomorphine (0.32 mg/kg) effects on overall firing rate and oscillatory activity. Dots indicate neurons that had significant oscillatory activity after apomorphine injection. Apomorphine produces a variety of effects on overall firing rate in different cells. Neurons had apomorphine-induced oscillations regardless of whether apomorphine induced overall rate decreases or increases (or little overall rate change). For each neuron, the average rate 5–10 min after drug is expressed as a percentage of the rate in the 5 min before drug. Bars indicate means \( \pm \) SE.

FIG. 6. Ventilation-related periodicities in baseline firing rate of 2 neurons. Note the different frequency scale on the power spectra (left) compared with those shown in Fig. 2. Poststimulus time histograms (PSTHs; right, bin width 20 ms) are triggered from event signals from the ventilator apparatus that occurred at the greatest piston extension, i.e., the maximum of lung inflation. PSTH time scales are long enough to show multiple cycles; arrows indicate the times of ventilator event signals. In each case, power spectra and PSTHs are constructed from the same 180-s spike train segments. The measured ventilator period (“vent.”) during the identical epoch is shown and demonstrates that, for each neuron, the spectral peak period and the ventilator period are the same (within 1%). PSTHs illustrate the variations in firing rate in relation to the ventilator event signals. The phase relationships of the rate variations to the ventilator signals are slightly different for the 2 neurons. The neuron illustrated in B had the most powerful ventilation-related periodicity in the present study. The 2 neurons in A and B also had significant slow baseline periodicities in the 20-to 50-s range (not shown).
SLOW OSCILLATIONS IN FIRING RATE IN THE BASAL GANGLIA

Sixteen percent of all GP, EPN, and SNPR neurons in awake rats had significant spectral peaks with periods in the range of 0.4–2.0 s. Distinct from slower periodic activity, which is presumably generated by endogenous processes, periodic activity in the 0.4- to 2.0-s range was clearly related to an external process, namely the artificial ventilation of the immobilized rats. Firing rate oscillations in this range in the SNPR have been previously reported in artificially ventilated rats (Wilson et al. 1977); however, these authors concluded that the oscillatory activity was not related to ventilation. Although it is possible that basal ganglia neurons in the present study are oscillating spontaneously in the 0.8- to 1.1-s range, the precise correspondence between ventilator period and spectral peak period strongly suggests driving (or at least entraining of a spontaneous oscillation) by some aspect of artificial ventilation. GP, EPN, and SNPR neurons can respond to sensory input of various modalities (Chernyshev and Weinberger 1998; DeLong et al. 1985; Joseph and Boussaoud 1985; Rothblat and Schneider 1995; Schwarz et al. 1984), and it is difficult in the preparation used here to determine which modality mediates the present influence of artificial ventilation on GP activity. Firing rate periodicities related to ventilation did not preclude the presence of significant periodicities in the slower range (2- to 60-s periods). Simultaneous oscillatory activity in two different bands has also been reported in other structures in awake rats (Chrobak and Buzsáki 1998).

In many cases, spectral analysis of spike trains resulted in multiple statistically significant peaks in the power spectrum in the 2- to 60-s period range. Such multiple peaks may represent multiple simultaneous oscillations with different periods, side lobes of a particularly powerful spectral peak, or harmonics due to a nonideal sinusoidal oscillation shape. Visual inspection of smoothed spike trains, particularly from epochs after DA agonist administration (Figs. 1 and 2), suggests a different interpretation. Even when firing rate oscillations were particularly strong and regular, their regularity was not perfect or “clockwork,” but often demonstrated phase shifts (most common), gradual drift in period, or skipped cycles. It is likely that these various irregularities contribute to the appearance of multiple significant spectral peaks in many cases. Notably, periodic neuronal activity related to artificial ventilation, which is extremely regular, resulted almost exclusively in single spectral peaks without significant sidelobes (Fig. 6). On the other hand, in baseline spike trains, in which 2- to 60-s periodic activity (when present) was typically less regular than in post-DA agonist spike trains, and in which multiple spectral peaks sometimes spanned a relatively wide range of periods (e.g., Fig. 2C), it is not possible to rule out the presence of multiple simultaneous firing rate oscillations.

Numerous lines of research have emphasized the behavioral importance of periodic neuronal activity (Cohen and Wallen 1980; Engel et al. 1997; Komisaruk 1970; Llinas and Ribary 1993; Smith et al. 1991). The modulation of slow periodicities in firing rate in the present study by DAergic agonists suggests the involvement of these patterns in behaviors and cognitive processes that are affected by DA. Firing rate oscillations in the seconds-to-minutes range may act to coordinate neuronal activity responsible for motor sequences, much as faster oscillations in sensory pathways may coordinate neuronal activity underlying perceptual binding (Engel et al. 1997). The behavioral actions of stimulants have been theorized to be due to an...
increase in the rate of expression of motor sequences (Lyon and Robbins 1975). The DA agonist-induced increase in basal ganglia firing rate oscillation frequency could, therefore, be a physiological basis for this increased expression rate. The increase in frequency could also be a substrate for the DA agonist–induced increase in internal “clock speed,” which has been associated with the perception of time in the seconds-to-minutes range in animals and humans (Meck 1996).

Alternatively, concerning the thalamocortical sensory pathways, it has been hypothesized that a switch in firing pattern from a relay mode to a slow oscillatory mode (as from waking to slow-wave sleep) indicates that useful information is no longer being transmitted (Steriade et al. 1993). In the basal ganglia, a shift from normal firing patterns (which include slow oscillations across a range of frequencies) to a DA agonist–induced state of more powerful oscillations within a narrower frequency range might also signal a reduction of meaningful temporal patterning in output to motor-related thalamic nuclei. The abnormal interaction of an animal with its environment during stereotypic behaviors may indicate that motor programs are proceeding without normally patterned sensorimotor feedback. In summary, modulation of slow, periodic oscillations in firing rate may be an important mechanism by which DA influences motor and cognitive processes in normal and dysfunction states.

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