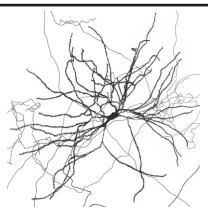

Spontaneous firing patterns of identified spiny neurons in the rat neostriatum

Charles J. Wilson and Philip M. Groves
Department of Psychology, University of Colorado, Boulder, Colo. 80309

ABSTRACT

Spontaneous firing patterns of 94 unidentified neurons and 34 identified spiny neurons were compared in the neostriatum of locally anesthetized immobilized rats. Intracellular and extracellular recordings were analyzed using first order interval histograms and autocorrelograms, and neurons were identified by their somato-dendritic morphology after intracellular injection of horseradish peroxidase. All neostriatal neurons tended to fire in irregular phasic bursts of activity. Considerable variation in mean firing rate, burst duration, interburst interval and the occurrence and rate of firing between bursts was apparent in both groups of neurons. There was no apparent difference between spiny neurons and the sample of unidentified extracellularly recorded neurons along any of these firing pattern parameters. Intracellular recordings from identified spiny neurons revealed noisy irregular periods of maintained 5-20 mV membrane depolarizations which corresponded to the occurrence of bursts of firing in spontaneously active neurons. These depolarizations occurred in neostriatal neurons exhibiting no spontaneous activity but were of insufficient amplitude to trigger impulse activity.

INTRODUCTION

The caudate nucleus, putamen and nucleus accumbens, which together make up the neostriatum of mammals, form the major recipient structure for afferents to the basal ganglia. Receiving input from widespread cortical areas, much of the intralaminar thalamic complex, and monoaminergic cell groups of the substantia nigra and brain stem raphe nuclei, the neostriatum provides the largest single afferent supply to basal ganglia output neurons in the substantia nigra pars reticulata and pallidum (for review see refs. 4 and 15). The way in which neostriatal neurons integrate activity derived from their afferent projections and the nature of the efferent neostriatal outflow is thus of central importance for the functioning of all basal ganglia structures.

Results from single unit recordings of neostriatal neurons have emphasized the low tonic firing rates of these cells (see e.g. refs. 3, 5, 11, 13, 21, 28). The relative silence of neostriatal neurons is no doubt due in part to their sensitivity to general anesthesia3,11,17, but recent observations made in alert, behaving animals demonstrate that it cannot be attributed solely to this acute experimental preparation1,6,23. In behaving animals, unidentified neostriatal neurons have been reported to have very low rates of tonic firing, but to exhibit phasic rate increases which may be temporally related to performance of learned movements1,23. Many of the neurons in these studies appear to have been nearly silent except for the occurrence of such phasic responses. These studies have not determined whether such bursts of action potentials represent a characteristic pattern of the neostriatal outflow, or rather the activity of interneurons involved in the local processing of afferent activity.

A minority of neostriatal neurons firing at higher rates has been consistently reported (e.g. see refs. 1, 11). In several instances differences in the rate and pattern of spontaneous activity in unidentified neostriatal neurons have been found to be related to other differences between these cells. For example, neurons with relatively high tonic spontaneous firing rates have been found to be most likely to show inhibitory responses to iontophoretic application to dopamine5 or to stimulation of substantia nigra or cerebral cortex11,21, to respond with EPSP-IPSP sequences to thalamic stimulation27, and to rarely or never exhibit antidromic responses to stimulation of substantia nigra21. Pure excitatory orthodromic responses are, on the other hand, more commonly reported for otherwise silent neurons, and these may also respond antidromically, to nigral stimulation21,27. Findings of this type have led some investigators to suggest that differences in spontaneous activity among neostriatal neurons may reflect differences between morphologically distinguishable cell types11, but this possibility has remained untested.

The majority of neostriatal neurons are of a single type characterized by its high density of dendritic spines10,12,18. These neurons possess long axons which under favorable conditions can be seen to exit the nucleus, and they are the origin of the bulk of neostriatal efferents26,30. Most single unit recordings in neostriatum are probably from cells of this type. In the experiments reported here, spontaneous single unit firing patterns were recorded extracellularly and intracellularly from the neostriatum of locally anesthetized, immobilized rats. Recorded spike trains were analyzed using interspike interval histograms and autocorrelograms and whenever possible, the neurons were identified by intracellular injection of horseradish peroxidase. The firing patterns of identified neostriatal spiny neurons were compared with those of a larger sample of unidentified units, both to characterize the firing patterns of these efferent neurons and to examine possible differences between their activity and that of neostriatal neurons as a whole.

MATERIALS AND METHODS

Male Sprague-Dawley rats, weighing from 200 to 400 g were anesthetized by ether inhalation and placed in a stereotaxic apparatus using blunt atraumatic ear bars (Kopf Instruments) coated with anesthetic ointment (Xylocaine). Ether administration was continued as needed by application to a gauze cone wrapped around the incisor bar. The skull was exposed by a short scalp incision and small burr holes were drilled in the skull overlying the head of the caudate-putamen on each side. The areas in and around the wound were thoroughly infiltrated with lidocaine hydrochloride (Xylocaine, with epinephrine) by subcutaneous injections around the wound and by topical administration to all cut edges. The exposed dura mater was cut and retracted to the side to allow safe insertion of microelectrodes. Exposed tissues were bathed in a small quantity of Ringer's solution and commercial eye drops were applied to prevent corneal drying. Ether anesthesia was then discontinued and the animal was immobilized with D-tubocurarine chloride (2.0 mg/kg i.p.) and artificially respired at 70-75 cycles/min using a Harvard Instruments rodent respirator attached to a rubber cone fitted snugly over the snout. Heart rate, body temperature and expired CO2 were monitored continuously and maintained with physiological limits. In some experiments, ECG was recorded from a surface electrode placed near the frontal pole of the cortex. Animals were observed to undergo spontaneous changes in ECG amplitude and frequency suggestive of sleep and alerting, and arousal responses to moderately noxious stimuli (e.g. tail pinch) were intact.

Glass microelectrodes were pulled to tip diameters of 0.1-0.3 um and were lightly dry-bevelled using the apparatus described by Baldwin2. They had sharply bevelled tips ranging from 0.2 to 0.5 um. Microelectrodes were filled with 20% horseradish peroxidase (Sigma Type II) in 0.05 M Tris buffer (pH 8.6) and 0.5 potassium chloride by diffusion over a period of 2-4 days at 4 degreeC. At the time of use, they had low-current DC resistances of 50-250 Mohm.

Extracellular and intracellular recordings of unit activity were amplified and displayed on an oscilloscope, and stored on magnetic tape for subsequent analysis. Upon encountering a spontaneously active neuron, one or two 15 min segments of extracellular unit activity were recorded after which the microelectrode was advanced in 1 um steps while continuously monitoring extracellular activity. In the case that advancing the electrode did not result in penetration of the recorded neuron, or if for some reason it could not be certain that the cell impaled was the same one recorded extracellularly, the neuron was considered to be unidentified and was not injected with HRP. Upon successful penetration of a recorded neuron, the record was examined to determine whether intracellular data should be collected. Spike trains from securely impaled neurons with membrane potentials in excess of 45 mV and action potentials of comparable magnitude were stored on magnetic tape for later analysis. Representative samples of the record were also photographed directly from the oscilloscope face. Neurons showing stable membrane potentials of 20 mV or greater, regardless of the quality of the intracellular recording, were injected with HRP by application of positive-going ejection pulses of 100-300 msec duration and 2-8 nA amplitude at a rate of 3-6 sec (duty cycle 0.60-0.95) for 1-5 min. No more than one neuron was ever injected with HRP within a single microelectrode track, and no more than 3 cells were injected on each side of the brain, to prevent confusion of injected cells.

All stored records were examined for stability of firing rate and for signs of damage due to the electrode. Extracellular spike trains meeting the criteria of stable firing rate and high signal-to-noise ratio (5:1 or greater) were analyzed in segments of up to 14 min. First order interval histograms and autocorrelograms were constructed using bin widths ranging from 0.8 to 51.2 msec. Whenever possible, more than one segment of extracellular data or an extracellular and an intracellular segment from the same neuron were examined. Spike train segments were examined for stationarity by comparing interval histograms from successive segments or from 5-7 min fragments of the 14 min segments. Spike trains exhibiting a continuous trend throughout the period of observation were rejected as non-stationary. When a spontaneous change in firing pattern occurred over a shorter period and was not accompanied by any indication of movement of the electrode (e.g. a change in action potential size or waveform), stationary periods of firing recorded before and after the change were analyzed separately. Stationary periods of firing before and after impalement of a neuron were always analyzed separately.

Procedures used in fixation and analysis of HRP-injected neurons have been described elsewhere34, along with a detailed morphological analysis of the injected cells. Locations of unidentified neurons were assessed relative to the positions of injected neurons.

RESULTS

Thirty-four neostriatal neurons were clearly identified as spiny neurons by their spine-free somata and proximal dendrites and their dense investment of dendritic spines beginning abruptly at a distance of about 20 um from their somata and continuing to the tips of the dendrites. An example illustrating these features of an injected neuron is shown in Fig. 1. In agreement with the previous reports of Kitai and his associates19,26, these neurons all possessed a clearly defined main axonal branch of larger diameter than the collateral branches which arose from it. This larger axonal branch ultimately joined a fascicle of internal capsule fibers and took a course toward globus pallidus. In some cases, 1-3 nearby neurons or neuroglia could be seen to contain HRP reaction product. In most cases, these cells were much more lightly stained and

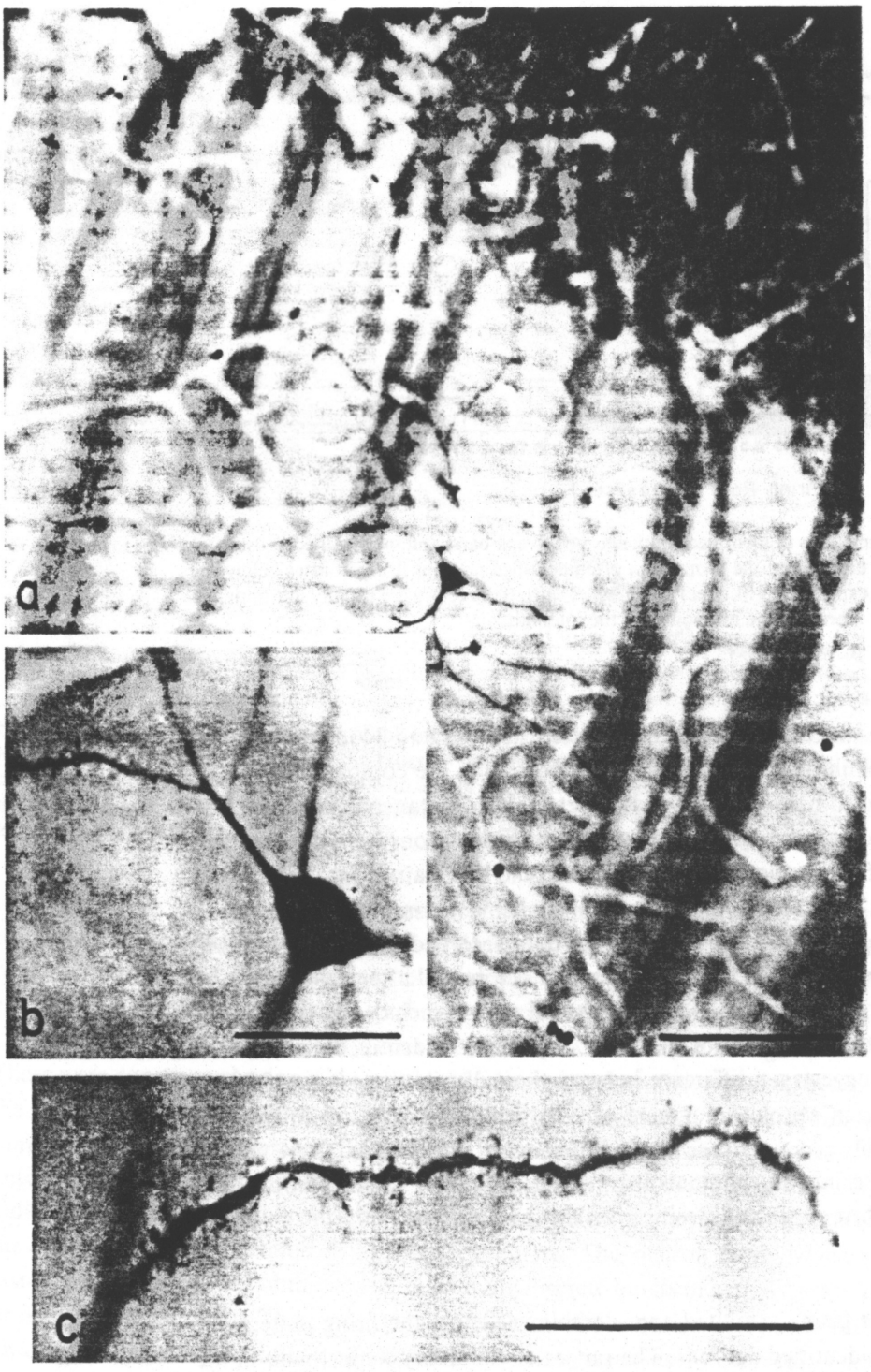

Fig. 1. Somato-dendritic morphology of a representative identified spiny neuron in rat neostriatum. a: low magnification view of neuron in sagittal 50 um section postfixed with osmium tetroxide. Rostral is to the right, dorsal is upward. The dense area at the upper right is subcortical white matter. Scale bar: 100 um. b: a higher magnification showing spine-free soma and proximal dendrites. Scale bar: 25 um. c: a more distal spiny dendrite from the same neuron, showing the high density of dendritic spines characteristic of these neurons.

there was no doubt which cell had been impaled by the microelectrode. In a few, however, this distinction was not so easily made, and these cells were not included in the sample of identified neurons. In addition there were 5 neurons which could not be identified due to their extreme state of degeneration, presumably caused by impalement with the microelectrode.

Mean firing rate

The mean firing rates of 94 unidentified striatal neurons and 34 identified spiny cells recorded extracellularly in the head of the neostriatum are compared in Fig. 2. Fourteen of the identified neurons exhibited no detectable spontaneous firing prior to penetration by the microelectrode. Since most unidentified neurons were not impaled, no reliable estimate of the proportion of silent cells could be obtained for them. Mean firing rates shown in Fig. 2 were unaffected by small movements of the recording microelectrode and represent the first sample of data recorded from each neuron. Higher firing rates were obtained for many cells just before and after penetration by the microelectrode but were attributed to damage and are not included in the sample.

Comparison of the firing rates of spontaneously active unidentified neurons and identified spiny cells suggests no difference between these distributions ($X2 = 5.08$, df = 15). The difference in absolute numbers of cells firing at high rates in the two distributions is probably accounted for by the difference in sample size. There was no apparent spatial clustering of spontaneously active cells, and no indication of a relationship between firing rate and position within the nucleus.

Firing patterns

Neostriatal spike trains exhibited considerable variety in the firing patterns of both identified and unidentified neurons. The ranges of variability were similar in the two groups and both contained cells whose activity could be described as tonic or phasic from a cursory examination on the oscilloscope screen. When examined using interval histograms and autocorrelograms, however, nearly all neurons of both types exhibited a tendency to fire in variable bursts separated by longer periods of firing at a relatively lower rate. This tendency was especially apparent in autocorrelograms computed using longer bin widths (24.6 or 51.2 msec) and appeared as an early high probability of firing following action potential generation. Firing probability decayed gradually to a more constant basal level over a period of 0.1-3.0 sec. Two examples of autocorrelograms of spontaneously active spiny neurons are shown in Fig. 3A and B. These were constructed using a bin width of 25.6 msec to show the overall structure of the bursts. The neuron shown in Fig. 3A exhibited a considerable degree of random tonic firing, which is reflected in the relatively high basal firing probability seen in the autocorrelogram. The flat appearance of the autocorrelogram to the right of the burst is indicative of both the highly variable random distribution of interburst intervals and the random pattern of tonic firing between bursts. The neuron from which the histogram in Fig. 3B was obtained exhibited more discrete bursts of activity with little or no interburst activity. These neurons also illustrate the variation of burst duration observed for both unidentified and identified neostriatal neurons. Differences of these types among neostriatal neurons were examined quantita-

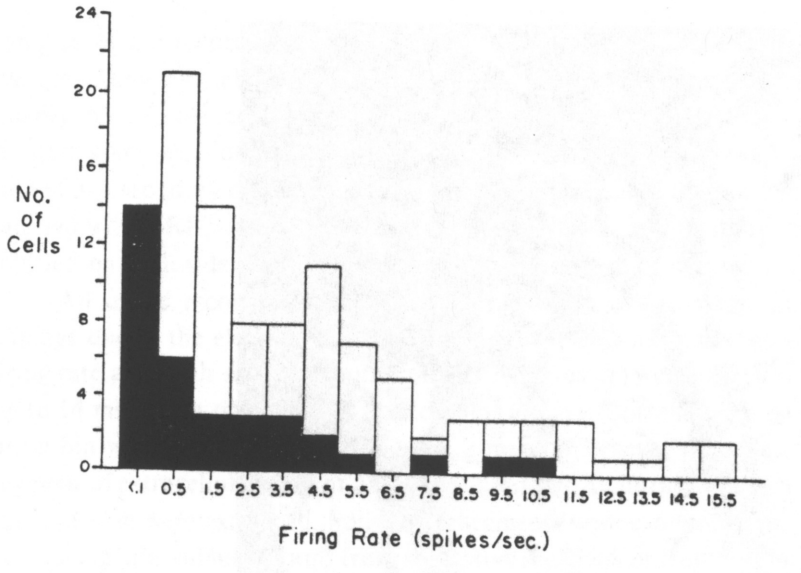

Fig. 2. Distribution of firing rates of identified spiny neurons (black bars) and unidentified neostriatal neurons (white bars). No estimate of the proportion of unidentified neurons firing at rates below the lowest detectable in these experiments (0.1/sec) is available, since these cells were usually not impaled. Numbers on the abscissa represent the midpoints of the intervals.

tively by measuring burst duration and burst strength from autocorrelograms constructed at long bin widths. Burst duration was defined as the time required for firing probability to reach the average value of the basal firing level measured graphically from the histogram. Burst strength was taken as the difference between peak and basal firing probability divided by the peak level. This latter measure yields values between O and 1, with a value of 0 reflecting a lack of bursts, and a value of 1 indicating that firing occurred exclusively within bursts. Burst duration varied from 0.1 to 3 sec for both unidentified and identified spiny neurons and showed no relationship with either burst strength or mean firing rate. In both samples there was a slight tendency for neurons firing at low rates to exhibit high burst strengths, as indicated by a small but statistically significant inverse correlation between these variables (r = -0.50, df = 92 for unidentified neurons, r = -0.38, df = 18 for identified spiny neurons).

Although most striatal neurons exhibited a flat basal firing probability to the right of the burst in autocorrelograms indicative of a random distribution of interburst intervals, a few cells in both samples exhibited a slow rhythmicity in the occurrence of bursts. Slow rhythms had periods of 0.6-0.7 sec and multiples of that period, and were similar to those previously reported for neurons of reticular formation22 and substantia nigra35. As in these latter cases, rhythmic firing could not be entrained by alteration of the respiratory rate. No rhythmicity in the 3-5 Hz range reported by investigators recording, from animals under barbiturate anesthesia17,28 could be detected.

The internal structure of spontaneous burst of firing in striatal neurons was examined in autocorrelograms constructed using bin widths of 0.8, 1.6 or 3.2 msec, and in first order interval histograms computed at the same bin widths. Interval histograms were all skewed toward long intervals, with the mean interspike interval being considerably greater than the modal interval. Modal intervals provided the best estimate of intraburst firing rate, and varied between 8 and 75 msec. There was no relationship between modal interval and burst duration or burst strength. Autocorrelograms constructed with short bin widths revealed no indication of rhythmic firing within bursts. Two examples from spontaneously active spiny neurons are shown in Fig. 3C and D. The spike train shown in Fig. 3C contained many short interspike intervals, with a modal interval of 20 msec. The neuron in Fig. 3D exhibited a longer modal interval and more regular firing within bursts, but this tendency was not sufficient to generate any reliable rhythmic firing within bursts. In all cases, interspike intervals within bursts appeared to be randomly distributed except for a tendency for action potentials not

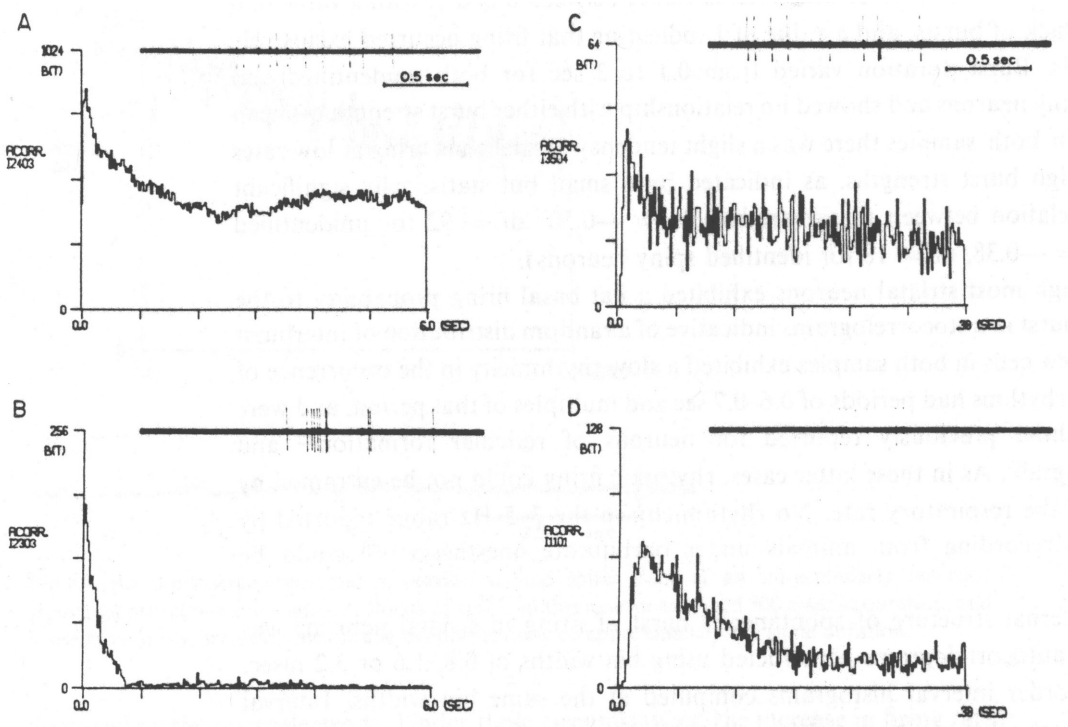

Fig. 3. Autocorrelograms and portions of the extracellularly recorded spike trains of 4 representative identified spiny neurons, illustrating the range of variation of firing pattern of these cells. Autocorrelograms in A and B are constructed with a long bin width to show the durations of bursts, and the basal firing probability. In C and D, a 1.6 msec bin width has been used to illustrate details of the intraburst firing pattern.

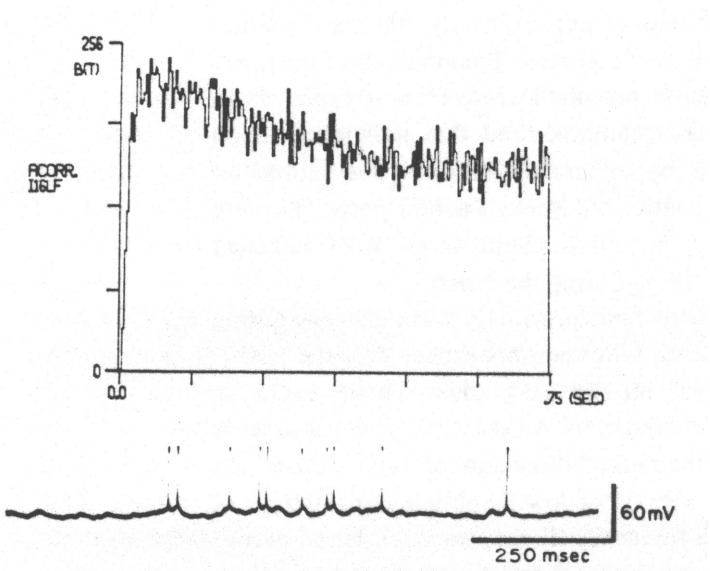

Fig. 4. An autocorrelogram and a portion of the spike train of an intracellularly recorded spontaneously active spiny neuron. Bursts of spikes in this neuron averaged 500 msec in duration, and arose from noisy, irregular membrane depolarizations of approximately the same duration.

to follow other spikes at intervals smaller than 8-20 msec.

The variation of firing pattern between neostriatal neurons, including identified spiny neurons, suggests the possibility that single neurons may undergo spontaneous changes in firing pattern. Examination of successive stable segments of spike trains from single neurons revealed that most of the range of variability observed between cells could be reproduced in single neurons if a sufficient period for examination were available. These changes in firing pattern could not be linked to position in the nucleus, nor to any gross indication of the state of the animal.

Intracellularly recorded firing patterns

Upon impalement with the microelectrode most neurons showed dramatic increases in firing rate. With relatively secure impalements, spontaneously active neurons continued to exhibit firing of the type previously described even when damaged by the microelectrode. Under these circumstances, the increase in firing rate had no effect on burst duration or interburst interval when compared to the extracellular record, but was accounted for by an increase in the frequency of firing within bursts and between bursts. A few spontaneously active neurons

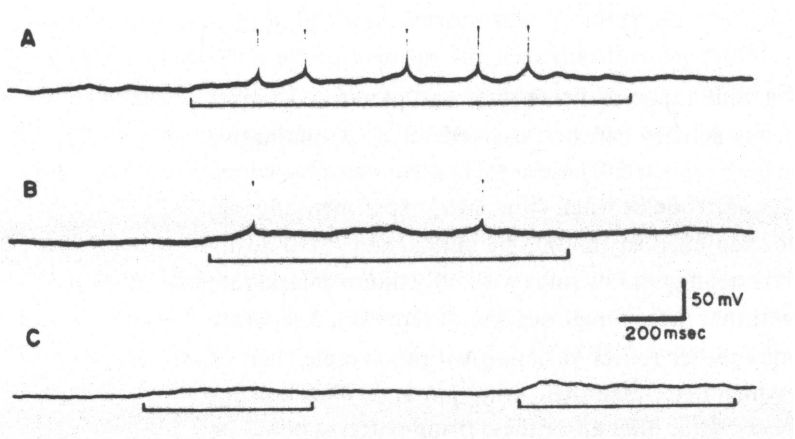

Fig. 5. Intracellularly recorded records from a 'silent' neostriatal neuron which exhibited no spontaneous firing prior to penetration by the microelectrode. The traces shown in A, B and C show the same neuron at different times during the process of repolarization which followed impalement of the neuron. Brackets indicate the occurrence of depolarizing episodes which in A and B are associated with bursts of action potentials similar to those seen in spontaneously active neurons.

repolarized in the first few minutes after impalement, and activity at rates comparable to that seen extracellularly could be recorded for a period of 10-30 min, allowing quantitative analysis of their intracellularly recorded firing patterns. The autocorrelogram of one such neuron (bin width 3.2 msec) and a sample of the photographic record of its spike train are shown in Fig. 4. This neuron exhibited firing in bursts of approximately 500 msec average duration and a modal interspike interval of about 30 msec. Examination of the intracellular record revealed that bursts of action potentials arose from irregular small amplitude depolarizations of the neuronal membrane, and that individual action potentials occurred at times determined by apparently random fluctuations of membrane potential during these depolarizations. Although action potentials were often followed by brief repolarizing after potentials, these were not of sufficient strength or duration to generate rhythmic firing during the bursts.

Similar firing patterns were obtained for some previously silent neurons during the period of membrane repolarization which followed impalement with the microelectrode. These neurons are of particular interest since their activity could be observed at various degrees of membrane polarization. An example of such a series is shown in Fig. 5. When first impaled, the injury discharge of this neuron was modulated by approximately 0.2-1.5 sec periods of low amplitude depolarizations (5-20 mV) associated with increased firing frequency (Fig. 5, trace A). Upon partial repolarization, action potentials occurred only during these periods of depolarization, and activity was similar to that seen in spontaneously active neurons (Fig 5, trace B). With further recovery from impalement, irregular periods of depolarization continued to occur at the same frequency and with the same duration, but usually failed to trigger action potentials (Fig. 5 trace C). Since these depolarizations, as well as those seen in intracellular recordings of spontaneously active neurons, were most clearly observed in the best recordings, and since they were associated with firing patterns indistinguishable from those seen extracellularly, they seem unlikely to have been due to electrode movement or other recording artefacts. Their occurrence in spontaneously active neurons, silent neurons provoked to fire by artificial depolarization, and neurons not firing action potentials at all suggests that they represent a temporal patterning in the synaptic input to the neostriatal spiny neuron and are affected little or not at all by the occurrence of action potentials in the postsynaptic neuron.

DISCUSSION

Neostriatal neurons exhibit a wide range of firing rates and patterns. In most preparations from which spontaneous activity can be observed at all, 3 qualitative categories of neuronal activity have been reported. These are: (1) silent neurons, which fire only when damaged by the microelectrode or when stimulated experimentally; (2) phasically active neurons which fire spontaneously in discrete bursts; and (3) tonically active neurons which fire more or less steadily at low rates with only minor phasic rate variations. The present results suggest that these categories do not represent 3 separate and distinct modes of firing, but may rather reflect variation within a single class of neurons along several dimensions which determine their firing patterns. This conclusion is supported not only by the observation that all of these firing patterns could be observed with a single morphological class of neurons in the neostriatum, but also by the continuous variation of these neurons along the dimensions of intraburst firing rate, firing between bursts, interburst interval and burst duration. Finally, in those spiny neurons from which stable intracellular recordings were obtained, these dimensions of the firing pattern were apparently related to the overall degree of membrane polarization and to the size, duration and frequency of occurrence of depolarizing episodes which were present in neurons regardless of their firing rate.

The spiny neostriatal neurons examined in these experiments are only one of a number of cell types which have been described from studies of Golgi-impregnated material10,12,18. If neurons of other types were present in the sample of unidentified neurons however, they were either indistinguishable from the spiny neurons or were too few in number to influence the overall distributions of the sample along any of the measured dimensions. In either case, it must be considered that markedly different spontaneous firing patterns may not reflect the behavior or morphologically distinguishable cell types in the neostriatum. Thus, the well-documented variations in the responses of neostriatal cells firing in different spontaneous patterns may instead represent alternative states of responsiveness of a single striatal neuron type.

A compelling body of evidence now indicates that a large proportion of neostriatal efferents originate from neurons of the type identified in the present experiments10,15,26,30. These efferent neostriatal fibers appear to be inhibitory in their action on tonically firing neurons of substantia nigra and pallidum8,13,37,38, which in turn inhibit their target neurons in the thalamus9,32,33, superior colliculus7, and perhaps other brain stem structures14,24. Bursts of firing observed in neostriatal spiny cells may therefore result in phasic pauses in the high frequency discharge of basal ganglia output neurons (in pallidum and substantia nigra) and a resultant disinhibition of their target cells. The independence of burst duration and firing rate in neostriatal spiny neurons allows that at least these 2 dimensions are available for the coding of information in single efferent axons of this structure.

The observation that depolarizing episodes associated with bursts of firing in spontaneously active neurons continue to occur in silent neostriatal neurons, and that artificial depolarization of these neurons may produce activity similar or identical to that of spontaneously active

neurons suggests that the low rates of firing observed in most neostriatal neurons is due simply to membrane polarization below the threshold for action potential generation. The same conclusion was drawn by Sugimori et al.31 in their study of the membrane properties and repetitive firing characteristics of neostriatal neurons in the cat. One explanation for this extreme state of polarization is the possibility that these neurons may be subject to a strong tonic inhibitory influence, either from within the neostriatum or via one of its afferents. Electron microscopic examination of identified neostriatal spiny neurons has revealed the presence of intrinsic synapses placed proximally on the dendrites, somata and initial segments of the axons of these cells34. One class of these are formed by the axon collaterals of other spiny neurons. Inhibition acting through this recurrent pathway in a population of slowly firing spiny neurons seems an unlikely source for a strong tonic inhibitory influence. especially in the case of animals lightly anesthetized with barbiturates or urethane, in which practically no spontaneous activity can be recorded at al5,11,17,21. Even in the unanesthetized neostriatum the low rate and phasic pattern of firing of spiny neurons makes them unlikely candidates for the source of a constant tonic inhibitory influence on each other, unless their mutual inhibitory effects were of very long duration. The most recent evidence suggests instead that the inhibitory effects exerted by spiny neurons are of quite short duration20,25. The recurrent self-inhibitory mechanism demonstrated in neostriatal spiny neurons by Park et al.25, which is likely to be similar or identical to that occurring between spiny neurons, is a more appropriate candidate for the origin of the initial 8-30 msec trough in firing probability which follows action potentials in spiny neurons. Other proximally placed synapses on neostriatal spiny neurons arise from an unknown intrinsic source34. lt cannot be excluded that the neurons giving rise to these synapses are tonically active and responsible for a constant inhibition of neostriatal neurons. lf they are, however, their activity must have gone undetected in numerous studies of extracellularly recorded neostriatal neuronal activity.

Although local inhibitory interactions seem likely to be involved in the patterning of spiny cell firing, such effects may not be necessary to account for either the low tonic firing rates or the bursty firing patterns of these neurons. Segundo et al.29 have examined the theoretical effects of various patterns of synaptic activity impinging on a model neuron. These authors found that in neurons receiving a large number of relatively weak uncorrelated inputs, activity in the input channels results in a constant bias on the postsynaptic neuron. Neurons under these circumstances tended to fire tonically, and the form of the resulting spike train was determined more by the properties of the neuron than by those of its afferent pattern of input. If some of the inputs became even weakly correlated, however, periods of high firing rate interspersed with others of relatively slow firing were seen to result. The duration and strength of the bursts generated in this way were determined primarily by the firing patterns of the input channels and by the form of their correlation. Presently available evidence from intracellular recording following stimulation of neostriatal afferents13, 16,19,27 suggests that most or all neostriatal afferents are excitatory in nature. These afferent fibers form contacts with neostriatal spiny neurons exclusively on the spiny portion of the dendrites, and almost always on long thin dendritic spines which are likely to reduce the effects exerted by individual synapses to negligible levels18,34. The sensitivity of the spiny neuron to brief single synaptic events is reduced still further by the long time constant of the membrane of these neurons31. The high degree of convergence and divergence implicit in the cruciform axo-dendritic organization of the neostriatal neuropil12 suggests that these synapses are derived from a large number of different (although functionally related) axons from other structures. Thus, spiny neurons may require the relatively rare occurrence of temporally coincident maintained activity in a large number of different afferent axons in order to be depolarized sufficiently to fire action potentials. In this case, the fine structure of the depolarizations and of the resulting spike train might be highly variable and determined primarily by the patterns of afferent activity.

Recent anatomical evidence reveals that areas of the cerebral cortex which are interconnected by means of cortico-cortical projections terminate within the same region of caudate-putamen15,36. Convergence of temporally coherent activity from these reciprocally interrelated cortical areas and perhaps from topographically related thalamo-striatal inputs might provide the correlated inputs required to activate the striatal spin neuron.

ACKNOWLEDGEMENTS

Supported in part by Grant DA 01467 and Research Scientist Development Award DA 00056 from the National Institute on Drug Abuse (to P. M. G.) and Grant NIH RR 07013 from the National Institute of Health Division of Research Resources to the Graduate School of the University of Colorado.

We thank Stephen J. Young for his assistance and advice, and S. T. Kitai and M. R. Park for their critical readings of the manuscript.

REFERENCES

1 Anderson, M. E., Discharge patterns of basal ganglia neurons during active maintenance of postural stability and adjustment to chair tilt, Brain Research, 143 (1977) 325-338.

2 Baldwin, D. J., Dry beveling of micropipette electrodes, J. neurosci. Meth., 2 (1980) 153-161.

3 Bloom, F. E., Costa, E. and Salmoiraghi, G. C., Anesthesia and the responsiveness of individual neurons of the

caudate nucleus of the cat to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis, J. Pharmacol. exp. Ther., 150 (1965) 244-252.
4 Carpenter, M. D., Anatomical organization of the corpus striatum and related nuclei. In M. D. Yahr (Ed.), The Basal Ganglia, Raven Press, New York, 1976, pp. 1-35.
5 Connor, J. D., Caudate nucleus neurones: correlation of the effects of substantia nigra stimulation with iontophoretic dopamine, J. Physiol. (Lond.), 208 (1970) 691-703.
6 DeLong, M. R., Putamen: activity of single units during slow and rapid arm movements, Science, 179 (1973) 1240-1242.
7 Deniau, J. M., Chevalier, G. and Feger, J., Electrophysiological study of the nigro-tectal pathway in the rat, Neurosci. Lett., 10 (1978) 215-220.
8 Deniau, J. M., Feger, J. and LeGuyader, C., Striatal evoked inhibition of identified nigro-thalamic neurons, Brain Research, 104 (1976) 152-156.
9 Deniau, J. M., Lackner, D. and Feger, J., Effect of substantia nigra stimulation on identified neurons in the VL-VA thalamic complex: comparison between intact and chronically decorticated cats, Brain Research, 145 (1978) 27-35.
10 DiFiglia. M., Pasik, P. and Pasik, T., A Golgi study of neuronal types in the neostriatum of monkeys, Brain Research, 114 (1976) 245-256.
11 Feltz, P. and Albe-Fessard, D., A study of an ascending nigro-caudate pathway, Electroenceph. clin. Neurophysiol., 33 (1972) 179-193.
12 Fox, C. A. Andrade, A. N., Hillman, D. E. and Schwyn, R. C., The spiny neurons in the primate striatum: a Golgi and electron microscopic study, J. Hirnforsch., 13 (1971/72) 181-201.
13 Frigyesi, T. L. and Purpura, D. P., Electrophysiological analysis of reciprocal caudato-nigral relations. Brain Research, 6 (1967) 440-456.
14 Gottesfeld, Z., Massari, V. J., Muth, E. A. and Jacobowitz, D. M., Stria medullaris: a possible pathway containing GABA-ergic afferents to the lateral habenula, Brain Research, 130 (1977) 184-189.
15 Grofova, I., Extrinsic connections of the neostriatum. In I. Divac and R. G. E. Oberg (Eds.), The Neostriatum, Pergamon Press, New York, 1979, pp. 37-51.
16 Hull, C. D., Bernardi, G. and Buchwald, N. A., Intracellular responses of caudate neurons to brain stem stimulation, Brain Research,22 (1970) 163-179.
17 Katayama, Y., Tsubokawa, T. and Moriyasu, N., Slow rhythmic activity of caudate neurons in the cat. Statistical analysis of caudate neuronal spike trains, Exp. Neurol., 68 (1980) 310-321.
18 Kemp, J. M. and Powell, T. P. S., The structure of the caudate nucleus of the cat: light and electron microscopy, Phil. Trans. B, 262 (1971) 383-401.
19 Kitai, S. T., Kocsis, J. D., Preston, R. J. and Sugimori. M., Monosynaptic inputs to caudate neurons identified by intracellular injection of horseradish peroxidase, Brain Research, 109 (1976) 601-606.
20 Lighthall, J. W., Park, M. R. and Kitai, S. T., Inhibition in slices of rat neostriatum, Brain Research, in press.
21 Liles, S. L., Single unit responses of caudate neurons to stimulation of frontal cortex, substantia nigra and entopeduncular nucleus in cats, J. Neurophysiol., 37 (1974) 254-265.
22 MacGregor, R. J., Miller, S. W. and Groves, P. M., Slow rhythms and correlations in spike trains from midbrain neurons, Exp. Neurol., 47 (1975) 581-595.
23 Matsunami, K. and Cohen, B., Afferent modulation of unit activity in globus pallidus and caudate nucleus: changes induced by vestibular nucleus and pyramidal tract stimulation, Brain Research, 91 (1975) 140-146.
24 Nagy, J. I., Carter, D. A., Lehmann, J. and Fibiger, H. C., Evidence for a GABA-containing projection from the entopeduncular nucleus to the lateral habenula in the rat, Brain Research, 145 (1978) 360-364.
25 Park, M. R., Lighthall, J. W. and Kitai, S. T., Recurrent inhibition in the rat striatum, Brain Research, 194 (1980) 359-369.
26 Preston, R. J., Bishop, G. A. and Kitai, S. T., Medium spiny neuron projection from the rat striatum: an intracellular horseradish peroxidase study, Brain Research, 183 (1980) 253-263.
27 Purpura, D. P. and Milliani, A., Intracellular studies of the corpus striatum. I. Synaptic potentials and discharge characteristics of caudate neurons activated by thalamic stimulation, Brain Research, 6 (1967) 325-340.
28 Sedgwick, E. M. and Williams, T. D., The response of single units in the caudate nucleus to peripheral stimulation, J. Physiol. (Lond.), 189 (1967) 281-298.
29 Segundo, J. P., Perkel, D. H., Wyman, H., Hegstad, H. and Moore, G. P., Input-output relations in computer-simulated nerve cells. Influence of the statistical properties, strength, number and interdependence of excitatory pre-synaptic terminals, Kybernetick, 4 (1968) 157-171.
30 Somogyi, P. and Smith, A. D., Projection of neostriatal spiny neurons to the substantia nigra. Application of a combined Golgi-staining and horseradish peroxidase transport procedure at both light and electron microscopic levels, Brain Research, 178 (1979) 3-15.
31 Sugimori, M., Preston, R. J. and Kitai, S. T., Response properties and electrical constants of caudate nucleus neurons in the cat, J. Neurophysiol., 41 (1978) 1662-1675.
32 Ueki, A., Uno, M., Anderson, M. and Yoshida, M., Monosynaptic inhibition of thalamic neurons produced by stimulation of the substantia nigra, Experientia (Basel), 33 (1977) 1480-1482.
33 Uno, M. and Yoshida, M., Monosynaptic inhibition of thalamic neurons produced by stimulation of the pallidal nucleus in the cat, Brain Research, 99 (1975) 337-380.
34 Wilson, C. J. and Groves, P. M., Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum. A study employing intracellular injection of horseradish peroxidase, J. comp. Neurol., 194 (1980)

599-615.
35 Wilson, C. J., Young, S. J. and Groves, P. M., Statistical properties of neuronal spike trains in the substantia nigra: cell types and their interactions, Brain Research, 136 (1977) 243-260.
36 Yeterian, E. and van Hoesen, G., Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections, Brain Research, 139 (1978) 43-63.
37 Yoshida, M. and Precht, W., Monosynaptic inhibition of neurons of the substantia nigra by caudato-nigral fibers, Brain Research, 32 (1971) 225-228.
38 Yoshida, M., Rabin, A. and Anderson, M., Monosynaptic inhibition of pallidal neurons by axon collaterals of caudato-nigral fibers, Exp. Brain Res., 15 (1972) 333-347.