In Vivo Development of the Spontaneous Activity of Rat Nigrostriatal Dopaminergic Neurons

James M. Tepper[1], Francine Trent[2] and Shoji Nakamura[3]

[1]Center for Molecular and Behavioral Neuroscience, [2]Department of Biological Sciences, Rutgers, The State University of New Jersey, Newark, NJ 07102 and [3]Kanazawa University Faculty of Medicine, Kanazawa 920, Japan

INTRODUCTION

Dopaminergic neurons, along with other monoamine neurons, are known to be among the earliest neurons in the central nervous system to differentiate morphologically and neurochemically, and to send axons to their target regions (Olson and Seiger, 1972; Seiger and Olson, 1973; Voorn et al., 1988). Despite our knowledge of the morphological development of dopaminergic neurons, little is known about the time course of the development of the electrophysiological properties of these neurons. If dopaminergic neurons are physiologically functional early in ontogeny, they may play a role in the development of their target structures, analogous to that shown for noradrenergic neurons in a number of studies (Kasamatsu and Pettigrew, 1976; Pettigrew and Kasamatsu, 1976; Blue and Parnevelas, 1982). Information on the development of dopaminergic neurons *in situ* may also be relevant to our understanding of the physiological functioning of dopaminergic neurons grafted to the dopamine-denervated striatum. Thus the present experiments were carried out to characterize the developmental profile of the *in vivo* spontaneous activity of rat nigrostriatal dopaminergic neurons from birth through maturity.

METHODS

Subjects

Subjects consisted of 68 Sprague-Dawley pups derived from pregnant dams (obtained from Charles River or The Institute for Animal Behavior at Rutgers). Pregnant females were checked daily for the presence of new litters, and the day of birth was considered to be postnatal day 1 (PD1). The ages of the rat pups used ranged from PD1 to PD28, and their weights varied from 6.5 g to 74.5 g. Pups were anesthetized by intraperitoneal injection of urethane (1.3 mg/g body weight), and supplemented by inhalation of metofane (methoxyfluorane) if necessary, and installed into a modified stereotaxic device described by Nakamura and colleagues (Nakamura et al., 1987). Body temperature was maintained at 37 $\pm$ 1° C with a solid state heating pad.

For purposes of comparison with nigrostriatal dopaminergic neurons from adult rats, 12 male Sprague-Dawley rats, over 75 days of age (weights ranging from 240-460 g) were anesthetized with urethane (1.3 g/kg, i.p.) and installed in a stereotaxic frame according to standard procedures (e.g., Tepper et al., 1984).

Electrical Stimulation

For purposes of antidromic identification, a small burr hole was drilled overlying the anterior-lateral neostriatum (coordinates 0.5-0.7 mm anterior to bregma, 2.4-3.5 mm lateral to the midline) and an bipolar, stainless steel stimulating electrode (Tepper et al., 1984) was inserted to depths ranging from 2.2-3.4 mm below the cortical surface. In adult rats the stimulating electrode

The Basal Ganglia III, Edited by G. Bernardi *et al.*
Plenum Press, New York

was positioned in the anterior-lateral dorsal neostriatum at coordinates 1.0 mm anterior to bregma, 3.7 mm lateral and 4.0 mm below the cortical surface. Constant current stimuli, 0.1 to 5.0 mA at a pulse duration of 500 µsec were delivered at a rate of 0.67 Hz by a Winston A-65 timer/stimulator and Winston SC-100 stimulus isolation units.

Recording

A 1.5 mm diameter burr hole was drilled overlying the substantia nigra at coordinates 0.8-1.5 mm anterior to lambda and 0.7-1.5 mm lateral to the midline for neonates and 2.1 mm anterior to lambda and 2.0 mm lateral to the midline for adults. Single unit extracellular discharges were recorded with glass micropipettes filled with 2% Pontamine Sky Blue in 2 M NaCl, possessing *in vitro* impedances of 5-10 MOhms. Electrode signals were amplified with a Neurodata IR183 preamplifier and displayed on a Tektronix 5113 storage oscilloscope. Typical filter settings were 100 or 1 kHz low pass and 10 kHz or 30 kHz high pass. All data were recorded on magnetic tape for off-line analysis.

Data Analysis

Spike trains were played back from tape off-line and input to a Macintosh II microcomputer through a National Instruments MIO16L multifunction board. Spontaneous activity was analyzed for firing rate, and pattern of activity by means of first order interspike interval histograms and autocorrelograms and a statistical analysis of burst firing. Analyses of spike waveforms were obtained by digital averaging of 5-10 action potentials.

For purposes of statistical analysis, data from rats were pooled and assigned to one of the following groups: PD1-3, PD4-6, PD7-10, PD11-15, PD16-21, PD22-28 and ADULT. A one way analysis of variance was performed on a number of parameters including spontaneous firing rate, number of spikes per burst, burst length, mean interspike interval, duration of the extracellularly recorded spontaneous action potential, antidromic threshold, antidromic latency, and proportion of antidromic spikes consisting of full, initial segment-somadendritic (IS-SD) spikes. Where appropriate, differences between specific age groups were tested with Scheffé's F Test at the $p<0.1$ level of significance.

Histology

At the end of each experiment, the stimulating site was marked by a small DC lesion made with the stimulating electrode. The last recording site was marked by iontophoresis of Pontamine Sky Blue through the recording electrode. Animals were perfused with 10-20 ml normal saline followed by 50-70 ml of 10% formalin. The brains were removed, post-fixed in 10% formalin and sectioned on a vibratome. Sections were stained with neutral red and each stimulation site and the site of the last recording marked by a Pontamine Sky Blue dot were noted, photographed and/or drawn at 1X with a Nikon Labophot microscope equipped with a drawing tube.

RESULTS

Neuronal Identification

Extracellular recordings were obtained from 165 antidromically driven neurons in 68 rat pups and from 26 neurons from 12 adult rats presumed to be dopaminergic nigrostriatal neurons. Neurons recorded from neonates in this study were assumed to be dopaminergic nigrostriatal neurons provided that they could be antidromically activated from ipsilateral neostriatum with latencies greater than 9 ms, and provided that later histological analysis indicated that the neurons were located within the region of the substantia nigra, pars compacta. Evoked responses were considered antidromic provided that they collided with appropriately timed spontaneous spikes, or, for neurons that exhibited little or no spontaneous activity, could follow twin pulse stimulation with interstimulus intervals corresponding to a train of 200 Hz. Neurons encountered in the vicinity of the substantia nigra pars compacta that were not antidromically driven were excluded from study. All 26 neurons from adult rats fulfilled previously published electrophysiological criteria for nigrostriatal dopaminergic neurons (Guyenet and Aghajanian, 1978; Deniau et al., 1978; Grace and Bunney, 1983a).

Mean Firing Rates

Spontaneously active nigrostriatal dopaminergic neurons could be recorded as early as PD1, although a number of antidromically responsive neurons exhibited little or no spontaneous firing at this age. The mean firing rate of nigrostriatal dopaminergic neurons increased with age from PD1-3 through PD22-28 ($F=30.18$, $df=6, 138$, $p<.001$), with a concomitant decrease in the mean interspike interval (ISI) over this developmental span ($F=11.99$, $df=6,132$, $p<.001$). Although not subjected to a statistical analysis, the number of non-spontaneously active neurons appeared to decrease steadily through the first 3 postnatal weeks. By PD22-28, mean firing rates and mean ISIs no longer differed from those in adults. Developmental changes in mean firing rate and interspike interval are illustrated in Figure 1.

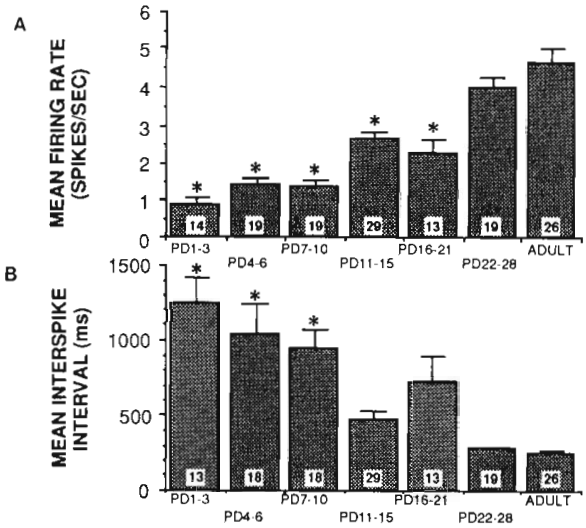

Figure 1. Changes in parameters of spontaneous activity of nigrostriatal neurons during development. A. Mean firing rate increases from PD1-3 through PD22-28. B. Mean interspike intervals decrease from PD1-3 through PD22-28. Numbers within the bars indicate number of neurons per group. Error bars represent SEM. Asterisks indicate significant difference from adult controls.

Spontaneous Firing Pattern

Firing pattern was analyzed by computing autocorrelograms from samples of spontaneous activity for each neuron and by computing the mean number of spikes per burst and the mean burst duration for neurons that exhibited at least one burst of 2 or more spikes. Burst onset was defined as an interspike interval of 80 ms or less, and the burst termination was defined as defined as the first interspike interval that exceeded 160 ms following the onset of a burst, according to criteria previously defined for nigral dopaminergic neurons in adult rats (Grace and Bunney, 1984).

The pattern of spike activity changed significantly over development. Dopaminergic neurons from the earliest postnatal group often displayed only sporadic spontaneous activity into which was imbedded long periods (up to several minutes but typically on the order of 5-45 seconds) of silence. PD1-3 neurons rarely fired in bursts. Over the next week, mean firing rate increased and some neurons began to exhibit short bursts consisting almost exclusively of two spikes with a very stereotyped interspike interval of 60.4 ± 0.65 ms in an otherwise random firing pattern. The spontaneous firing rate continued to increase over the next week. During this stage (PD7-15) nigrostriatal neurons exhibited a transient phase of very regular, almost pacemaker-like rhythmic activity, occasionally interrupted by the two-spike bursts. This firing pattern was most apparent in autocorrelograms that displayed multiple initial peaks, resembling repetitive firing of nigral pars compacta neurons in adult rats (Wilson et al., 1977). Over the next week the incidence of rhythmic firing decreased, as the occurrence of doublet bursts as well as longer bursts increased. The was a significant developmental increase in both the duration of the burst ($F=5.79$, $df=6, 78$, $p<.001$) and the number of spikes per burst ($F=4.88$, $df=6, 78$, $p<.001$) but not in the interval between the first and second spikes in a burst. By PD16-21, neither the average burst duration nor the number of spikes per burst differed from adults. Sample spike trains and their associated autocorrelograms from different developmental phases are illustrated in Figure 2. Additional burst statistics are presented in Table 1.

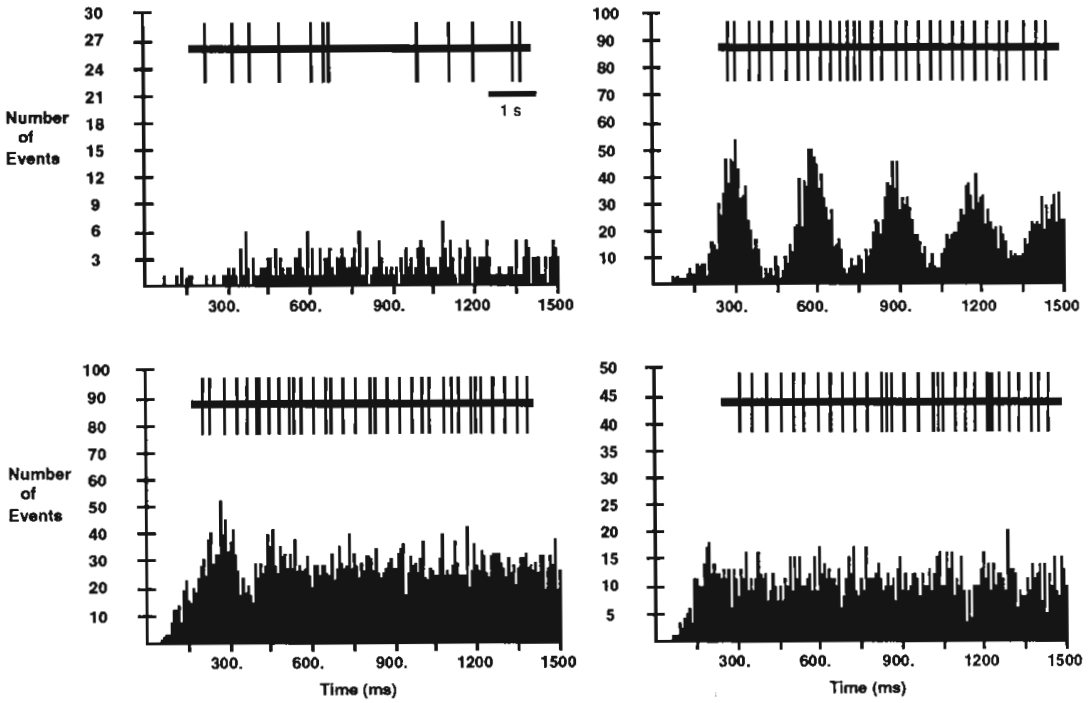

Figure 2. Autocorrelograms and portions of the spike trains from which they were constructed illustrating developmental changes in the pattern of spontaneous activity of nigrostriatal neurons. Top left. PD3 rat shows sporadic random firing. Top right. PD9 rat shows the very regular, almost pacemaker-like pattern transiently expressed during the second postnatal week. Bottom left. PD25 rat shows essentially mature firing pattern including some bursting. Bottom right. Adult control showing typical irregular pattern.

Action Potential Morphology

The morphology of the extracellularly recorded spontaneous action potential waveform also changed significantly during postnatal development, as illustrated in Figure 3. Neurons from the youngest animals exhibited action potentials of relatively low amplitude with a poor signal to noise ratio. Spike waveforms were of significantly greater duration in the neonates compared to adults ($F=7.99$, $df=6, 125$, $p<.001$), due in part to a broadening of the SD spike component in neurons from the youngest animals. In contrast, as soon as the IS component of the spike became reliably distinguishable (around PD 4-6), it did not change in either amplitude or duration through adulthood. There was a significantly greater delay between the IS and SD components of the action potential in the neonates than in adults. From birth through the third postnatal week, spike amplitudes increased continuously due to an increase in the amplitude of the SD component of the spike. A progressive shortening of the IS-SD delay was also apparent over this span. By the end of the third postnatal week, the morphology of the extracellularly recorded spike waveform was not significantly different from that of nigral neurons in adult rats.

Antidromic Response Properties

Antidromic responses could be reliably elicited by neostriatal stimulation in the earliest animals tested, pups as young as 6 hours post-partum, as illustrated for one PD1 rat in Figure 4. Similar to antidromic responses of nigrostriatal dopaminergic neurons from adults, striatal-evoked antidromic responses in neonatal rats most often consisted of the IS spike only, with the action potential failing to invade the SD portion of the neuron even at modest rates of stimulation (Guyenet and Aghajanian, 1978; Deniau et al., 1978, Tepper et al., 1984). However, the proportion of antidromic spikes consisting of a full IS-SD spike was significantly greater in neurons from neonates than from adults ($F=4.5$, $df=6, 210$, $p<.001$). Full spike (IS-SD) antidromic responses often exhibited a striking delay between the IS and SD components of the spike of up to a few milliseconds, particularly in neurons from the youngest animals. As previously reported for adult nigrostriatal neurons (Collingridge et al., 1980; Tepper et al., 1984), many neonatal nigrostriatal neurons

(53.2+7.7%) exhibited multiple, discrete antidromic latencies, even at constant stimulus currents. There were no significant developmental changes in the proportion of neurons exhibiting these multiple antidromic latencies. Neither the mean antidromic latency nor the mean antidromic

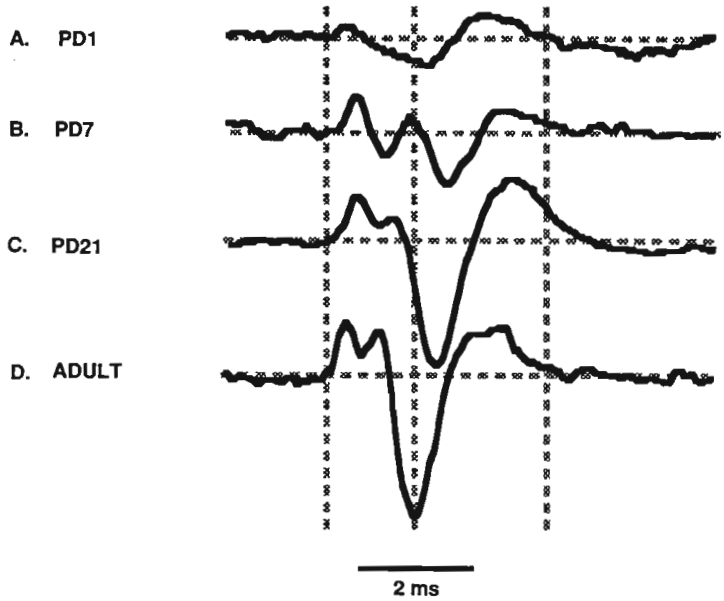

Figure 3. Representative developmental changes in the morphology and duration of extracellularly recorded spontaneous action potentials of nigrostriatal neurons. Dashed lines denote onset of IS spike, peak of SD spike, and return of SD spike to baseline for the adult control shown in D. Note progressive increase in the amplitude of the SD spike through PD21, and an overall reduction in spike duration due to a decrease in the IS-SD interval and a reduction in SD spike width. Each trace is the average of 5 single spikes from the same neuron. In this and in Figure 4, positivity is upwards.

threshold current (minimum current necessary to elicit 100% antidromic responding on non-collision trials) exhibited a significant developmental trend. Antidromic latencies and estimated conduction velocities are listed in Table 1 below.

Table 1. Developmental profile of additional neurophysiological parameters of nigral dopaminergic neurons. Cells bursting : Proportion of neurons firing at least one burst of greater than 2 spikes. Burst duration: Mean duration of all bursts of two or more spikes in ms. N Spikes/burst: Mean number of spikes per burst. AD latency: Antidromic latency in ms. Conduction velocity: Mean axonal conduction velocity in m/s estimated by dividing the straight line distance between recording and stimulating sites by the antidromic latency for each cell. Asterisks indicate significant difference from adult group.

	PD1-3	PD4-6	PD7-10	PD11-15	PD16-21	PD22-28	ADULT
CELLS BURSTING	3/13(23.1)	3/18(16.7)	1/18(5.6)	5/27(18.5)	4/13(30.8)	6/20 (30.0)	15/26(57.7)
BURST DURATION	60.1±2.2*	75.6±9.8*	61.0±2.8*	68.3±2.3*	115.8±20.4	108.4±17.1	167±28.7
N SPIKES/BURST	2.10±.10*	2.16±.09*	2.00±.01*	2.04±.01*	2.45±.18	2.33±.14	3.43±.44
AD LATENCY	15.5±.88	17.1±.43	17.08±.78	18.88±.69*	15.76±1.2	15.5±.93	14.95±.32
CONDUCTION VELOCITY	0.26±.027*	0.24±.011*	0.32±.027*	0.31±.022*	0.46±.032	0.46±.023	0.49±.011

DISCUSSION

Identification of Nigrostriatal Dopaminergic Neurons

Although the parameters of the spontaneous activity of nigral dopaminergic neurons in adult rats have been so well characterized as to rate, pattern and spike waveform that it is quite common to identify extracellular recordings as originating from dopaminergic neurons on the basis of these properties, since the electrophysiology of dopaminergic nigrostriatal neurons in neonates had not previously been characterized, this method was deemed unreliable for the present study. Instead, after it became clear that neonatal nigral neurons could be antidromically activated from neostriatum, and that the antidromic latencies and response properties were very similar to those in adults, neurons were tentatively identified as dopaminergic nigrostriatal neurons provided that they could be antidromically activated from ipsilateral neostriatum at appropriate latency (>9 ms), and provided that subsequent histological analysis indicated that the recording site was localized to the substantia nigra.

These criteria are sufficient to identify dopaminergic neurons since only two types of nigral neurons have been shown to project out of the substantia nigra: dopaminergic neurons located mainly in pars compacta but also to a lesser extent in pars reticulata which project to primarily to neostriatum, and non-dopaminergic neurons located mainly in pars reticulata which project primarily to tectum and thalamus, but occasionally to neostriatum (Guyenet and Aghajanian, 1978). In adults, discrimination between dopaminergic and non-dopaminergic nigrostriatal neurons is unequivocal since dopaminergic neurons exhibit antidromic latencies some 2-4 times greater than non-dopaminergic neurons, and because the antidromic response of dopaminergic neurons usually consists of IS spikes, even at low rates of stimulation (0.67 Hz) such as those employed in the present study (Guyenet and Aghajanian, 1978; Grace and Bunney, 1983a; Tepper et al., 1986). The nigrostriatal neurons recorded in the present study exhibited long-latency antidromic responses that usually consisted of the IS only spike, consistent with their identification as nigrostriatal dopaminergic neurons.

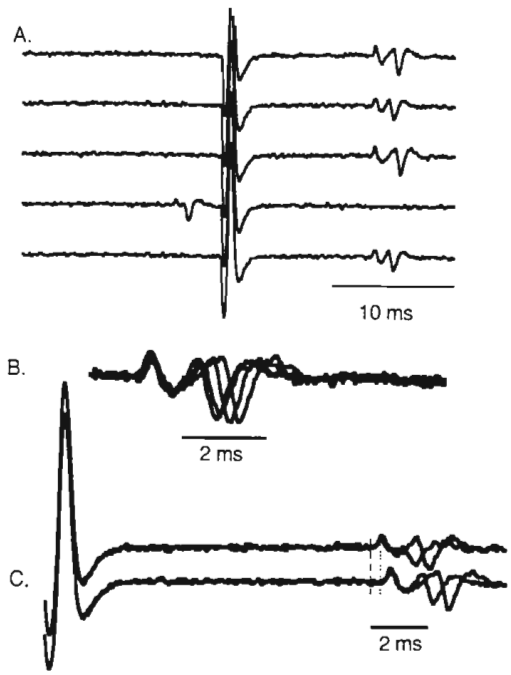

Figure 4. Antidromic responses of nigral dopaminergic neuron in a PD1 rat pup. A. Five consecutive sweeps illustrating antidromic responding from neostriatum. A collision with a spontaneous spike is shown in the fourth trace. Note variability of IS-SD delay. B. Four superimposed sweeps at higher time resolution showing constant latency to IS spike but long and variable IS-SD delay. C. Multiple discrete antidromic latencies to a constant stimulating current. Dashed lines indicate onset of IS spike for each pair of sweeps.

Firing Rate

The spontaneous firing rate of nigrostriatal neurons increased steadily from birth through the third postnatal week with a concomitant decrease in the mean interspike interval. This trend and its time course closely resembles that previously reported for locus coeruleus neurons in the rat (Nakamura et al., 1987), and confirm a report by Pitts et al., (1988) that the firing rates of nigrostriatal neurons from 4 week old rats do not differ from adults. Similar increases in spontaneous firing rates for feline basal ganglia neurons over postnatal development have been reported (Levine et al., 1982).

Firing Pattern

The pattern of spontaneous activity also changed markedly from birth through adulthood. In extracellular recordings obtained in adult rats *in situ*, nigral dopaminergic neurons fire principally in two different modes. The most commonly observed is an irregular pattern in which there is an initial prolonged trough in the autocorrelogram which then rises to an asymptotic value indicative of the mean firing rate. Less commonly observed is a pacemaker-like or repetitive mode, characterized by an initial trough in the autocorrelogram followed by a series of progressively diminishing peaks that eventually plateau out into the mean firing rate asymptote (Wilson et al., 1977). Bursting activity is seen imbedded in both of these modes, and is represented in the autocorrelogram by an early peak immediately following the initial trough.

Autocorrelograms from the youngest animals indicated that firing was almost totally random and irregular.There was very little bursting, and no repetitive activity. From the middle of the second week through the middle of the third week, neonatal nigral neurons exhibited a transient phase in which a large proportion of the neurons fired in a repetitive pacemaker pattern. Although not often seen in such high proportions in dopaminergic neurons from adult rats *in vivo*, this type of very regular firing pattern is typical of nigral dopaminergic neurons recorded in an *in vitro* slice preparation (Grace, 1987). From birth until PD15, when bursting occurred, it consisted of short bursts of only two spikes, with a very stereotyped interspike interval around 60 ms. By the fourth week, neonatal neurons exhibited autocorrelation histograms that displayed both types of adult firing modes, and proportion of spikes occurring in bursts and the average burst length did not differ from adults.

Spike Morphology

Recordings from the neonates tended to be relatively noisy, and the spikes were usually of lower amplitude and greater duration than that seen in the adult, except during periods of depolarization. During the early postnatal period,many neurons were encountered in which the IS spike appeared similar to that in the adult, but in which the SD spike followed at an unusually long delay, and was often equal to or smaller in amplitude than the IS spike. There was no apparent relationship between the firing rate of a neuron and the IS-SD delay. These phenomena are not typical of dopaminergic neurons from mature animals (Guyenet and Aghajanian, 1978; Tepper et al., 1984), except during spikes occurring late in bursts, when, as the soma becomes progressively more and more depolarized, the SD component of the action potential grows progressively smaller and increases in duration, presumably due to increasing depolarization-dependent inactivation of soma-dendritic sodium channels (Grace and Bunney, 1983a,b).

Antidromic Responses

The conduction times from substantia nigra to neostriatum, measured by the antidromic latency, remain constant from PD1 through adulthood, reflecting an increase in conduction velocity of approximately 2.5 times. A similar conservation of conduction time has also been noted for noradrenergic coeruleo-cortical axonal conduction in neonatal and adult rats (Nakamura et al., 1987). This suggests that whatever the roles played by the nigrostriatal dopaminergic system in neonatal neuronal development and adult motor functioning, the timing of dopaminergic nigrostriatal neurotransmission, presumably in relation to that of other afferents to neostriatum, would seem to be of critical importance.

As early as PD1, antidromic responses of many nigrostriatal neurons were observed to occur at discrete, multiple latencies. This phenomenon has been described previously for dopaminergic neurons in adult rats, and has been attributed to the highly branched nature of their terminal ar-

borizations (Collingridge et al., 1980; Tepper et al., 1984). The fact that such multiple latencies were observed at the same frequency in neonates as in adults suggests that dopaminergic terminal fields are highly developed and capable of sustaining impulse traffic at least as early as the day of birth.

Antidromic responses consisted of full IS-SD spikes significantly more often in neonates than adults. When full IS-SD antidromic responses occurred, there was often a very long delay (up to several ms) between the IS and the SD components, similar to that seen in spontaneous spikes described above. The delay was sometimes so great that the waveforms of these neurons in some ways resembled the waveforms of two coupled cells, previously reported to occur in nigral dopaminergic neurons in adults (Grace and Bunney, 1983c; Freeman et al., 1985). That this phenomenon does not represent recordings from electrotonically coupled neurons in the present results is argued by the large temporal variability between the two spike components, the consistent obliteration of both components of the spike during collision with spontaneous spikes, the failure to observe single spike waveforms of "normal" morphology representing the firing of one member of the pair during spontaneous activity, and the absence of an IS-SD break on the initial component of the second spike component. This phenomenon did not seem to be an artifact of cell damage, as it was obtained in neurons that were recorded from for up to 45 minutes without showing any signs of deterioration. Rather, the high proportion of IS-SD antidromic spikes as well as the increased delay between the two components may reflect a state of relative somadendritic depolarization (Grace and Bunney, 1983a,b).

Conclusions

Many of the physiological characteristics of neontal nigrostriatal neurons were remarkably similar to those obtained from fetal mesencephalic neurons grafted into the dopamine-denervated striatum by Fisher et al., (in press). These investigators reported that dopaminergic graft neurons display mean spontaneous firing rates below those of dopaminergic neurons *in situ* from adult rats, exhibit atypically long-duration action potentials, display a high frequency of pacemaker-type firing patterns, and burst activity that is largely constrained to the occurrence of two spikes with interspike intervals approximating 70 ms. These parameters appeared to change with the age of the graft, being most pronounced in grafts allowed to develop post-operatively for minimal times (~2 months), and more closely approximating values for mature nigral dopaminergic neurons *in situ* after post-operative development for 9 months. Interestingly, some properties i.e., spike duration and frequency and complexity of bursting activity did not change with time, and in the present study, measures of the complexity of bursting were among the last to mature. Thus, the electrophysiological properties of fetal dopaminergic neurons grafted to the striatum of 6-hydroxydopamine treated animals more closely resemble dopaminergic neurons *in situ* from neonatal animals than from adult animals, even after months of post-grafting development. These data suggest that grafted dopaminergic neurons may mature considerably more slowly than dopaminergic neurons *in situ*.

Several lines of evidence point towards the conclusion that dopaminergic nigral neurons in neonatal rats exist in a more depolarized state than in the adult. They are: (1) Decreased spike amplitude and increased spike duration. (2) Increased delay between the IS and SD components of both spontaneous and antidromically driven spikes. (3) Increased proportion of antidromic responses consisting of IS-SD spikes. The reason(s) for the relative depolarization of these neurons are not yet clear, but could be related to immature membrane properties of the neonatal neurons, as has been demonstrated with *in vitro* intracellular recordings in other systems (McCormick and Prince, 1987; Williams and Marshall, 1987), differences in tonic inhibitory GABAergic input from striatonigral and/or pallidonigral pathways (Graybiel and Ragsdale, 1983; Swann et al., 1989; Tepper et al., 1990), or an altered functioning or subsensitivity of somadendritic dopamine autoreceptors (Lacey et al., 1987; Pitts et al., 1988).

In summary, nigral dopaminergic neurons are active in neonatal rats at least as early as the day of birth, and show several signs of existing in a depolarized state relative to dopaminergic neurons of mature rats. At this time the dopaminergic axons are capable of conducting impulses to terminal zones in the neostriatum, and have already arborized to a considerable extent. Nigrostriatal conduction time is conserved from birth through maturity, over which time conduction velocity increases by a factor of 2.5. Between the third and fourth weeks of age, most of the

properties of the spontaneous activity of these neurons have reached, or are close to those of dopaminergic nigral neurons in mature rats.

Acknowledgements

We thank Judith S. Rankin for excellent technical assistance and Dr. Anne Mayer and the Institute of Animal Behavior for supplying us with rat pups. This research was supported by MH 45286, a Rutgers University Research Council Grant and a Henry Rutgers Research Fellowship awarded to JMT.

REFERENCES

Blue, M.E., & Parnavelas, J.G. (1982) The effect of neonatal 6-hydroxydopamine treatment on synaptogenesis in the visual cortex of the rat. *J. Comp. Neurol. 205*:199-205.

Collingridge, G.L., James, T.A., & MacLeod, N.K. (1980) Antidromic latency variations in nigral compacta neurons. *Experientia 36*:970-971.

Deniau, J.M., Hammond, C., Riszk, A., & Feger, J. (1978) Electrophysiological properties of identified output neurons of the rat substantia nigra (pars compacta and pars reticulata): Evidence for the existence of branched pathways. *Exp. Brain Res. 32*:409-422.

Fisher, L.J., Young, S.J., Tepper, J.M., Groves, P.M. & Gage, F.H. (1990) Electrophysiological characteristics of cells within mesencephalon suspension grafts. *J. Neurosci.* (in press).

Freeman, A.S., Meltzer, L.T., & Bunney, B.S. (1985) Firing properties of substantia nigra dopaminergic neurons in freely moving rats. *Life Sci. 36*:1983-1994.

Grace, A.A. (1987) The regulation of dopamine neuron activity as determined by *in vivo* and *in vitro* intracellular recordings.In L.A. Chiodo and A.S. Freeman (Eds.) *Neurophysiology of Dopaminergic Systems - Current Status and Clinical Perspectives*, Lakeshore Publishing Co., Grosse Pt., pp.1-66.

Grace, A.A., & Bunney, B.S. (1983a) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons-1. Identification and characterization. *Neuroscience 10*:301-315.

Grace, A.A., & Bunney, B.S. (1983b) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons-2. Action potential generating mechanisms and morphological correlates. *Neuroscience 10*:317-331.

Grace, A.A., & Bunney, B.S. (1983c) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons - 3. Evidence for electrotonic coupling. *Neuroscience 10*:333-348.

Grace, A.A., & Bunney, B.S. (1984) The control of firing pattern in nigral dopamine neurons: Burst firing. *J. Neurosci. 4*:2877-2890.

Graybiel, A.M., & Ragsdale, C.W., Jr. (1983) Biochemical anatomy of the striatum. In: P.C. Emson (Ed.)*Chemical Neuroanatomy*, Raven Press, New York, pp 427-504.

Guyenet, P.G., & Aghajanian, G.K. (1978) Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra. *Brain Res. 150*:69-84.

Kasamatsu, T., & Pettigrew, J.D. (1976) Depletion of brain catecholamines: Failure of ocular dominance shift after monocular occlusion in kittens. *Science 194*:206-209.

Lacey, M.G., Mercuri, N.B., & North, R.A. (1987) Dopamine acts on D2 receptors to increase potassium conductance in neurons of the rat substantia nigra zona compacta. *J. Physiol. (Lond.) 392*:397-416.

Levine, M.S., Fisher, R.S., Hull, C.D., & Buchwald, N.A. (1982) Development of spontaneous neuronal activity in the caudate nucleus, globus pallidus-entopeduncular nucleus, and substantia nigra of the cat. *Dev. Brain Res. 3*:429-441.

McCormick, D.A., & Prince, D.A. (1987) Post-natal development of electrophysiological properties of rat cerebral cortical pyramidal neurones. *J. Physiol. (Lond.) 393*:743-762.

Nakamura, S., Kimura, F., & Sakaguchi, T. (1987) Postnatal development of electrical activity in the locus ceruleus. *J. Neurophysiol. 58*:510-524.

Olson, l., & Seiger, A. (1972) Early prenatal ontogeny of central monoamine neurons in the rat: Fluorescence histochemical observations. *Z. Anat. Entwickl.-Gesch. 137*:301-316.
Pettigrew, J.D., & Kasamatsu, T. (1978) Local perfusion of noradrenaline maintains visual cortical plasticity. *Nature 271*:761-763.

Pitts, D.K., Freeman, A.S., & Chiodo, L.A. (1988) Dopamine neuron ontogeny: Electrophysiological studies. *Soc. Neurosci. Abstr. 14*:408.

Seiger, A., & Olson, L. (1973) Late prenatal ontogeny of central monoamine neurons in the rat.Florescence histochemical observations. *Z. Anat. Entwickl.-Gesh. 140*:281-318.

Swann, J.W., Brady, R.J., & Martin, D.L. (1989) Postnatal development of GABA-mediated synaptic inhibition in rat hippocampus. *Neuroscience 28*:551-561.

Tepper, J.M., Nakamura, S., Young, S.J., & Groves, P.M. (1984) Autoreceptor-mediated changes in dopaminergic terminal excitability: Effects of striatal drug infusions. *Brain Res. 309*:317-333.

Tepper, J.M., Sawyer, S.F., Young, S.J., & Groves, P.M. (1986) Intracellular recording and HRP staining of rat nigral neurons. *Soc. Neurosci. Abstr. 12*:1542.

Tepper, J.M., Trent, F., & Nakamura, S. (1990) Postnatal development of the electrical activity of rat nigrostriatal dopaminergic neurons. *Dev. Brain. Res.*, in press.

Voorn, P., Kalsbeek, A., Jorritsma-Byham, B., & Groenewegen, H.J. (1988) The pre- and postnatal development of the dopaminergic cell groups in the ventral mesencephalon and the dopaminergic innervation of the striatum of the rat. *Neuroscience 25*:857-887.

Williams, J.T., & Marshall, K.C. (1987) Membrane properties of adrenergic responses in locus coeruleus neurons of young rats. *J. Neurosci. 7*:3687-3694.

Wilson. C.J., Young, S.J., & Groves, P.M.(1977) Statistical properties of neuronal spike trains in the substantia nigra: Cell types and their interactions. *Brain Res. 136*:243-260.