

Mesocortical Dopaminergic Neurons.

1. Electrophysiological Properties and Evidence for Soma-Dendritic Autoreceptors

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GARIANO, R. F., J. M. TEPPER, S. F. SAWYER, S. J. YOUNG AND P. M. GROVES. *Mesocortical dopaminergic neurons. 1. Electrophysiological properties and evidence for soma-dendritic autoreceptors.* BRAIN RES BULL 22(3) 511-516, 1989.—Mesencephalic dopaminergic neurons were electrophysiologically identified by a variety of criteria, including antidromic activation from prefrontal or cingulate cortex, neostriatum, or nucleus accumbens in urethane-anesthetized rats. The mean firing rate of 98 mesocortical dopaminergic neurons was 2.9 ± 0.3 spikes/sec and did not differ from the mean firing rate found for nigrostriatal or nucleus accumbens dopaminergic neurons. Spontaneously active mesocortical dopaminergic neurons were inhibited by intravenous administration of either apomorphine (6 μ g/kg) or amphetamine (0.25 mg/kg). Whereas most antidromic responses of nigrostriatal and mesoaccumbens neurons consisted of the initial segment spike only, cortically-elicited antidromic responses typically consisted of a full initial segment-soma-dendritic spike. These findings are discussed with regard to the presence of soma-dendritic autoreceptors on mesocortical dopaminergic neurons.

Dopamine Autoreceptor Prefrontal cortex Ventral tegmental area Neostriatum Amphetamine

A variety of electrophysiological and biochemical evidence suggests that mesencephalic dopaminergic neurons projecting to the neostriatum and nucleus accumbens possess autoreceptors on their soma-dendritic and terminal regions that function in the autoinhibition of spontaneous activity (18), and transmitter synthesis and release (33,39). In contrast, considerable uncertainty exists concerning the physiological properties of those mesencephalic dopaminergic neurons projecting to the prefrontal and anterior cingulate cortices. It has been reported that these cells display unusually high levels of spontaneous activity (5) and dopamine turnover (2,20) compared to midbrain dopaminergic neurons projecting to subcortical structures (1, 3, 7, 8, 19, 35, 38, 40). These fast-firing mesocortical cells were also found to be relatively insensitive to the inhibitory effect of iontophoretic or systemic administration of the directly acting dopamine agonist, apomorphine (5), and it has been proposed that these properties may reflect an absence of autoreceptors on cortically-projecting dopaminergic neurons (5). However, other investigators have reported that dopaminergic

mesocortical neurons are, like nigrostriatal dopaminergic neurons, typically slow-firing (7,8) and sensitive to intravenous administration of either apomorphine or amphetamine (25,36). The present study was undertaken in order to reexamine the electrophysiological and neuropharmacological properties of dopaminergic neurons that project to prefrontal and anterior cingulate cortex and to compare them with those of nigrostriatal and mesoaccumbens dopaminergic neurons. Portions of this work have been presented in abstract form (11,12).

METHOD

Subjects

Male Sprague-Dawley rats (n=67) weighing between 220 g and 400 g at the time of recording were used for all experiments. Animals were anesthetized with urethane (1.3 g/kg, IP), the left femoral vein was cannulated for intravenous drug administration,

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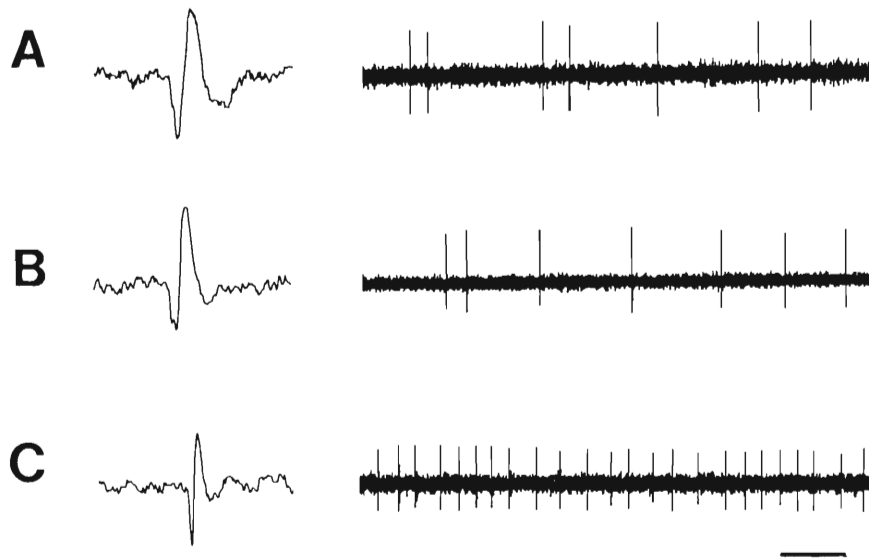


FIG. 1. Spontaneous action potentials of nigrostriatal (A) and mesoprefrontal (B) dopaminergic neurons. Note the wide triphasic waveform and the slight inflection in the initial phase, the initial segment-soma-dendritic (IS-SD) delay. Traces on the right show the typical slow irregular firing rate and pattern of these neurons. (C) Spontaneous action potential of a nondopaminergic mesoprefrontal neuron exhibits a narrower waveform without an IS-SD delay. When active, these neurons may fire in a more regular manner, as shown. Positive is down in this and all other figures. Calibration bar = 3.6 msec for traces on the left and 250 msec for those on the right.

and animals were secured in a Kopf stereotaxic apparatus. Body temperature was maintained at $37 \pm 1^\circ\text{C}$ by a thermostatically controlled heating pad. Stereotaxic coordinates were determined according to the atlas of König and Klippel (21).

Drugs

Apomorphine (Sigma; 6 $\mu\text{g}/\text{kg}$), D-amphetamine sulfate (Smith Kline and French; 0.25 mg/kg) and haloperidol lactate (McNeil Pharmaceuticals; 0.1 mg/kg) were dissolved in normal saline (0.1% ascorbate was added in the case of apomorphine) for intravenous administration. The effects of these drugs were examined on only one cell per animal to avoid complications arising from residual drug effects.

Electrical Stimulation

Bipolar enamel-coated stainless steel electrodes of 200 μm diameter and tip separation of 200–300 μm were positioned in the prefrontal cortex (10.2–11.4 mm anterior to lambda, 0.4–1.2 mm lateral to the midline, 2.0 mm ventral to the cortical surface), anterior cingulate cortex (A 8.5–9.5, L 0.4–0.6, V 2.2), or the dorsal lateral neostriatum (A 8.2, L 3.6, V 3.8) or nucleus accumbens (A 8.8, L 1.6, V 7.1) and fixed in place with cyanoacrylate glue and dental cement. Every experiment employed a prefrontal cortex electrode, and approximately half of the experiments were carried out with an electrode in the anterior cingulate cortex as well. Electrical stimuli consisted of single monophasic pulses of durations ranging from 10 to 750 μsec at 0.5–3.0 mA, delivered at a rate of 1 Hz. Stimulating electrodes were calibrated periodically throughout all experiments to control for possible changes in impedance.

Recordings

Extracellular single-unit recordings were obtained from neurons in the ventral tegmental area (A 1.8–2.4, L 0.1–1.2, V

6.5–8.2) and substantia nigra pars compacta (A 1.8–2.4, L 1.7–2.2, V 6.5–8.0) using glass micropipettes, filled with 3 M NaCl and possessing in vitro impedances of 4–10 M Ω measured at 500 Hz. Dopaminergic neurons were identified on the basis of their triphasic waveform, action potential duration greater than 2.5 msec, irregular or bursting firing pattern, and antidromic activation with slow conduction velocity (3, 7, 19, 35, 38, 40). Cortically-evoked responses were considered antidromic if they collided with appropriately timed spontaneous action potentials (10). For neurons in which collision testing was not possible due to low spontaneous activity, responses were tested for the ability to follow suprathreshold twin pulse electrical stimulation corresponding to 300–500 Hz. Neurons antidromically activated for a minimum of twenty-five trials were analyzed for the probability that the antidromic spike invaded either the initial segment only (IS spike) or the initial segment and soma-dendritic regions (IS-SD spike).

Following the collection of antidromic data for each neuron, the electrical stimulation was stopped and spontaneous activity was measured for 1–5 minutes to establish a baseline measure of firing rate. In some animals apomorphine (6 $\mu\text{g}/\text{kg}$) or amphetamine (0.25 mg/kg) was then administered intravenously. Post-drug firing rate was determined at 1–2 minutes following the completion of the drug injection.

All data were recorded on magnetic tape for off-line analysis. At the end of most recording sessions, current was passed through the recording electrode tip (1 μA , 500 msec, 1 Hz, 30 minutes) and stimulating electrode (1 mA, 2 sec) to create a lesion and mark the site for later histological verification.

Histology

At the end of each experiment, the animal was deeply anesthetized and perfused transcardially with normal saline followed by 10% formalin. The midbrain and frontal cortex were cut in 80 μm coronal sections, stained with neutral red, mounted on



FIG. 2. Comparison of antidromic responses of mesencephalic neurons (asterisks indicate stimulus artefacts). (A) Top: Three overlaid traces show antidromic spikes elicited in a ventral tegmental area dopaminergic neuron by stimulation of the prefrontal cortex. Note the constant latency and the characteristic full spike response displaying distinct initial segment-soma-dendritic components. Bottom: Spontaneous spike occurring just outside of the collision interval (antidromic latency + refractory period) fails to affect the antidromic response, while a spontaneous spike within the collision interval obliterates the evoked action potential, confirming the antidromic nature of the response. (B) Three superimposed traces showing antidromic activation of a substantia nigra dopaminergic neuron from the neostriatum. The antidromic response typically consists of the IS spike only. Bottom traces demonstrate collision testing as in A. (C) Antidromic responses in a nondopaminergic mesoprefrontal neuron occur with short latency. Calibration bar = 10 msec.

gelatin-subbed slides, cover slipped and examined to verify recording and stimulation sites.

RESULTS

Extracellular single unit recordings were obtained from one hundred seventy three neurons that were identified as dopaminergic on the basis of a wide triphasic waveform, action potential (>2.5 msec), and antidromic activation from either medial prefrontal cortex ($n=88$), anterior cingulate cortex ($n=7$), neostriatum ($n=53$) or nucleus accumbens ($n=22$) with slow conduction velocity (0.41–0.57 m/sec) (3, 7, 8, 14, 19, 35, 38, 40). Three cells could be activated from both the medial prefrontal and anterior cingulate cortices. Examples of spontaneous activity of antidromically identified mesoprefrontal and mesostriatal dopaminergic neurons are shown in Fig. 1. Note that mesocortical, mesoaccumbens and mesostriatal neurons exhibit the wide, triphasic action potential with a notch or inflection on the initial positive component, and the relatively slow and irregular firing pattern characteristic of identified midbrain dopaminergic neurons (3, 7, 14, 16, 35, 38). Examples of antidromic identification of mesocortical and nigrostriatal neurons are shown in Fig. 2. Neurons responding antidromically to prefrontal cortex stimulation were found throughout the ventral tegmental area and medial substantia nigra pars compacta (Fig. 3).

Recordings were obtained from 13 additional neurons that could be antidromically activated from prefrontal cortex but which did not satisfy the criteria for dopaminergic neurons. These cells exhibited a narrower action potential, more regular spontaneous activity, and relatively fast conduction velocities (Figs. 1C, 2C and Table 1), characteristics typical of nondopaminergic neurons of substantia nigra and ventral tegmental area (7, 19, 34).

The mean spontaneous firing rates of these neurons, grouped according to the site from which antidromic responding was elicited, as well as the range of spontaneous firing rates, antidromic latency, estimated conduction velocity, and proportion of full initial segment-soma-dendritic antidromic responses to total antidromic responses are presented in Table 1. The mean firing rates of dopaminergic neurons did not differ according to projection

site, $F(4,168)=0.65$, $p>0.5$. Similarly, no differences were obtained with respect to estimated conduction velocity among the dopaminergic neurons, although the nondopaminergic neurons exhibited a significantly greater conduction velocity than the dopaminergic neurons [2.0 vs. 0.5 m/sec; $t(181)=3.56$, $p<0.0001$], as previously reported (7, 14, 19, 34, 40).

When responding to antidromic stimulation, even at low stimulus rates (1 Hz), nigrostriatal and mesoaccumbens neurons only occasionally (26% of the time) exhibited a full, IS-SD spike, most often showing only the IS component of the antidromic spike (Table 1), as previously reported (7, 14, 16, 17, 19, 22, 29, 40). However, full IS-SD antidromic responses occurred significantly more frequently among combined mesoprefrontal and mesocingulate dopaminergic neurons than combined nigrostriatal and mesoaccumbens neurons, $t(144)=5.65$, $p<0.0001$, as shown in Fig. 2 and Table 1. The antidromically responding nondopaminergic mesocortical neurons always exhibited a full IS-SD antidromic response of stimulation rates of 1 Hz (Fig. 2C).

When challenged by intravenous administration of 6 $\mu\text{g}/\text{kg}$ apomorphine, a dose previously shown to act preferentially on dopaminergic autoreceptors in substantia nigra (26), mesoprefrontal dopaminergic neurons exhibited a mean reduction in spontaneous firing rate of $39.4\% \pm 7.3\%$ ($n=7$). A negative correlation between baseline firing rate and the magnitude of the apomorphine-induced inhibition was found, but failed to reach significance at the $p=0.05$ level [$r=-.7$, $t(5)=2.13$, $p=0.09$]. This inhibition could be completely reversed by subsequent intravenous administration of haloperidol (0.1 mg/kg; $n=3$), as shown for one representative mesoprefrontal dopaminergic neuron in Fig. 4. There was no difference in the response of these mesocortical dopaminergic neurons when compared to nigrostriatal and mesoaccumbens neurons to which an identical dose of apomorphine was administered (Table 2).

In fourteen additional mesoprefrontal dopaminergic neurons, 0.25 mg/kg amphetamine was delivered intravenously. Three of these neurons displayed no appreciable spontaneous activity prior to or after amphetamine administration. The remaining eleven neurons exhibited a mean firing rate reduction of $31.4\% \pm 5.8\%$. Amphetamine (0.25 mg/kg, IV) was also administered while

did not satisfy the criteria for dopaminergic neurons. These cells

tration of haloperidol (0.1 mg/kg; $n=3$), as shown for one

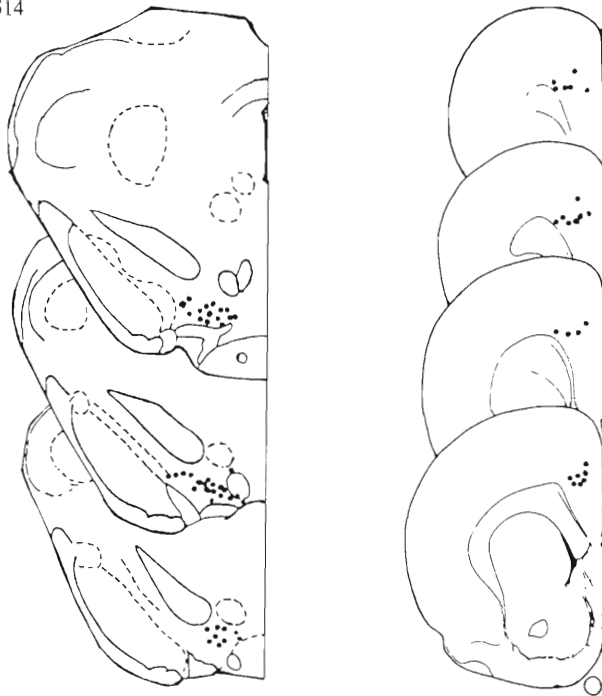


FIG. 3. Locations of cell bodies of electrophysiologically identified mesoprefrontal dopaminergic neurons (black dots; left) and of cortical stimulating sites (right) determined histologically. In animals in which several mesocortical dopaminergic neurons were encountered, only the site of the last neuron recorded was lesioned. Approximate coordinates, top to bottom, are A 2.4, A 2.2, A 1.9 (left), and A 11.2, A 10.7, A 10.0, A 9.0 (right).

TABLE 1
ELECTROPHYSIOLOGICAL PROPERTIES OF MESENCEPHALIC DOPAMINE NEURONS ACCORDING TO THEIR PROJECTION SITES

Proj.	Latency (msec)	CV (m/sec)	FR (spikes/sec)	FR Range	% Full Spikes
STR	12.9±0.5(53)	0.55	3.3±0.3(53)	0.0-8.7	22.3±4.3(45)
NAC	12.6±1.2(22)	0.51	3.6±0.5(22)	0.9-9.8	35.8±11.0(15)
PFC	22.9±0.9(88)	0.48	2.8±0.3(88)	0.0-10.2	63.3±4.8(76)
ACC	23.4±4.9 (7)	0.41	3.5±1.9 (7)	1.0-6.6	64.6±14.2 (7)
PF+AC	—	—	2.7±1.5 (3)	1.0-3.9	32.5±11.5 (3)
NDA	5.7±1.2(13)	2.00	4.7±2.1(13)	0.0-14.7	100±0.0 (13)

Values are given as the mean ± S.E.M. Numbers in parentheses refer to the size of the cell group for each measurement. Proj. = projection site; CV = conduction velocity; FR = firing rate; % Full Spikes = percentage of antidromic responses that were full action potentials; STR = striatum; NAC = nucleus accumbens; ACC = anterior cingulate; PFC = prefrontal; PF+AC = dopamine neurons projecting to both prefrontal and anterior cingulate cortices; NDA = dopaminergic mesoprefrontal neurons.

recording from 4 of the nondopaminergic neurons, and no consistent effect was observed. A fifth nondopaminergic mesocortical cell was similarly unaffected by apomorphine (6 µg/kg). These results are summarized in Table 2.

DISCUSSION

One population of mesocortical neurons described in this study exhibited long duration action potentials (>2.5 msec), a slow irregular firing pattern, and long latency antidromic activation

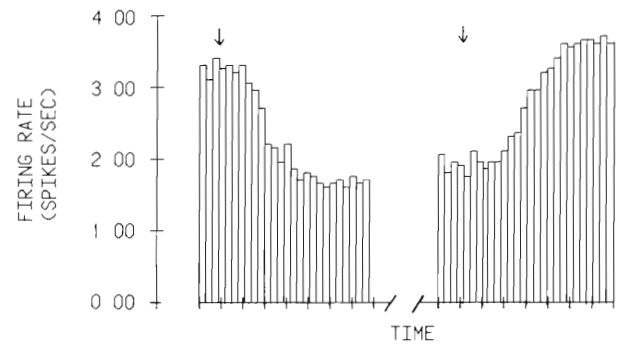


FIG. 4. Firing rate histogram shows the effects of intravenous apomorphine and haloperidol on the discharge rate of a spontaneously active mesoprefrontal dopaminergic neuron. Prior to injection, this neuron exhibited a stable baseline firing rate of approximately 3.2 spikes/sec. Within several seconds following injection of apomorphine (6 µg/kg; 1st arrow), there is a significant decrease in the firing rate. Subsequent administration of haloperidol (0.1 mg/kg; 2nd arrow) completely reversed the effect of apomorphine. Bin width = 3 sec. Marks on horizontal axis denote 10 second intervals. The haloperidol injection was given 5 minutes after the apomorphine injection.

TABLE 2

PHARMACOLOGICAL RESPONSES OF ANTIDROMICALLY IDENTIFIED DOPAMINERGIC AND NONDOPAMINERGIC NEURONS

Proj.	FR	Drug	%INH	N
PFC	3.5 ± 0.7	APO	39.4 ± 7.3	7
	3.6 ± 0.3	AMP	31.4 ± 5.8	11
STR	3.9 ± 0.6	APO	28.2 ± 4.4	12
	4.1 ± 0.8	AMP	35.1 ± 5.5	18
NAC	3.8 ± 0.4	APO	34.4 ± 4.9	12
NDA	6.6	APO	0.0	1
	8.7 ± 2.8	AMP	3.2 ± 3.4	4

Amphetamine (AMP; 0.25 mg/kg) or apomorphine (APO; 6.0 µg/kg) were administered intravenously. %INH = percent inhibition of firing rate; N = number of neurons tested. Other headings are as in Table 1.

from prefrontal (n=88) or anterior cingulate cortex (n=7), or from both regions (n=3), when studied with extracellular single unit recording. These properties are typical of substantia nigra and ventral tegmental area neurons that have previously been identified as dopaminergic by a number of electrophysiological and histochemical techniques (3, 7, 16, 17, 19, 34, 35).

These mesocortical dopaminergic neurons displayed a very similar electrophysiological profile to nigrostriatal and mesolimbic dopaminergic neurons with respect to action potential waveform, mean spontaneous firing rate and estimated conduction velocities. Similar results have been reported for smaller populations of mesocortical dopaminergic neurons by Wang (35), who found an average firing rate of 2.87 spikes/sec, by Shepard and German (25), who found an average firing rate of 3.3 spikes/sec, and by Deniau *et al.* (8), who found mesocortical neurons with a conduction velocity of 0.53 m/sec and firing rates ranging from 0-8 spikes/sec. Furthermore, these investigators reported, as found in the present study, that mesocortical neurons are sensitive to the firing rate suppressant action of systemically administered apomorphine (25) and amphetamine (36), properties thought to be due to the presence of soma-dendritic dopamine autoreceptors (4,18). While low dose apomorphine-induced suppression of substantia nigra dopaminergic cell activity is primarily attributable

mesocortical dopaminergic neurons by Wang (35) who found an

to activation of soma-dendritic autoreceptors, amphetamine-induced inhibition can involve other factors, for example, activation of inhibitory feedback pathways from neostriatum (1,4). However, since the inhibitory effect of amphetamine on ventral tegmental area dopaminergic neurons has been shown to persist after transection of potential inhibitory feedback pathways from the forebrain, it is highly likely that local events involving increased activation of soma-dendritic autoreceptors account for the inhibitory effects of amphetamine on these cells (18,36).

It is difficult to reconcile our findings and those of others (7, 8, 25, 35, 36) with reports that mesocortical dopaminergic neurons fire at much higher rates [9.3 spikes/sec (5); 6.5 spikes/sec (37)], although it is conceivable that procedural differences resulted in dissimilar cell samples. It seems unlikely, however, that differences in anesthesia account for different discharge rates and responsivity of mesocortical dopaminergic neurons reported by different investigators, since the same anesthetic, chloral hydrate, has been employed in several studies reporting conflicting data on the level of spontaneous activity and responsivity to dopamine agonists of mesocortical dopaminergic neurons (5, 25, 36, 37), and conversely, since comparable slow firing rates and sensitivity to agonists have been reported by investigators employing different anesthetics (7, 8, 25, 35, 36, 40).

The relative lack of response of fast-firing dopaminergic neurons to apomorphine (5) does not necessarily indicate that these neurons lack soma-dendritic autoreceptors. The frequency-dependent nature of autoreceptor activation, both at the terminals and the soma-dendritic region, has been repeatedly demonstrated (6, 30–33, 37), with agonist effects diminishing as the spontaneous activity of the cell increases. Thus a lack of responsiveness to apomorphine is expected in fast-firing cells. In addition, dopamine receptors have been reported to desensitize, or undergo tachyphylaxis, when repeatedly exposed to elevated levels of agonist (15,24), and it is possible that dopaminergic cells that fire tonically at very high rates exhibit desensitized autoreceptors.

It is possible that a subpopulation of mesocortical dopaminergic neurons exists that lack cell body autoreceptors. Others have suggested (25) that the fast-firing mesocortical dopaminergic neurons (5) comprise a separate subpopulation distinguished by a lack of axon collaterals to the striatum and by their position in the most medial aspect of the ventral tegmental area. While fast-firing mesoprefrontal dopaminergic neurons were reported to be in a region medial to most of the cell population in the present study [compare the locations of the cells of Fig. 3 with those of Fig. 8

in (5)], we could find no obvious mediolateral gradient with regard to firing rate. Indeed, of the 98 mesocortical dopaminergic cells recorded, only four had firing rates in excess of 8 spikes/sec, and all of these were located in the mid to lateral portions of the ventral tegmental area. Furthermore, it is improbable that most of our recordings were from neurons that collateralize to the striatum, as these constitute a minority of the mesocortical cell population and are located almost exclusively in the region of the medial substantia nigra pars compacta (9,27).

The only notable distinction between mesocortical dopaminergic and nigrostriatal and mesoaccumbens dopaminergic neurons was the character of their antidromic response: mesocortical neurons responded with the full spike significantly more often than nigrostriatal or mesoaccumbens dopaminergic neurons, as shown in Fig. 2. The high percentage of IS spikes seen in nigrostriatal and mesoaccumbens dopaminergic neurons appears to be due, at least in part, to the orthodromic coactivation of inhibitory efferents to the substantia nigra by the antidromic stimulus (14), since kainic acid lesions of the striatum increase the frequency of the full spike response in antidromically-activated nigrostriatal dopaminergic neurons (22,29). In the case of antidromic activation of mesocortical dopaminergic neurons, striatal and accumbens inhibitory efferents to the ventral tegmental area would be activated only indirectly and with longer latency, thus allowing for a higher probability of invasion of the cell body by the antidromic action potential.

In conclusion, we have recorded from a large sample of mesocortical dopaminergic neurons that display characteristics typical of other mesencephalic dopaminergic neurons and consistent with the presence of soma-dendritic autoreceptors. Of note, recent biochemical data indicate that autoreceptors that modulate dopamine release are present on the terminals of mesocortical dopaminergic neurons as well (23, 28, 39). The accompanying paper (13) details electrophysiological consequences of activation of the terminal autoreceptors located on a subset of the mesocortical neurons described in the present paper.

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