Mesocortical Dopaminergic Neurons. 2. Electrophysiological Consequences of Terminal Autoreceptor Activation

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GARIANO, R. F., S. F. SAWYER, J. M. TEPPER, S. J. YOUNG AND P. M. GROVES. *Mesocortical dopaminergic neurons. 2. Electrophysiological consequences of terminal autoreceptor activation.* BRAIN RES BULL 22(3) 517–523, 1989.—Measurement of drug- and stimulation-induced changes in the electrical excitability of dopaminergic terminals was employed to assess the effects of stimulation of dopamine terminal autoreceptors in the prefrontal cortex in urethane-anesthetized rats. Systemic or local administration of amphetamine decreased, whereas systemic administration of haloperidol increased the excitability of prefrontal cortical dopaminergic terminals of ventral tegmental area dopaminergic neurons. Mesoprefrontal dopaminergic terminal excitability was also responsive to spontaneous and stimulation-induced alterations in the rate of impulses reaching the terminal fields. These results are comparable to those previously reported for nigrostriatal and mesoaccumbens dopaminergic neurons, and are discussed with regard to the operational characteristics of autoinhibition in the mesocortical dopaminergic system.

Dopamine   Autoreceptor   Autoinhibition   Ventral tegmental area   Prefrontal cortex   Amphetamine   Terminal excitability

AN abundance of data suggests that nigrostriatal dopaminergic neurons possess autoreceptors on their terminals that regulate synthesis and release of dopamine [(6, 11, 23, 36, 42); see (46) for review]. Stimulation of these terminal autoreceptors, either by local or systemic administration of dopamine agonists, produces a reversible decrease in the excitability of the dopaminergic terminals to direct electrical stimulation in vivo, whereas application of dopaminergic antagonists increases terminal excitability (19, 38, 39). Similar alterations in terminal excitability have also been described for dopaminergic mesoaccumbens neurons (27), as well as for central serotonergic (33) and noradrenergic (28,29) terminals, using appropriate autoreceptor-activating drugs. In each case, these effects have been shown to be due to a direct action on terminal autoreceptors and not to transynaptic or nonautoreceptor-mediated mechanisms (27, 33, 38, 39, 41).

Biochemical evidence for the existence of terminal autoreceptors on dopaminergic neurons projecting to prefrontal and anterior cingulate cortices is less clear than that for projections to subcortical regions (3–5, 10, 22), and results from previous electrophysiological studies (7,43) have led some investigators to suggest that mesoprefrontal and mesocingulate dopaminergic neurons either possess a reduced density or a virtual absence of cell body

impulse-modulating, as well as terminal synthesis-modulating, autoreceptors (7,34). Recent biochemical evidence indicates that autoreceptor-mediated modulation of dopamine release occurs in the prefrontal cortex (2, 30, 37, 45), while direct autoreceptor-mediated modulation of dopamine synthesis does not (4,5). Dopaminergic agents inhibit dopamine synthesis in the cortex (3,10), but these effects may depend on concomitant inhibition of dopamine release and thus be only indirectly related to autoreceptor activation (12,44).

In the accompanying paper, we examined the electrophysiological properties of mesoprefrontal and mesocingulate dopaminergic neurons and the effects on these neurons of pharmacological manipulations known to influence cell body dopamine autoreceptors (15). In the present report, we have applied the electrophysiological method of terminal excitability testing to rat mesoprefrontal dopaminergic neurons in order to investigate directly the effects of autoreceptor stimulation and blockade at the cortical terminals of these neurons in vivo. Portions of this work have been reported in abstract form (13,14).

METHOD

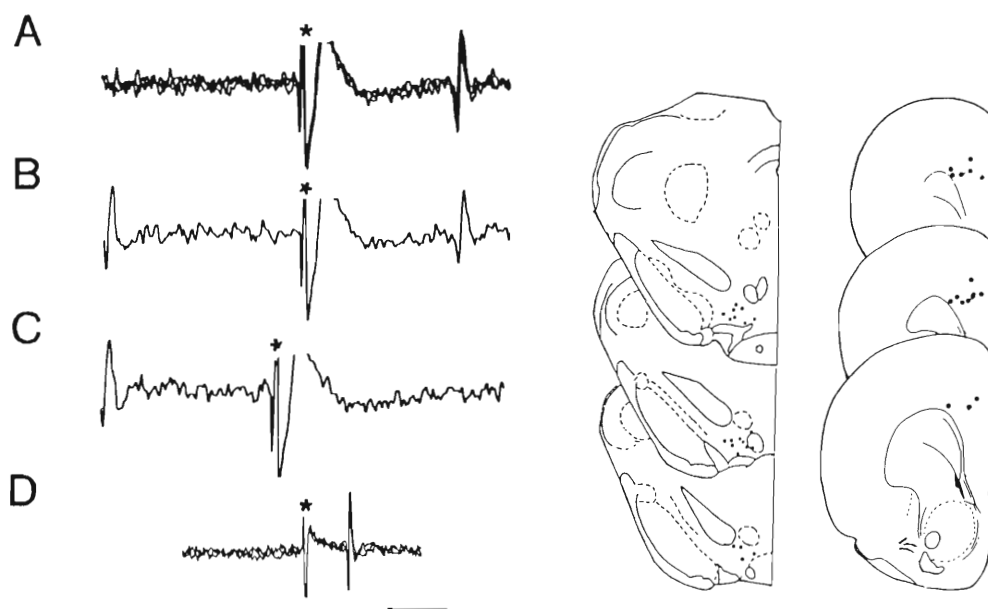The subjects, anesthesia, general surgical procedures, drug

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FIG. 1. Antidromic activation of mesoprefrontal neurons. (A) Three overlayed traces of successive antidromic spikes elicited in a ventral tegmental area dopaminergic neuron by stimulation of the prefrontal cortex (asterisk indicates stimulus artefact). Note the full IS-SD spike responses. (B) Spontaneous spike occurring outside the collision interval fails to affect the antidromic response, while a spontaneous spike within the collision interval (C) obliterates the evoked action potential, confirming the antidromic nature of the response. (D) Antidromic activation of a nondopaminergic mesoprefrontal neuron. Note the shorter antidromic latency and narrower action potential in comparison to the dopaminergic neuron in (A). Calibration bar=10 msec. At right are shown locations of cell bodies of electrophysiologically identified mesoprefrontal dopaminergic neurons and their antidromic stimulation sites in the cortex (black dots), determined histologically. Approximate coordinates [according to (24)], top to bottom, are: A 2.4, A 2.2, A 1.9 (left) and A 11.2, A 10.7, A 10.2 (right).

preparation, recording and stimulating parameters, and histology were described in the preceding paper (15).

Terminal Excitability Measurement

Well-isolated single unit extracellular recordings were obtained from neurons in the ventral tegmental area that were characterized as dopaminergic or nondopaminergic on the basis of previously published electrophysiological criteria [(1, 8, 9, 16, 17, 21); see the preceding paper (15) for details]. Once a stable recording was obtained, attempts were made to antidromically activate the neuron from 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). Details of the terminal excitability testing procedure have been previously published (38,39). Briefly, after antidromic activation was obtained, the stimulus current was set to the minimum value sufficient to elicit an antidromic response on at least 95% of stimulus trials. This stimulus current is termed the 'threshold.' Lower currents evoking lower proportions of antidromic responding were also determined, in a counterbalanced fashion, using at least 25–50 stimulus presentations in each case. After a stable baseline of terminal excitability was obtained, drugs (amphetamine, 0.25 mg/kg or haloperidol 0.1 mg/kg) were administered intravenously through a femoral catheter. The threshold and lower currents were then redetermined. Changes in terminal excitability were quantified by determining the percent change in the predrug threshold current after drug administration. Changes in threshold of less than 5% were considered negligible. The effects of drugs were tested on only one cell per animal.
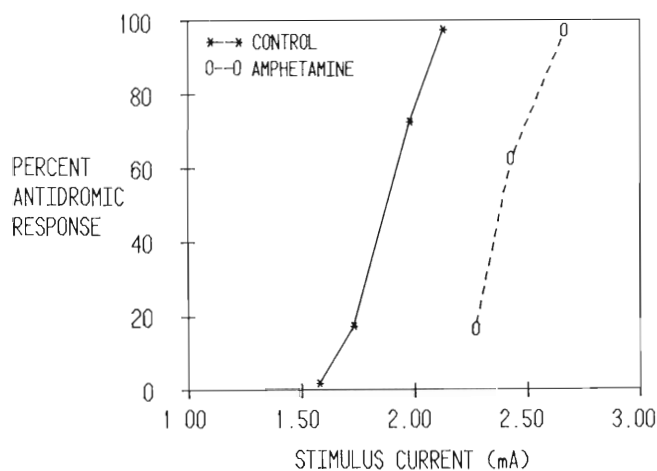

FIG. 2. Effect of intravenous administration of amphetamine (0.25 mg/kg) on terminal excitability in a mesoprefrontal dopaminergic neuron. The curve at the left (*) shows that prior to drug administration a current of 2.05 mA evoked an antidromic response on nearly every stimulus trial, with lower currents eliciting lower proportions of antidromic responding. Following injection of amphetamine (O), this threshold current increased to 2.65 mA, and the entire current-response curve shifted uniformly to the right, indicating a decreased terminal excitability at all currents tested.

In some animals, the effects of high-frequency conditioning stimulation of the terminal fields in prefrontal cortex were examined. In these cases, a baseline measure of threshold was first obtained. The prefrontal cortex was then stimulated by a train of pulses delivered at threshold (800–1200 msec of 0.2–0.5 msec pulses at 10 Hz) and the antidromic excitability was monitored during and after the conditioning stimuli.

RESULTS

Terminal excitability testing was successfully performed on thirty mesoprefrontal dopaminergic neurons. A full description of the electrophysiological characteristics of these neurons appears in the preceding paper (15). This subset of neurons had firing rates ranging from 0.0–8.8 spikes/sec, with a mean ± S.E.M. of 2.4 ± 0.4 spikes/sec. The mean latency of antidromic responses elicited from the medial prefrontal cortex was 20.7 ± 1.7 msec, corresponding to an estimated conduction velocity of 0.50 m/sec. An example of an antidromic response in a dopaminergic mesoprefrontal neuron is shown in Fig. 1A–C. The cell bodies of the mesoprefrontal dopaminergic neurons were located throughout the ventral tegmental area, extending to the medial portion of the substantia nigra, pars compacta, as shown in Fig. 1.

Changes in Dopaminergic Terminal Excitability in Response to Amphetamine and Haloperidol

Amphetamine was employed as an indirectly-acting dopamine agonist to increase extracellular levels of endogenous dopamine (25). Of the twelve cells administered amphetamine (0.25 mg/kg) intravenously, seven exhibited a decrease in terminal excitability (i.e., an increase in threshold) of 23 ± 5%. An example from one cell is shown in Fig. 2. In one atypical case, intravenous amphetamine administration resulted in a 17% increase in terminal excitability. The remaining four cells did not show any significant change in terminal excitability. Pooling all 12 cases, amphetamine was found to produce a statistically significant decrease in terminal excitability [12 ± 5%; $t(11) = 2.38$, $p < 0.05$]. Intravenous administration of the dopamine receptor antagonist haloperidol (0.1 mg/kg) partially reversed the reduction in terminal excitability caused by amphetamine (mean decrease in threshold = 16 ± 4%; n = 3). These twelve dopaminergic cells exhibited a reduction in firing rate of 26 ± 6% in response to intravenous administration of amphetamine.

In two additional cases, amphetamine (10 μM; 0.6 μl given over 5 minutes) was locally infused into the cortical stimulating site. Both neurons responded with decreased terminal excitability (mean = 22 ± 6%). The excitability curves for one of these infusion experiments are shown in Fig. 3.

Thirteen cells were found in the ventral tegmentum that did not satisfy the criteria for dopaminergic neurons (action potential duration = 1.7 ± 0.4 msec) but that were antidromically activated from prefrontal cortex (latency = 5.7 ± 1.2 msec). Systemic administration of amphetamine in four cases tested did not consistently alter either the terminal excitability or the firing rate of these presumably nondopaminergic neurons [see (15)].

The effects of intravenous administration of haloperidol (0.1 mg/kg, IV) were examined on terminal excitability in 5 additional mesoprefrontal dopaminergic neurons. In four of these cells, there was an increase in terminal excitability (mean decrease in threshold = 11 ± 1%), while the fifth cell was unaffected. Pooling all 5 cases, haloperidol was found to produce a statistically significant increase in terminal excitability [9 ± 2%; $t(4) = 3.74$, $p = 0.02$]. The increase in terminal excitability following haloperidol is illustrated

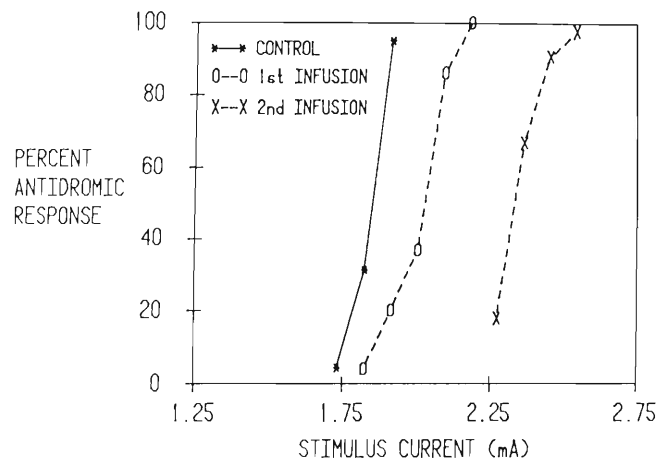FIG. 3. Dose-dependent effects of intracortical infusion of amphetamine (10 μM, 0.6 μl given over 5 minutes) on the terminal excitability of a mesoprefrontal dopaminergic neuron. Administration of amphetamine increased the threshold current from approximately 1.85 mA (*) to 2.10 mA (○), and the entire current-response curve shifted to the right. After a second identical infusion (×), a further shift to the right in the current-response curve occurred.

for one mesoprefrontal dopaminergic neuron in Fig. 4.

Impulse-Dependent Changes in Mesocortical Dopaminergic Terminal Excitability

Midbrain dopaminergic neurons generally display a slow and irregular pattern of spontaneous activity, often containing isolated bursts of from 2–10 spikes (18). It was a common observation that a stimulating current that was sufficient to elicit an antidromic response on 100% of the trials during which the neuron was firing in its single spike mode became subthreshold during or immediately following the occurrence of a spontaneous burst. An example
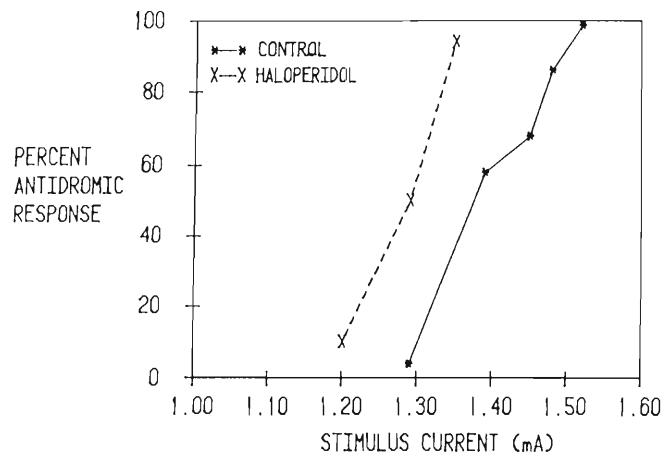

FIG. 4. Effects of intravenous administration of haloperidol (0.1 mg/kg) on the terminal excitability of a mesoprefrontal dopaminergic neuron. Haloperidol caused an approximately 10% shift to the left in the terminal excitability curve, indicating an increase in terminal excitability consequent to haloperidol-induced blockade of terminal dopaminergic autoreceptors.
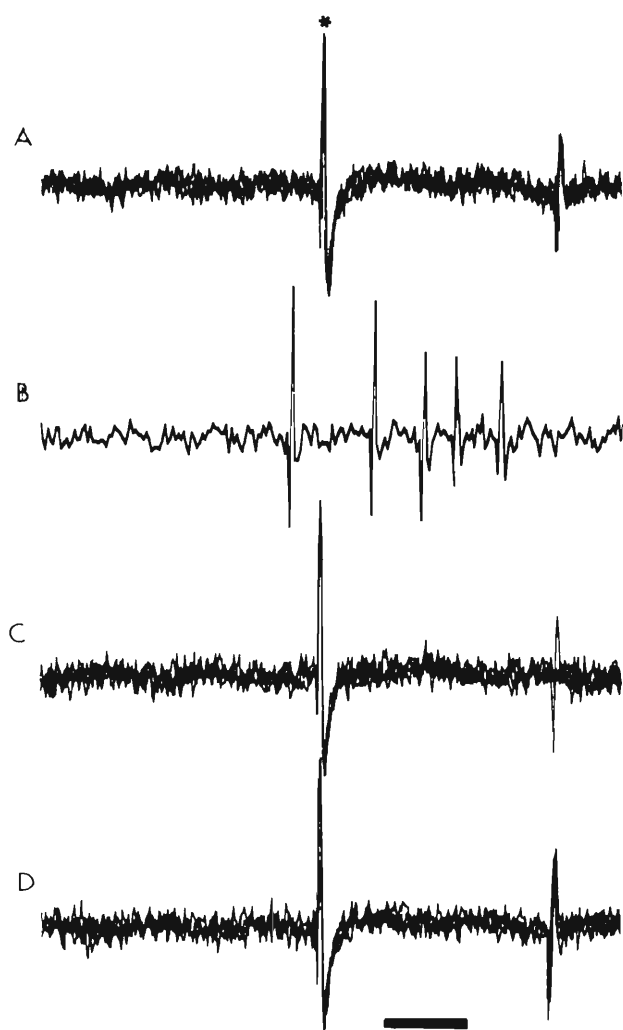
FIG. 5. Terminal excitability changes subsequent to a burst of activity in an otherwise quiescent mesoprefrontal dopaminergic neuron. (A) Four overlayed consecutive traces show antidromic (initial segment) responding with the current set at the threshold value. (B) A spontaneous burst of action potentials occurs between stimulus deliveries. (C) Of the next four stimulus trials following the burst, only one was able to elicit an antidromic response. (D) Within 4–5 seconds of the burst 100% antidromic responding was reinstated. Calibration bar=10 msec in A, C and D, 60 msec in B.

FIG. 6. Effect of high-frequency stimulation of the terminal field of a mesoprefrontal dopaminergic neuron on terminal excitability. (A) Four overlayed traces show antidromic responding with the current set at the threshold value. (B) High-frequency stimulation of the terminal field delivered with the same electrode used to elicit antidromic responses. (C) Of the next three stimulus trials following high-frequency stimulation, only one elicited an antidromic response. Subsequently, terminal excitability returned to the prehigh-frequency stimulation level (D). Calibration bar=10 msec in A, C, and D, 65 msec in B.

of this impulse-dependent decrease in terminal excitability is shown in Fig. 5. In Fig. 5A the stimulus current was set at threshold while recording from a cell with very little spontaneous activity, and an antidromic response follows each stimulus delivery. Following the occurrence of a burst consisting of 5 spikes (Fig. 5B), the same stimulus current was able to elicit an antidromic response on only one of the subsequent four stimulus deliveries (Fig. 5C), indicating a decrease in terminal excitability. Within four seconds after the burst, the excitability of the terminal membrane returned to the preburst level, as indicated by the return to 100% antidromic responding (Fig. 5D).

A similar effect could be produced by applying high-frequency stimulation (800–1200 msec of 0.2–0.3 msec pulses delivered at 10 Hz) to the terminal fields of dopaminergic mesoprefrontal neurons, as illustrated in Fig. 6. Two of ten cells tested exhibited no apparent change in terminal excitability in response to high-
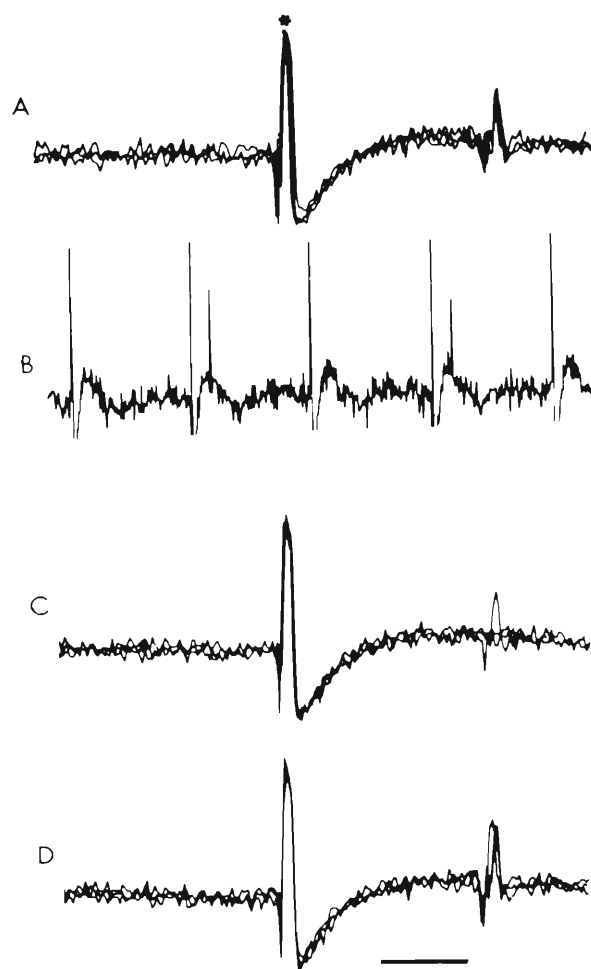
frequency stimulation, while eight cells responded with a transient decrease in terminal excitability such that the threshold current could no longer elicit antidromic responses on 100% of the stimulus trials. The threshold returned to prestimulation levels within 2 to 4 seconds of the cessation of the conditioning stimulus. This phenomenon appears dependent on stimulus-evoked release of endogenous dopamine, as suggested by experiments on four animals, in which prior administration of haloperidol (0.1 mg/kg, IV) attenuated the effects of subsequent high-frequency stimulation. Application of high-frequency stimulation to the terminals of five nondopaminergic mesoprefrontal neurons did not alter the threshold of these cells.

Three dopaminergic cells exhibited variable baseline excitability curves such that a threshold could not be determined. In these cases, the stimulus current was set to elicit subthreshold respond-

(Fig. 5B), the same stimulus current was able to elicit an

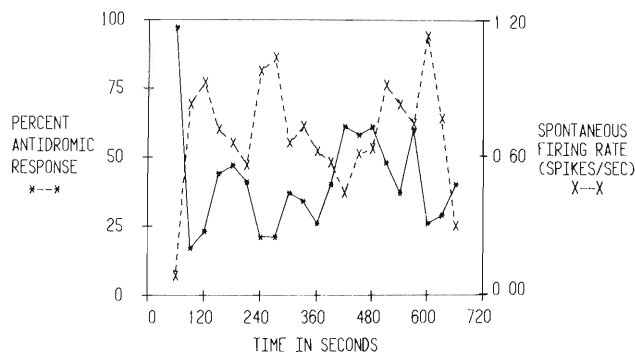within 2 to 4 seconds of the cessation of the conditioning stimulus.

FIG. 7. The excitability of mesoprefrontal dopaminergic terminals is coupled to impulse flow. The ability of a constant stimulus strength to elicit antidromic action potentials (*) and the spontaneous firing rate (×) in a single cell are plotted for successive 30 second intervals over the course of 10.5 minutes. Note that the two curves are inversely related ($r = -.72$, $df = 19$, $p < 0.001$), suggesting that mesoprefrontal dopaminergic terminals are responsive to physiologic fluctuations in impulse flow.

ing and was applied for several minutes at a rate of 1/sec. The percent antidromic response and firing rate were determined for successive 30 second intervals. The results for one case are shown in Fig. 7. A significant inverse relationship was found between firing rate and percent antidromic response for each of these three cells ($r = -.7$, $-.8$, $-.7$, $df = 19$, 10, 11, $p < 0.01$ for each neuron). Haloperidol (0.05 mg/kg, IV) was subsequently administered to one of these cells and the above relationship was uncoupled (data not shown).

DISCUSSION

Mesoprefrontal dopaminergic terminal excitability was significantly decreased by systemic or local administration of the indirectly-acting dopamine agonist amphetamine, and this effect could be reversed by subsequent administration of the dopamine receptor antagonist, haloperidol. Conversely, mesoprefrontal terminal excitability was significantly increased by the administration of haloperidol alone. These results suggest that the changes in terminal excitability represent a specific, receptor-mediated phenomenon. The magnitude of the changes in cortical terminal excitability induced by amphetamine and haloperidol were comparable to those previously reported for neostriatal and nucleus accumbens dopaminergic terminals (19, 27, 38, 39). Considerable evidence suggests that these amphetamine and haloperidol-induced changes in dopaminergic terminal excitability are mediated by dopamine autoreceptors. Studies in the nigrostriatal and mesoaccumbens dopamine systems have shown that the effects of dopamine agonists on terminal excitability persist after chemical lesions of the terminal regions that destroy postsynaptic elements but spare the terminals (27,41) and that the effects of amphetamine are eliminated by prior treatment with either alphamethylparatyrosine or specific dopamine D2 receptor antagonists (38). Further, similar excitability changes are not seen at nonterminal regions of monoaminergic axons in the medial forebrain bundle (28, 29, 33, 38, 39). Finally, in the present study, amphetamine was ineffective in altering the terminal excitability of nondopaminergic mesolimbic (27) and nondopaminergic mesoprefrontal neurons.

The observation that haloperidol alone was effective at increasing mesoprefrontal terminal excitability suggests that, as with nigrostriatal dopamine neurons (38,39), there is a sufficient concentration of endogenous dopamine in the cortical terminal

fields in vivo to stimulate the autoreceptors; thus, they appear to play a physiological role in the absence of exogenous autoreceptor agonists. This conclusion is supported by the relationship between mesocortical dopaminergic terminal excitability and the rate of impulses reaching the terminals. Three paradigms were employed to show that cortical dopamine autoreceptors are responsive to impulse-dependent dopamine release. First, high-frequency stimulation of the prefrontal cortex resulted in transient reductions in the percent antidromic response, an effect abolished by prior treatment with the dopamine receptor antagonist haloperidol. High-frequency stimulation presumably causes an increased release of endogenous dopamine which is then available to interact with terminal autoreceptors and thereby decrease terminal excitability. Similar effects have been reported in the striatum following high-frequency stimulation of nigrostriatal axons in the medial forebrain bundle (39), and at cortical terminals of noradrenergic neurons following high-frequency stimulation of the terminal regions (28).

Second, we noted that bursts of spontaneous activity were followed by brief periods of decreased terminal excitability, as previously reported for nigrostriatal dopaminergic neurons (39). These observations suggest that terminal autoreceptors on individual mesoprefrontal dopaminergic neurons are responsive to impulse-dependent changes in dopamine release by the same neuron, i.e., a form of terminal self-inhibition (20, 31, 39). The time course of recovery to baseline levels of terminal excitability, both after spontaneous bursts or high-frequency stimulation, is in accord with in vivo voltammetric measurements showing that stimulus-induced increases in extracellular dopamine concentration in the striatum decay over a period of 2–4 seconds (26,35).

Third, neurons with variable levels of spontaneous activity showed a clear inverse relationship between firing rate and terminal excitability over time, similar to that seen in nigrostriatal dopaminergic neurons (39) and noradrenergic neurons projecting to cerebral cortex (28). Thus, over a period of several minutes, the dopamine autoreceptors exhibit an apparent physiological sensitivity to moment-to-moment fluctuations in endogenous dopamine release secondary to changes in impulse flow. This relationship was uncoupled by subsequent administration of haloperidol, demonstrating that it is receptor-mediated, and not simply the consequence of increased impulse flow.

It is noteworthy that there was one instance of an increase in terminal excitability following intravenous administration of amphetamine. This occurred in a neuron in which the firing rate was unusually sensitive to intravenously administered amphetamine (54% reduction). Although the usual effect of intravenous amphetamine at dopaminergic terminals is to facilitate dopamine transmission (25), in this case the decrease in impulse flow may have sufficiently diminished the level of impulse-dependent dopamine release at the terminal sites to offset the dopaminomimetic actions of amphetamine, resulting in an overall decrease in dopamine release, and thus an increase in terminal excitability. This phenomenon routinely occurs in noradrenaline containing cells of the locus coeruleus following low intravenous doses of amphetamine, and has been interpreted as showing that low doses of amphetamine, which markedly reduce impulse flow in these neurons, decrease noradrenaline release in the terminal regions (25, 29, 32).

A minority of cells did not respond to either amphetamine (n = 4) or haloperidol (n = 1) or high-frequency stimulation (n = 2) with changes in terminal excitability. These cells could not be distinguished from those that did respond to these manipulations, either on the bases of firing rate, conduction velocity, location of the cell within the ventral tegmental area, or response of firing rate to systemic amphetamine. While it is possible that these particular cells lack terminal autoreceptors, an equally plausible explanation

is that in these cells antidromic activation was obtained from nonterminal regions of the axon within the cortex, since the excitability of dopaminergic preterminal axons in the medial forebrain bundle is unaltered by either local or systemic administration of dopamine agents or by high-frequency stimulation (19, 38, 39).

We have previously argued that autoreceptor-associated alterations in terminal excitability are coupled to autoreceptor-mediated regulation of transmitter release in central monoaminergic neurons (28, 29, 33, 38–41). The dopamine autoreceptors examined in the present study are thus likely to underlie the autoreceptor-modulated release of dopamine recently reported to occur in the medial prefrontal cortex (2, 30, 37, 45). Recent work (12,44) suggests that autoreceptors on cortical dopaminergic terminals may be functionally limited to directly regulate the release, but not the synthesis, of dopamine at these terminals. If this hypothesis is correct, it implies that the autoreceptor-mediated alterations in

electrical excitability of terminal membranes observed in the present study may be related specifically to modulation of dopamine release but not synthesis.

In conclusion, the terminal excitability experiments described above, taken with the results described in the companion paper (15), suggest that mesocortical dopaminergic neurons are comparable to nigrostriatal and mesolimbic dopaminergic neurons with respect to electrophysiological parameters of both soma-dendritic and terminal autoreceptors.

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