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Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated

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ABSTRACT **In the mammalian neostriatum, dopamine modulates neuronal responses mediated by activation of excitatory amino acid receptors. The direction of this modulation varies with the specific subtype of excitatory amino acid receptor activated. Responses evoked by iontophoretic application of glutamate (Glu) and the non-*N*-methyl-D-aspartate (NMDA) agonists quisqualate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid were significantly attenuated when dopamine was applied. In contrast, responses evoked by NMDA were markedly potentiated. The enhancement of NMDA-evoked excitations was mimicked by bath application of SKF 38393, a D_1 receptor agonist. The D_1 receptor antagonist SCH 23390 blocked the dopamine enhancement of NMDA-induced excitations. Quinpirole, a D_2 receptor agonist, attenuated responses evoked by both NMDA and non-NMDA receptor agonists. These results indicate that the complex modulatory actions of dopamine in the neostriatum are a function of the excitatory amino acid receptor as well as the specific dopamine receptor subtype activated. These findings are of clinical relevance since the actions of dopamine and excitatory amino acids have been implicated in neurological and affective disorders.**

An understanding of the interactions between dopamine and excitatory amino acids (EAAs) in the neostriatum is of clinical and scientific relevance because abnormalities in the actions of these substances have been implicated in neurological disorders, such as Parkinson disease (1) and Huntington disease (2), and in affective disorders (3). The development of successful therapeutic interventions in abnormalities such as these may be aided considerably by understanding the cellular interactions between EAAs and dopamine.

The neostriatum receives dense dopamine projections from the substantia nigra and glutamatergic projections from all areas of the cerebral cortex (4, 5). The most common cell type in the neostriatum, a medium-sized neuron whose dendrites are densely covered with spines (6, 7), appears to be the major target of inputs from both neocortex and substantia nigra (6–10). There is considerable evidence to indicate that glutamate (Glu)-containing and dopamine-containing inputs terminate on the same spines of this neuron (11, 12). This dendritic spine is thus a potential site for physiological interactions between dopamine and Glu.

Glu and dopamine bind to different types of postsynaptic (and presynaptic) receptors that have been defined by pharmacological and molecular cloning techniques (13–15). Dopamine may act via at least five receptor subtypes (14, 16) classified into two families (D_1 and D_2), according to their affinities to standard ligands (13). Similarly, although multiple subunits of Glu receptors have been identified (17–19), receptor subtypes can be classified into families according to their selective ligands (20, 21).

The present study concentrates on the actions of Glu, quisqualate (Quis)/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and *N*-methyl-D-aspartate (NMDA) because of possible differential functional roles of receptors for these EAAs agonists in the neostriatum. Glu-containing corticostriatal inputs are mediated primarily by Quis/AMPA and/or kainate receptors (22, 23). Although NMDA receptors are present in the neostriatum (24, 25), their contributions to evoked synaptic responses are relatively small (22, 23, 26), but direct application of NMDA onto neostriatal neurons induces unique responses characterized by membrane oscillations and bursts of action potentials in rodents, cats, and humans (23, 27–29). The effects of dopamine on the electrophysiology of neostriatal cells have been extensively studied (30). Its actions are complex and both excitatory and inhibitory responses occur (30–37).

The present study was performed to examine the interactions between specific subtypes of both EAA and dopamine receptors. EAA receptor agonists (Glu, AMPA, Quis, and NMDA) were iontophoretically applied onto neostriatal neurons in brain slices and the ability of dopamine and its specific D_1 or D_2 receptor agonists to modify responses evoked by EAAs was assessed. The major result of these experiments was that dopamine differentially affects responses evoked by activation of specific EAA receptors. It attenuates all responses evoked by Glu and many evoked by Quis or AMPA but markedly potentiates responses evoked by activation of NMDA receptors. The ability of dopamine to enhance responses appears to be mediated by activation of D_1 receptors while its ability to attenuate may be mediated by activation of both D_1 and D_2 receptors.

MATERIALS AND METHODS

Neostriatal slices were obtained from 33 adult rats (2–4 months) and caudate nucleus slices were from 3 adult cats (3–5 years). Rats were sacrificed by cervical dislocation. Brains were dissected, and coronal slices (400 μm thick) were cut from blocks containing the neostriatum and incubated in Ringer's solution (124 mM NaCl/5.0 mM KCl/2.0 mM $MgSO_4$/1.25 mM NaH_2PO_4/26.0 mM $NaHCO_3$/2.4 mM $CaCl_2$/10 mM glucose, pH 7.2–7.4 at 35–37°C). Cats were anesthetized (sodium methohexital, 35 mg/kg, i.v.) and placed in a stereotaxic frame. After removing the skull and dura, a lethal dose of sodium pentobarbital (100 mg/kg, i.v.) was injected. The brain was removed rapidly and placed in ice-cold oxygenated Ringer's solution. Similar procedures were subsequently used for rat and cat tissue. Tissue slices were transferred to the recording chamber at least 60 min

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Abbreviations: NMDA, *N*-methyl-D-aspartate; Quis, quisqualate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAA, excitatory amino acid.

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after sectioning. In the chamber, the slice was superfused continuously by Ringer's solution (35–37°C). A warm moist gas mixture (95% O_2/5% CO_2) flowed over the top surface of the slice.

Intracellular current clamp recordings were obtained. Glass recording micropipettes were filled with 3 M potassium acetate (60–100 MΩ). EAAs and dopamine were applied iontophoretically using a five-barreled pipette (8–12 μm, external diameter) positioned close (100–200 μm) to the recording electrode. Pipettes contained Glu (0.1 M, pH 8.5), Quis (0.1 M, pH 8), or AMPA (0.1 M, pH 8.5), NMDA (0.1 M, pH 8), dopamine (0.2 M, pH 4.5), and saline for current balancing and control. To demonstrate the specificity of NMDA-induced responses, in several experiments 2-amino-5-phosphonovalerate (0.1 M, pH 8.5), a selective NMDA receptor antagonist, was placed in the pipette instead of Quis or AMPA. Holding currents of appropriate polarity were 15–20 nA. Bath application was used in experiments assessing dopamine receptor agonists (SKF 38393, a D_1 agonist at 2–25 μM and quinpirole, a D_2 agonist at 1–25 μM) and antagonists (SCH 23390, a D_1 antagonist at 10–20 μM).

Each EAA was iontophoretically ejected by an ascending series of current intensities until the threshold for inducing action potentials was obtained. The duration of the ejection pulse varied from 5 to 15 sec but was held constant for each substance in each cell. The interval between ejection pulses varied from 1 to 3 min to avoid cumulative effects of the drugs and sensitization or desensitization of the receptors. Reproducible responses were evoked by EAAs when these precautions were taken. Hyperpolarizing current pulses (0.2–0.5 nA, 50–200 msec, 0.5 or 1 pulse per sec) were applied through the recording electrodes to estimate conductance changes during drug application. Controls consisted of application of currents through the saline-containing barrel that were of similar polarity and equal to or of greater amplitude than those required to produce effects with EAAs or with dopamine. Control applications of saline never produced effects on membrane or action potentials in the recorded cells.

To test the effects of dopamine or its receptor agonists, a single EAA ejection intensity was chosen, usually just above or just below threshold for inducing action potentials. Responses induced by the EAAs were first characterized, then reassessed in the presence of dopamine (iontophoretic application) or of its receptor agonists (in the bath), and then retested several minutes after discontinuing dopamine (iontophoretic application) or for 1–2 hr after bath application of agonists. In iontophoretic experiments, dopamine application began 1–2 min before the EAA and continued during the EAA ejection. Differences between control and experimental conditions were evaluated with paired *t* tests. Values were considered statistically significant if $P < 0.05$. Only significance levels are reported.

RESULTS

Data were obtained from 55 neurons (46 from rats and 9 from cats). Electrophysiological properties of cells recorded from rats or cats were similar and data were pooled. Basic membrane properties of recorded cells were also similar to those previously described (38, 39): resting membrane potential, −72.4 ± 1.1 mV (average ± SEM); action potential amplitude, 71.3 ± 1.1 mV; input resistance, 19.7 ± 0.9 MΩ. Neurons did not fire spontaneously, but action potentials could be evoked by depolarizing current pulses.

Iontophoretic application of Glu or Quis induced a rapid membrane depolarization accompanied by repetitive single action potentials (Fig. 1*A Inset*, traces 1 and 2). Bursts were never induced by Glu or Quis. When iontophoresis ceased, the membrane repolarized rapidly. AMPA also induced single action potentials but the membrane depolarized relatively slowly and, after the ejection current was turned off, repolarization also occurred slowly (data not shown). Glu-, Quis-, or AMPA-induced membrane depolarizations could be blocked by bath application of 6-cyano-7-nitroquinoxaline-2,3-dione, a specific antagonist for non-NMDA receptors (40).

NMDA induced a unique pattern of activation of neostriatal neurons (Fig. 1*A Inset*, trace 3). After an initial slowly occurring membrane depolarization, slow rhythmic oscillations consisting of large-amplitude membrane depolarizations accompanied by action potentials were induced. The initial phase of the depolarization was accompanied by a burst of high-frequency action potentials followed by lower-amplitude longer-duration spikes. Each oscillation was terminated by a sudden and pronounced afterhyperpolarization. This pattern occurred almost invariably in cats. In rats, both bursts and repetitive single action potentials were observed. The response induced by NMDA was completely blocked by ejection of 2-amino-5-phosphonovalerate ($n = 4$) before and during NMDA application.

Interactions between iontophoretic applications of dopamine and EAAs were examined in 28 neurons (9 in cats and 19 in rats). When dopamine was applied alone, there were no changes in resting membrane potential or input resistance. When applied in conjunction with the EAAs, dopamine produced contrasting effects depending upon the EAA being assessed. Dopamine attenuated all responses induced by Glu or AMPA and most by Quis but potentiated responses evoked by NMDA (Table 1). Dopamine produced statistically significant decreases in the amplitude of the membrane depolarization (23 ± 8.2% reduction; $P < 0.025$) and completely abolished Glu-induced action potentials (Fig. 1 *A* and *B*, traces 1) in all neurons tested ($n = 13$). It also decreased the amplitude of the depolarization induced by Quis (seven of nine cases, one cell increased, and one cell did not respond; Fig. 1 *A* and *B*, traces 2) or AMPA ($n = 2$) (data not shown). The inhibitory action of dopamine could also be demonstrated when dopamine onset occurred after the EAA agonist was ejected. When dopamine was applied for 5–15 sec during the depolarization induced by Glu or Quis, it reduced the amplitude of the EAA-evoked depolarizations by 2–10 mV and reduced or abolished action potentials ($n = 5$).

Dopamine potentiated responses evoked by NMDA. There was a marked increase in the amplitude of the evoked depolarization (189 ± 33% increase; $P < 0.001$), a decrease in the latency to evoke action potentials (30 ± 8.6% reduction; $P < 0.005$), and increases in both bursts and repetitive action potentials (Fig. 1 *A* and *B*, traces 3). This effect occurred in all tested neurons ($n = 25$, Table 1). Responses evoked by all EAAs that were altered by dopamine recovered to control levels after dopamine was discontinued (data not shown).

The differential modulation exerted by dopamine could also be demonstrated in the same neuron. Dopamine potentiated NMDA-evoked and attenuated Glu-evoked responses in eight cells, potentiated NMDA-evoked and attenuated Quis-evoked responses in seven cells, and potentiated NMDA-evoked and attenuated Glu- or Quis-induced responses in four cells.

The interactions among responses evoked by EAAs and bath application of D_1 or D_2 receptor agonists were studied in 22 neurons (Table 1). When dopamine agonists were applied alone, there were no changes in membrane potential or input resistance. The enhancement of NMDA-induced responses was mimicked by bath application of the D_1 agonist SKF 38393 (Fig. 2, traces A and B). The D_1 agonist produced an increase in the amplitude of NMDA-evoked depolarizations and firing frequency in 11 of 12 cells (1 cell displayed a reduction). The effects of SKF 38393 were more variable on responses evoked by Quis or AMPA (Glu was not tested).

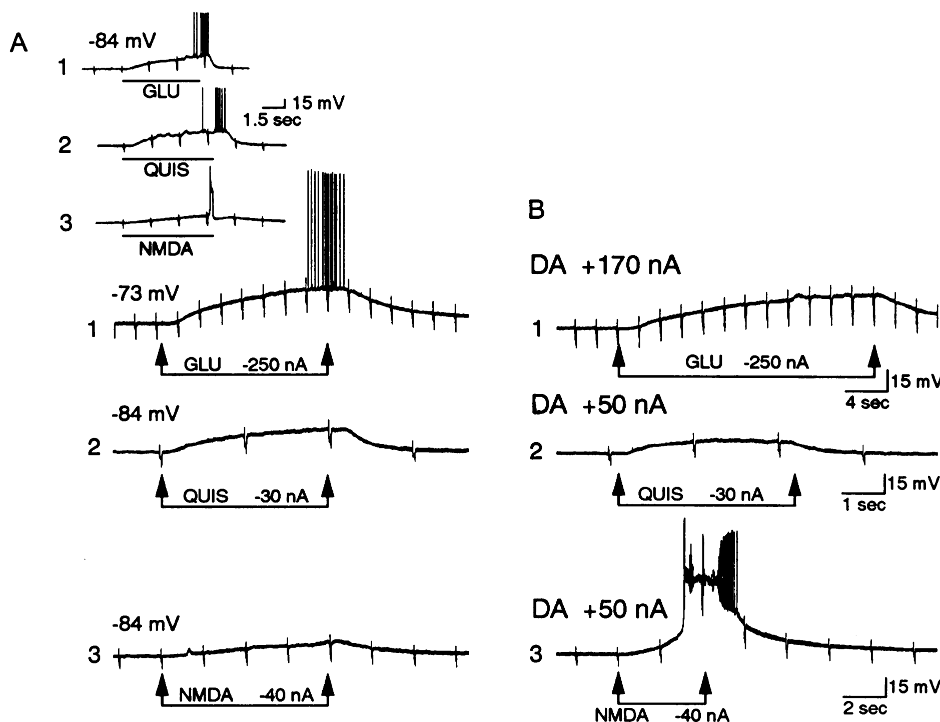

FIG. 1. Contrasting effects of dopamine (DA) on responses evoked by application of Glu, Quis, or NMDA. (*A Inset*) Typical responses of neostriatal neurons to iontophoretic application of Glu, Quis, or NMDA. All responses were recorded from the same cell. The horizontal bars indicate the duration of ejection current. (*A*) Control responses evoked before application of dopamine. (*B*) Effect of the same current used in *A* but in the presence of dopamine. The membrane depolarizations and action potentials induced by Glu or Quis were reduced or eliminated (traces 1 and 2). Note that the effect occurred despite a longer-duration Glu ejection in the presence of dopamine. In contrast, the depolarization evoked by NMDA was greatly increased by dopamine (traces 3) even though the duration of the NMDA current pulse was reduced. This intensity of NMDA ejection current evoked a depolarization subthreshold for induction of action potentials before dopamine was applied. Because of space limitations recoveries of responses are not illustrated in this and the subsequent figure. Upward arrows indicate current onset and offset. Current intensities for EAA ejections are shown between the arrows. Dopamine ejection (currents shown above traces) began 30–60 sec before the EAA ejection. In both figures, numbers on the left and immediately above the traces are resting membrane potentials.

The D_1 agonist decreased the membrane depolarization induced by Quis in 2 of 3 cells (1 cell increased) (Fig. 2, traces C and D). It enhanced responses evoked by AMPA in 3 of 4 cells (1 cell was unchanged). The potentiation of NMDA-induced responses by iontophoretic application of dopamine could be effectively antagonized by bath application of the selective D_1-receptor antagonist SCH 23390, providing additional evidence for receptor specificity of this effect of dopamine (Fig. 2, traces E–H) ($n = 2$).

Quinpirole, a D_2 receptor agonist, produced decreases in responses evoked by Quis, AMPA, and NMDA. Quinpirole reduced NMDA-evoked responses in 8 of 10 cells (2 cells unaffected; Fig. 2, traces I and J), and Quis or AMPA evoked responses in 3 of 3 cells.

Table 1. Interactions between dopamine and EAAs

	No. responses potentiated or attenuated/no. total responses			
	Glu	Quis	AMPA	NMDA
Dopamine				
Potentiation	0/13	1/9	0/2	25/25
Attenuation	13/13	7/9	2/2	0/25
SKF 38393 (D_1)				
Potentiation	NT	1/3	3/4	11/12
Attenuation	NT	2/3	0/4	1/12
Quinpirole (D_2)				
Potentiation	NT	0/1	0/2	0/10
Attenuation	NT	1/1	2/2	8/10

When the number of potentiated and attenuated responses is less than the total, the difference represents nonresponsive cells. NT, not tested.

When responses induced by EAAs are categorized as those evoked by activation of non-NMDA (Glu, Quis, and AMPA) vs. NMDA receptors, dopamine attenuated 96% (23/24) of non-NMDA responses and potentiated 100% (25/25) of NMDA responses. Activation of D_1 receptors potentiated 92% (11/12) of responses induced by activation of NMDA receptors and 57% (4/7) responses induced by activation of non-NMDA receptors. In contrast, activation of D_2 receptors attenuated 100% of responses evoked by non-NMDA receptor agonists (3/3) and NMDA (8/8).

DISCUSSION

The major finding of this study is that the effect of dopamine in the neostriatum is dependent upon the specific subtypes of both EAA and dopamine receptors activated. Dopamine can either potentiate or attenuate responses evoked by EAAs. Responses evoked by Glu, Quis, or AMPA are primarily attenuated when dopamine is present. In contrast, responses evoked by NMDA are potentiated. The dopamine receptor subtype provides additional specificity to these effects. Activation of D_1 receptors potentiates responses evoked by NMDA but has a more variable effect on responses evoked by Quis or AMPA. Activation of D_2 receptors primarily attenuates responses evoked by Quis, AMPA, or NMDA.

Dopamine's differential modulation of responses evoked by application of Glu, Quis, or AMPA and NMDA has not been reported previously for the neostriatum although similar differential effects were reported in our study of developing human neocortex (41). The finding that similar effects occur in the neostriatum of rats and cats implies that dopamine's

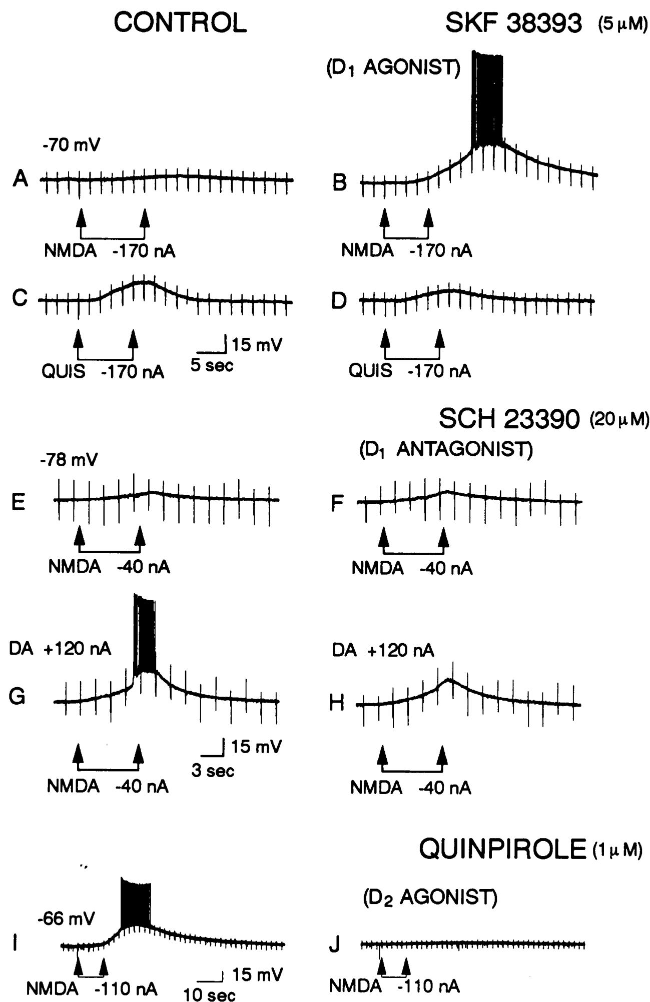

FIG. 2. Interactions among responses evoked by EAAs and dopamine (DA) receptor agonists and antagonists. Traces are from three neurons. Traces A–D are from one cell and show the effects of SKF 38393 on responses evoked by application of NMDA (traces A and B) or Quis (traces C and D). Bath application of the D_1 receptor agonist enhanced the response evoked by NMDA and decreased the depolarization induced by Quis. Note that a shorter-duration pulse of NMDA was used in the presence of SKF 38393. Control traces A and C show depolarizations subthreshold to induction of action potentials. Traces E–H are from the second cell and show that bath application of the D_1 receptor antagonist SCH 23390 (20 μM) blocks the dopamine-induced potentiation of a response evoked by NMDA. Traces E and G show the enhancing effects by dopamine- of NMDA-induced responses. Traces F and H show that SCH 23390 blocked the potentiation. The membrane depolarization is less pronounced and action potentials are not induced. SCH 23390 alone had virtually no effect on the NMDA-induced response (compare traces E and F). Traces I and J are from the third cell and show that bath application of the D_2 receptor agonist, quinpirole (1 μM), markedly attenuated a response evoked by application of NMDA.

modulatory actions are widespread and conserved in different brain regions and across species.

A number of previous studies have reported both excitatory and inhibitory effects of dopamine in the neostriatum (42–45). For example, concentration-dependent excitatory or inhibitory actions of dopamine or its receptor-specific agonists on Glu-induced responses in neostriatal neurons have been described (44, 45). When dopamine or its agonists were applied with low-ejection currents, the effects of Glu were enhanced, whereas at higher currents, the effects of Glu were inhibited. The present observation that Glu-, Quis-, or AMPA-induced responses are decreased by dopamine is in agreement with previous results indicating that dopamine attenuates depolarizing postsynaptic potentials in the neostriatum (34, 36) and that these potentials are mediated primarily by activation of non-NMDA receptors (22).

Responses induced by Glu, Quis, or AMPA are believed to be mediated primarily by Na^+ and K^+ currents although there is a contribution of Ca^{2+} (46). The dopamine-induced attenuation of responses evoked by these EAA agonists may be mediated by a decrease in Na^+ current (36, 47). The present results do not differentiate dopamine's effects on ionic currents mediated by activation of receptors from those generated by activation of voltage-dependent ion channels. Interestingly, in the presence of dopamine or its receptor specific agonists, the action potential threshold was often elevated, suggesting that one action of these substances could be on Na^+ channels. Activation of D_2 receptors mimics the dopamine-induced decrease in Na^+ currents (47) and activates single K^+ channels (48) possibly accounting for the effects of quinpirole in the present study. Activation of D_1 receptors has also been reported to decrease excitability and decrease Na^+ currents (47). Although similar effects were observed in a few cells in the present study, activation of D_1 receptors typically potentiated responses to EAAs. Further experiments are needed to determine why this difference occurred.

The interaction of dopamine and NMDA may involve K^+ or Ca^{2+} currents. Dopamine decreases a low-threshold slowly-inactivating K^+ current activated by depolarization (49). Inhibition of this current could potentiate the effects of NMDA. Activation of NMDA receptors is associated with membrane channels that are permeable to Ca^{2+} (50). The effects of dopamine on Ca^{2+} currents have not been studied in the neostriatum, but in the hypothalamus, dopamine, acting via D_2 receptors, inhibits Ca^{2+} currents (51). If activation of D_2 receptors also reduces Ca^{2+} currents in the neostriatum, the reduction in NMDA-evoked excitations by quinpirole is explicable. The enhancement of NMDA-induced responses by the D_1 receptor agonist is more difficult to account for. It may involve interactions with second messenger systems (52, 53) and/or a D_1 receptor response that produces partial relief of the Mg^{2+} blockade of the NMDA receptor channel complex.

It might be argued that if D_1 and D_2 receptors produce opposing effects on NMDA-induced responses, then the net effect of dopamine would be annulled. However, coupling of receptors may be both spatially and functionally very specific (54, 55). In addition, the density of D_1 receptors is much higher in the neostriatum than the density of D_2 receptors (55) and their activation may overcome the effects of D_2 activation.

There is now growing evidence that different subtypes of dopamine receptors are localized on the same neostriatal cell (47). Thus, dopamine would be capable of activating both receptor subtypes on each cell. Although the present experiments did not assess D_1 and D_2 receptor activation in the same cell, nearly all cells tested responded to one or the other specific receptor agonist, providing indirect support for the hypothesis of colocalization.

Although our results are interpreted as being due to postsynaptic activation of receptors, presynaptic effects or direct effects on voltage-dependent ion channels cannot be ruled out. Test substances were generally applied within 100–200 μm of the recording electrode. Thus, they would be expected to have their major actions postsynaptically. However, neurons in the local area could also be affected by the iontophoretic application and certainly bath application would have widespread effects. Additional experiments will need to be performed to disassociate the pre- from the postsynaptic actions of these substances.

The results of the present study suggest a complex modulatory role of dopamine in the neostriatum. There appears to

be a tight functional coupling between EAA and dopamine receptors so that the specific modulatory role for dopamine is determined by the particular EAA receptor activated. *In vivo*, the endogenous substances are Glu and dopamine. Thus, the primary action of dopamine appears to be to attenuate excitatory responses mediated by Glu. This effect can involve activation of both D_1 and D_2 dopamine receptors. However, if large-amplitude depolarizations are induced and the Mg^{2+} blockade of the NMDA receptor is removed, dopamine via D_1 receptor activation can potentiate the depolarization. If inputs to the neostriatum activate EAA receptor subtypes differentially, dopamine may regulate excitability by enhancing neuronal inputs that activate NMDA receptors and depressing inputs that activate non-NMDA receptors, providing a mechanism for differential "gain" control (56, 57).

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