Modulation of Synaptic Transmission by Dopamine and Norepinephrine in Ventral but not Dorsal Striatum

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Nicola, Saleem M. and Robert C. Malenka. Modulation of synaptic transmission by dopamine and norepinephrine in ventral but not dorsal striatum. J. Neurophysiol. 79: 1768–1776, 1998. Although the ventral striatum (nucleus accumbens; NAc) and dorsal striatum are associated with different behaviors, these structures are anatomically and physiologically similar. In particular, dopaminergic afferents from the midbrain appear to be essential for the normal functioning of both nuclei. Although a number of studies have examined the effects of dopamine on the physiology of NAc or striatal cells, results have varied, and few studies have compared directly the actions of dopamine on both of these nuclei. Here we use slice preparations of the NAc and dorsal striatum to compare how synaptic transmission in these nuclei is modulated by catecholamines. As previously reported, dopamine depressed excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in the NAc. Surprisingly, however, neither EPSPs nor IPSPs in the dorsal striatum were affected by dopamine. Similarly, norepinephrine depressed excitatory synaptic transmission in the NAc by an α-adrenergic-receptor-dependent mechanism but was without effect on excitatory transmission in the dorsal striatum. Inhibitory synaptic transmission was not affected by norepinephrine in either structure. These results suggest that the functional roles of dopamine and norepinephrine are not the same in the dorsal striatum and the NAc.

INTRODUCTION

Because of the similarities in their cytoarchitecture, neurochemistry and afferent and efferent connections, the nucleus accumbens (NAc) usually is considered to be the ventromedial extent of the striatum or the “ventral striatum” (Heimer and Wilson 1975; Heimer et al. 1982; Swanson and Cowan 1975). The major cell type in both nuclei is the GABAergic medium spiny neuron, which makes profuse synaptic contacts with neighboring spiny neurons (Chang and Kitai 1985; Groves 1983; O’Donnell and Grace 1993; Pennartz and Kitai 1991; Smith and Bolam 1990) and sends its projection axon to the globus pallidus (Heimer et al. 1982). Both nuclei also receive profuse dopaminergic innervation from the midbrain (Fuxe 1965; Ungerstedt 1971). However, a difference between the two nuclei is that the NAc receives excitatory projections from the amygdala, hippocampus, and allo- and mesocortical areas, whereas the dorsal striatum receives excitatory inputs mainly from the neocortex and thalamus (Groves 1983; McGeorge and Faull 1989; Pennartz et al. 1994; Smith and Bolam 1990). These distinct afferent inputs are likely to be part of the reason why the NAc and striatum are responsible for quite different behaviors. The NAc is associated with natural reward and is thought to be a central locus for the actions of several drugs of abuse, particularly the psychostimulants (Le Moal and Simon 1991). In contrast, the dorsal striatum is required for the execution of planned motor behavior (Graybiel et al. 1994) and is implicated in the pathophysiology of Parkinson’s disease and Huntington’s chorea. Both nuclei may be involved in psychiatric diseases such as schizophrenia (Swerdlow and Koob 1987).

One element that is common to almost all hypotheses that attempt to explain the behavioral functions of the NAc and striatum is the paramount importance of the midbrain dopaminergic projection. Despite convincing behavioral evidence of the importance of dopamine (DA), however, little is known about the physiological actions of DA on neurons in these structures. Recently, we and others have shown that in the NAc, DA presynaptically depresses both excitatory (Harvey and Lacey 1996; Nicola et al. 1996; Pennartz et al. 1992) and inhibitory (Nicola and Malenka 1997) synaptic transmission by activation of a D1-like DA receptor. Similar studies conducted in the striatum, however, have yielded conflicting and confusing results. Some laboratories have reported that DA causes a depression of excitatory synaptic responses mediated by non-ND-methyl-D-aspartate (NMDA) receptors in the striatum via activation of D2 receptors (Hsu et al. 1995; Levine et al. 1996b; Umemiya and Raymond 1997). This effect was suggested to be postsynaptic because of the lack of change in paired-pulse facilitation on application of DA (Levine et al. 1996b) and because of the attenuation by DA of the depolarizing response to iontophoretic application of glutamate or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) to striatal cells (Cepeda et al. 1993). In contrast, other studies found no change in the striatal excitatory synaptic response when DA was applied (Malenka and Kocsis 1988) or in the response to iontophotically applied AMPA (Calabresi et al. 1995). A D2-receptor–dependent attenuation of excitatory synaptic transmission was observed in slices taken from animals exposed to treatments intended to upregulate D2 receptors (Calabresi et al. 1988, 1992, 1993). It also has been reported that D1 receptor activation can depress the amplitude of excitatory postsynaptic potentials (EPSPs) in striatal cells by modifying their membrane rectification properties (Calabresi et al. 1987), although recently it has been suggested that D1 receptors may in fact enhance EPSPs (Umemiya and Raymond 1997). Finally, there is also disagreement about the effects of DA on NMDA-receptor–mediated responses. Some groups have reported that DA, via activation of D1 receptors, enhances NMDA-receptor–mediated synaptic or iontophoretic responses in the striatum (Cepeda et al. 1993; Levine et al. 1996a,b) or NAc (Harvey and Lacey 1997),
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FIG. 1. Dopamine depresses excitatory postsynaptic potentials (EPSPs) in the nucleus accumbens (NAc) but not in the striatum. A: sample traces (top) and time course (bottom) of a typical experiment illustrate the lack of effect of dopamine (100 μM) on EPSPs recorded from a striatal cell. B: traces (top) and time course of a typical experiment (bottom) demonstrate that dopamine (75 μM) depresses EPSPs in the NAc. C: averages of similar experiments conducted in striatal slices (n = 16, 100 μM dopamine) and NAc slices (n = 8, 50–75 μM dopamine).

whereas others have not observed this effect (Calabresi et al. 1995).

One hypothesis that encompasses several, although certainly not all, of these previous results is that excitatory synaptic responses in the striatum are depressed by D2 receptors and potentiated by D1 receptors. Such effects are in marked contrast to the general consensus that DA-induced synaptic depression in the NAc is dependent on D1 receptor activation (Harvey and Lacey 1996; Higashi et al. 1989; Nicola and Malenka 1997; Nicola et al. 1996; Pennartz et al. 1992; but see O’Donnell and Grace 1994). In an attempt to make some sense out of this confusing literature, we have directly compared the actions of DA on both excitatory and inhibitory synaptic transmission in the NAc and striatum. Because of the likely functional importance of adrenergic inputs, we also compared the effects of norepinephrine (NE) on synaptic transmission in the two nuclei.

METHODS

Preparation of slices and electrophysiological recordings were performed as described previously (Nicola and Malenka 1997; Nicola et al. 1996). Rats (15- to 20-day-old Sprague-Dawley) were deeply anesthetized with Halothane, and the brain removed to ice-cold Ringer solution [which contained (in mM) 126 NaCl, 1.6 KCl, 1.2 NaH₂PO₄, 1.2 MgCl₂, 2.5 CaCl₂, 18 NaHCO₃, and 11 glucose]. Sagittal NAc slices and coronal striatal slices were cut to a thickness of 400 μm. After ≈1 h for recovery, slices were transferred to a perfusion chamber (2–3 ml/min) and bathed with continuously bubbled (95% O₂-5% CO₂) Ringer solution containing either 25 μM picrotoxin when excitatory responses were recorded or 10 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX) and 75 μM N-methyl-2-amino-5-phosphonovaleric acid (d,l-APV) when inhibitory postsynaptic potentials (IPSPs) were recorded.

Slices were stimulated with bipolar electrodes placed within the striatum or NAc. Field recordings were made with glass electrodes filled with Ringer solution. Whole cell current-clamp recordings using the “blind” technique were made with electrodes (5–12 MΩ) containing (in mM) 117.5 cesium gluconate, 17.5 CsCl, 8 NaCl, 10 N-2-hydroxyethylpiperazine- N’-2-ethanesulfonic acid (HEPES), 0.2 ethylene glycol-bis(β-aminoethyl ether)-N,N,N’,N’-tetraacetic acid (EGTA), 2.5 MgATP, and 0.1 GTP, pH 7.2. The membrane potential was held at −80 mV for EPSPs and 0 mV for IPSPs. Series resistances ranged from 15 to 50 MΩ. In some experiments, the perforated patch technique was employed as follows (Isaac et al. 1996). Electrodes (3–4 MΩ) were tip-filled by submersion for 30 s in a solution containing (in mM) 117.5 cesium gluconate, 20 HEPES, and 0.2 EGTA, pH 7.2. Electrodes then were backfilled with the same solu-
tion containing 1 mg/ml amphetamine B [prepared by addition of a freshly prepared 60 mg/ml stock solution in dimethyl sulfoxide (DMSO)] and 0.1% pluronic F-127 (from a 20% stock solution in DMSO). After obtaining a seal, access resistances favorable for current-clamp recordings (20–90 MΩ) developed within 10–30 min and remained stable throughout the experiment.

For all experiments, data were filtered at 1 kHz, digitized at 3–10 kHz, and collected using software (written by D. Selig), which provided an on-line analysis of the initial slope of the rising phase of the EPSP and the amplitude of IPSPs and field responses. Stimuli were given at 0.1 Hz, and points on the illustrated graphs represent the mean of all points in 1-min bins. The illustrated data sweeps are averages of 1.5- to 2-min bins. Statistical tests were performed as described previously (Nicola et al. 1996). Paired t-tests were used to determine whether responses were of different magnitude in an agonist compared with the baseline. When an additional comparison was required (such as whether a second drug influenced the action of an agonist), two-way repeated-measures analyses of variance were computed. For all analyses, P ≤ 0.05 was considered statistically significant.

Freshly prepared drug stock solutions were diluted with saline just before bath application to the slice. DA HCl and (±)-norepinephrine were prepared at 1,000 times final concentration in water containing 50 mM sodium metabisulphite, s-(+) -Amphetamine, s-(−)-propranolol, phentolamine mesylate, and D,L-APV were dissolved in water, and GBR12935, 6,7-dinitroquinoxaline-2,3-dione (DNQX), and 6-nitro-7-sulphamoylbenzof[7]quinoxaline-2,3-dione (NBQX) were dissolved in DMSO so that the final concentration of DMSO when applied to the slice was 0.1%.

RESULTS

Monosynaptic EPSPs were recorded from whole cell current-clamped cells in the NAc and striatum as previously described (Nicola et al. 1996). These responses were elicited by electrical stimulation within each nucleus, and were pharmacologically isolated with the γ-aminobutyric acid-A (GABA_A) antagonist picrotoxin (25 μM). To compare the modulation of excitatory synaptic transmission by DA in the striatum and NAc, we first exposed 16 striatal slices to DA (100 μM) applied through the perfusion medium. DA application did not result in changes in input resistance or in the current necessary to hold the cell at −80 mV (data not shown), consistent with our earlier observations in NAc cells (Nicola and Malenka 1997; Nicola et al. 1996). Surprisingly, however, DA also did not affect the magnitude of the evoked EPSP [94 ± SE 3% of baseline, P > 0.05, Fig. 1, A and C], in direct contrast to its strong depressant effects on excitatory responses recorded in the NAc (Harvey and Lacey 1996; Nicola and Malenka 1997; Nicola et al. 1996; Pennartz et al. 1992). To confirm our earlier observations, we applied DA (50–75 μM) to eight NAc cells and found that EPSPs were reduced reversibly to 56 ± 5% of baseline (P < 0.001, Fig. 1, B and C).

One potential, albeit unlikely, explanation for the lack of effect of DA in the striatum is that DA reuptake may be much stronger in the striatum than in the NAc, perhaps as a result of greater expression of transporter proteins. We performed two experiments to test this hypothesis. First, we applied DA to striatal slices first in the absence and then, while recording from the same cell, in the presence of the DA transporter inhibitor GBR12935. As shown in Fig. 2A, the presence of GBR12935 (10 μM) did not significantly enhance the effects of DA (100 μM) on the EPSP (100 ± 5% of baseline in the absence of GBR12935; 91 ± 4% of baseline in the presence of GBR; P > 0.18, n = 5). In a second experiment, we applied amphetamine, which reverses the DA uptake transporter (Seiden et al. 1993) and depresses excitatory potentials in the NAc by a mechanism dependent on DA receptors (Nicola et al. 1996). If DA uptake was stronger in the striatum than in the NAc, amphetamine would be expected to have particularly pronounced effects on striatal EPSPs. However, as illustrated in Fig. 2B, amphetamine (10 μM) did not significantly reduce the EPSP (89 ± 5%, P > 0.05, n = 7), whereas in 9 NAc cells, amphetamine reduced the EPSP to 58 ± 5% of baseline (P < 0.001). Thus stronger DA reuptake in the striatum than in the NAc is unlikely to explain the lack of effect of DA on striatal EPSPs.

Given the previous reports that DA reduces excitatory responses in striatal cells (Hsu et al. 1995; Levine et al. 1996b; Umemiya and Raymond 1997), we thought it important to compare the effects of DA in the striatum and NAc in the most direct manner possible. We therefore performed
simultaneous field recordings of excitatory synaptic responses in both the striatum and NAc in slices containing both nuclei. One stimulating electrode was placed in the striatum to evoke excitatory responses detected by a recording electrode in the same nucleus (Malenka and Kocsis 1988), while a second stimulating electrode was placed in the NAc and evoked responses detected by a second recording electrode in the NAc (Fig. 3A). Stimuli were delivered alternately to one nucleus and the other, with a 5-s interval between alternate stimuli. Application of DA (100 μM) to this preparation caused a depression to 63 ± 4% of baseline in the synaptic responses recorded by the NAc electrode, whereas the striatal synaptic responses recorded simultaneously remained at 100 ± 6% (P < 0.04, n = 4, Fig. 3, B–D). These results are direct evidence of a genuine difference in the effects of DA on excitatory synaptic transmission in the striatum and NAc.

Although we observed no effects of DA on EPSPs mediated by non-NMDA receptors, previous reports have suggested that NMDA-receptor–mediated responses in striatal cells may be enhanced by activation of D1 receptors (Cepeda et al. 1993; Levine et al. 1996a,b; but see Calabresi et al. 1995). To examine this possibility, we recorded striatal NMDA-receptor–mediated synaptic potentials in the presence of NBQX (5 μM) and picrotoxin (25 μM) with perforated patch recording techniques. This ensured that “wash-out” of this putative postsynaptic effect did not occur. Application of DA (75 μM) to six cells held at −60 mV did not significantly alter the NMDA-receptor–mediated EPSP (88 ± 4% of baseline, P > 0.05; not shown). Application of DA (100 μM) caused no change in the amplitude of IPSPs (99 ± 3%, n = 5, P > 0.4; Fig. 4, A and B). Application of amphetamine (10 μM) was also without effect (99 ± 6%, P > 0.5, n = 4; Fig. 4, A and C) despite consistent effects of both DA and amphetamine on IPSPs in the NAc (Nicola and Malenka 1997).

To test whether the differences between the NAc and striatum in the modulation of synaptic transmission by DA extend to other catecholamine transmitters, we examined whether synaptic transmission in these structures is affected by NE. Application of NE (100 μM) had no effect on the...
amplitude of synaptic field potentials recorded in the striatum (99 ± 2% of baseline, \( P > 0.5, n = 6; \) Fig. 5). In the NAc, however, we previously found that NE caused a robust depression of the synaptic response due to activation of \( \alpha \)-adrenergic receptors (Nicola et al. 1996). For the sake of comparison, we illustrate these data in Fig. 6. The \( \beta \)-adrenergic receptor antagonist propranolol (10 \( \mu \)M) did not alter the ability of NE (100 \( \mu \)M) to depress the NAc synaptic potential (73 ± 4%, \( P < 0.05, n = 7 \) in the presence of propranolol vs. 73 ± 3%, \( P < 0.0001, n = 11 \) in its absence; Fig. 6, A, B, and E). The \( \alpha \) antagonist phentolamine, however, prevented the depression induced by NE (98 ± 2%, \( P > 0.05, n = 5; \) Fig. 6, C–E). Thus activation of \( \alpha \)-adrenergic receptors depresses excitatory synaptic transmission in the NAc but not in the striatum.

In a final set of experiments, we examined the effects of NE on inhibitory synaptic transmission in the striatum and NAc. Similar to its lack of effect on excitatory synaptic responses, NE (100 \( \mu \)M) had no effect on IPSPs recorded from striatal cells (99 ± 1% of baseline, \( n = 4, P > 0.2; \) Fig. 7A). Surprisingly, and in contrast to its effects on excitatory synaptic responses in the NAc, NE also had no effect on IPSPs recorded from NAc cells (99 ± 5% of baseline, \( n = 4, P > 0.5; \) Fig. 7B). Thus in both the NAc and striatum, NE did not affect inhibitory synaptic transmission.

DISCUSSION

Behavioral experiments have demonstrated that the ventral striatum (NAc) is involved in behaviors that differ from those that involve its dorsal counterpart. For instance, psychostimulant-induced hyperlocomotion requires activation of DA receptors in the NAc, whereas the repetitive stereotypic behaviors observed in animals given psychostimulants require DA in the dorsal striatum (Amalric and Koob 1993). Similarly, there is evidence that the NAc, but not the striatum, is a major component of the neural mechanisms responsible for natural reward and for psychostimulant abuse (Le Moal and Simon 1991). The striatum, on the other hand, is required for other processes, most notably for the initiation and planning of motor behavior (Amalric and Koob 1993).

Current models of the basal ganglia propose that both the dorsal and ventral striatum are important components of sensorimotor, cognitive, and limbic circuits. These circuits are, however, segregated anatomically based on the topography of the cortical afferent projections to the dorsal and ventral striatum (Goldman-Rakic and Selemon 1990; Parent 1990). Although there is much evidence that the modulation of these circuits by DA is behaviorally important, the mechanisms by which DA accomplishes this have remained enig-
matic. One distinct possibility, which is supported by some previous results, is that the actions of DA are different for each of these circuits. For example, although most studies of the NAc agree that DA depresses excitatory synaptic transmission via D1-like receptors that act to reduce glutamate release (Harvey and Lacey 1996, 1997; Higashi et al. 1989; Nicola and Malenka 1997; Nicola et al. 1996; Pennartz et al. 1992), several studies have suggested that reduction of excitatory synaptic transmission in the striatum is due to activation of postsynaptic D2 receptors (Cepeda et al. 1993; Hsu et al. 1995; Levine et al. 1996b) and that D1 receptor activation may in fact potentiate NMDA-receptor–mediated (Cepeda et al. 1993; Levine et al. 1996a,b) and non-NMDA-receptor–mediated (Umemiya and Raymond 1997) excitatory synaptic transmission.

However, consistent with earlier findings from other laboratories (Calabresi et al. 1995; Malenka and Kocsis 1988), we find that DA has no significant effect on excitatory synaptic transmission in the striatum. This lack of effect cannot be attributed to stronger DA uptake in the striatum than NAc because application of DA with the DA uptake inhibitor GBR12935 or application of amphetamine, which reverses the DA transporter, also did not affect excitatory synaptic responses. Furthermore, this difference in the effects of DA on excitatory synaptic transmission in the NAc and the striatum was observed when DA was applied while simultaneous recordings were made from the two nuclei in the same slice preparation. Thus we are confident that the differences we observed are real and not artifactual.

Nevertheless, there are explanations that potentially may resolve the discrepancy between our and some previous results. For example, the rats used in this study (<3 wk old) were younger than those used by others (Cepeda et al. 1993; Hsu et al. 1995; Levine et al. 1996b) although Umemiya and Raymond (1997), who reported a DA-induced depression of excitatory postsynaptic currents in the striatum, used rats of similar age to ours. Our recording techniques also differed from those used previously: others (Cepeda et al. 1993; Hsu et al. 1995; Levine et al. 1996b) used intracellular electrodes in interface chambers at warm temperatures (32–37°C), whereas this study employed whole cell electrodes in a perfusion chamber at room temperature (21–25°C). One possibility is that the postsynaptic effects of D2 receptor activation were not observed during our whole cell recordings due to so-called “wash-out.” However, in field recordings in which wash-out is not a possibility, we still did not observe a DA-induced synaptic depression in striatal slices (unpublished observations; see also Malenka and Kocsis 1988). Furthermore, wash-out was not likely to be a problem in our perforated-patch recordings of NMDA-receptor–mediated responses, in which no effect of DA was observed.

Notwithstanding the possibility that our experimental conditions may have precluded the observation of postsynaptic effects of DA, our results suggest that the presynaptic effects of DA observed in the NAc are absent in the striatum. Inhibitory synaptic transmission in the striatum was similarly not modulated by DA, again in contrast to the NAc (Nicola and Malenka 1997). The simplest explanation for these differences between NAc and striatum is that the D1-like receptor responsible for depression of transmitter release (Nicola and Malenka 1997; Nicola et al. 1996) in the NAc is not expressed in the same number or location in the striatum. For instance, the receptor may be expressed on hippocampal but not neocortical synaptic terminals, which would preclude observation of depression of excitatory synapses in the striatum by activation of this receptor.
ences observed here, the concentration of NE measured in the NAc is low to moderate, whereas it is not detectable in the striatum. NE depressed excitatory synaptic transmission in both nuclei was un-differentially regulate the pattern of cortical excitation in the NAc and striatum. NE depressed excitatory synaptic transmission observed in the hippocampal CA3 region (Scanziani et al. 1993). Anatomic studies employing radiolabeled antagonists have found both α₁- and α₂-adrenergic receptors in the striatum and NAc (Sargent Jones et al. 1985; Unnerstall et al. 1984). However, adrenergic innervation of these nuclei is sparse (Fuxe 1965; Swanson and Hartman 1975) although not completely absent (Lindvall and Björklund 1974). Consistent with the differences observed here, the concentration of NE measured in the NAc is low to moderate, whereas it is not detectable in the striatum (Versteeg et al. 1976). Taken together, these observations suggest that NE released from the relatively small number of adrenergic fibers and terminals may act in a paracrine fashion, activating adrenergic receptors on many cells in the NAc (Herkenham 1987).

Another catecholamine, NE, also had different synaptic effects in the NAc and striatum. NE depressed excitatory synaptic transmission in the NAc but not in the striatum; inhibitory synaptic transmission in both nuclei was unchanged by NE. The NE effect on excitatory transmission in the NAc is likely to be due to activation of α-adrenergic receptors because it was blocked by the α antagonist phentolamine but not the β antagonist propranolol. Thus this effect is similar to the α-adrenergic receptor-dependent decrease in excitatory synaptic transmission observed in the hippocampal CA3 region (Scanziani et al. 1993). Anatomic studies employing radiolabeled antagonists have found both α₁- and α₂-adrenergic receptors in the striatum and NAc (Sargent Jones et al. 1985; Unnerstall et al. 1984). However, adrenergic innervation of these nuclei is sparse (Fuxe 1965; Swanson and Hartman 1975) although not completely absent (Lindvall and Björklund 1974). Consistent with the differences observed here, the concentration of NE measured in the NAc is low to moderate, whereas it is not detectable in the striatum (Versteeg et al. 1976). Taken together, these observations suggest that NE released from the relatively small number of adrenergic fibers and terminals may act in a paracrine fashion, activating adrenergic receptors on many cells in the NAc (Herkenham 1987).

One possibility that arises from the similarities between the actions of NE and DA on excitatory transmission is that the receptor responsible for both effects is the same. There is evidence from other systems that DA can bind to and activate some adrenergic receptors, most notably of the β subtype (Goldberg 1972; Malenka and Nicoll 1986). However, at least two pieces of evidence argue against this possibility for the actions of these catecholamines in the NAc (see Nicola et al. 1996 for further discussion). First, amphetamine-induced depression of excitatory transmission remained intact in the presence of phentolamine, which completely abolished the effect of NE (Nicola et al. 1996). Second, although DA depresses IPSPs in the NAc, NE does not, suggesting that a NE receptor is not responsible for DA’s effects on IPSPs.

In vivo recordings have reported that DA can reduce single-unit activity and EPSPs evoked by stimulation of excitatory afferent nuclei (such as the cortex) in both the striatum (Abercrombie and Jacobs 1985; Brown and Arbuthnott 1983; Herrling and Hull 1980; Johnson et al. 1983; Mercuri et al. 1985; Rolls et al. 1984) and NAc (DeFrance et al. 1985; Yang and Mogenson 1984; Yim and Mogenson 1982, 1988). Our results suggest, however, that the modulation of synaptic transmission by DA in the NAc and striatum differs dramatically. Thus DA-induced depression of excitatory synaptic transmission by a presynaptic D1 receptor-dependent mechanism contributes to the reduction of evoked cell firing in the NAc but not in the striatum. Other mechanisms, such as postsynaptic D1-receptor–mediated effects on ion currents (Calabresi et al. 1987; Pacheco-Cano et al. 1996; Schiffmann et al. 1995; Surmeier et al. 1992) may have contributed to the depressant effects of DA that have been observed in the behaving animal.

The differences reported here in the synaptic actions of DA and NE in the NAc and striatum indicate that the physiological role of catecholamines in each of these nuclei in the behaving animal is likely different. One consequence predicted by our results is that the effects of DA on the integration of synaptic inputs by cells in the NAc will be more pronounced than in the striatum, thereby providing a means by which the midbrain dopaminergic nuclei can differentially regulate the pattern of cortical excitation in these structures. This conclusion has important consequences for theories of the function of these areas and the specific role of DA and DA receptors in the basal ganglia.

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