Short Review

Developmental Neuroscience

Dev Neurosci 1998;20:1–18

Received: November 21, 1997
Accepted: December 4, 1997

Carlos Cepeda
Michael S. Levine

Mental Retardation Research Center,
University of California at Los Angeles,
Los Angeles, Calif., USA

Dopamine and N-Methyl-*D*-Aspartate Receptor Interactions in the Neostriatum

Key Words
Dopamine
Electrophysiology
Neostriatum
N-methyl-*D*-aspartate
Receptor interactions

Abstract
This review examines dopamine (DA) and glutamate receptor interactions in the neostriatum (NS) primarily from a neurophysiological perspective. Historically, a clear understanding of the function of DA in the NS has been difficult because it was considered a classical neurotransmitter with either excitatory or inhibitory actions and because many of the data were obtained by use of varying methodologies. When DA is considered a neuromodulator whose role is to alter how NS cells respond to glutamatergic inputs, many of its actions can be accounted for and predicted with great accuracy within a model of receptor subtype. In this model, DA via activation of D1 receptors potentiates responses mediated by activation of N-methyl-*D*-aspartate (NMDA) receptors. DA via activation of D2 receptors attenuates responses mediated by activation of non-NMDA receptors. Outcomes of combinations of NMDA and D2 and non-NMDA and D1 receptors are not as predictable. The mechanisms underlying the D1-NMDA receptor interactions appear to involve alterations in cell excitability mediated by activation of Ca^{2+} conductances and/or phosphorylation of NMDA receptors. Less is known about mechanisms underlying the D2-non-NMDA receptor interaction. The functional implications of this model in setting membrane potentials, signal-to-noise ratio, plasticity and excitotoxicity are discussed.

The neostriatum (NS) plays a crucial role in the integration and regulation of motor programs, cognitive functions and motivational processes [Chesselet and Delfs, 1996; Graybiel, 1995; Rolls, 1994; Schultz, 1997]. This region of the basal ganglia has received considerable attention because a number of pathological conditions have been associated with alterations in NS function. The most prominent of these are Parkinson's and Huntington's diseases, each associated with a specific NS pathology. Parkinson's disease is caused by loss of the dopaminergic substantia nigra neurons which produces depletion of dopamine (DA) in the NS while Huntington's disease is related to degeneration of subpopulations of γ-aminobutyric acid (GABA)-containing medium-sized spiny neurons [Di Figlia, 1990]. Medium-sized spiny neurons constitute the vast majority of cells in the NS and their initial responses to afferents are controlled primarily by the confluence of glutamate-containing inputs from the neocortex and DA-containing inputs from the substantia nigra. Morphological evidence has shown that both cortical and nigral terminals converge on single spines of medium-sized NS neurons [Freund et al., 1984; Smith and Bolam,

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–5866/98/0201–0001$15.00/0

This article is also accessible online at:
http://BioMedNet.com/karger

Michael S. Levine, PhD
Mental Retardation Research Center
760 Westwood Plaza, University of California, Los Angeles
Los Angeles, CA 90024–1759
Tel. +1 (310) 825 7595, Fax +1 (310) 206 5060, E-Mail mlevine@mednet.ucla.edu

1990]. Consequently, a tight interaction exists between these two neurotransmitter systems.

Glutamate and DA produce their effects by activation of a variety of receptor subtypes. Glutamate receptors have been classified into two general forms, ionotropic receptors which are ligand-gated cation channels, and metabotropic receptors which are coupled to various signal transduction processes [Monaghan et al., 1989; Hollmann and Heinemann, 1994]. The ionotropic glutamate receptors are further subdivided according to their preferential agonists as N-methyl-*D*-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate (KA) [Watkins et al., 1990].

There is also considerable diversity among DA receptors as five different receptor subtypes have been cloned. A number of experimental methods can functionally distinguish the D1 and D2 receptor families, although multiple DA receptor subtypes have been identified in both families [Civelli et al., 1993; Sibley and Monsma, 1992]. In this review we will use D1 and D2 to indicate the families and subscripted notation (D_{1A}, D_{1B}, D_2, D_3, and D_4) to indicate the specific subtype. The D1 family has two subtypes, the D_{1A} and D_{1B} in the rodent [Monsma et al., 1990; Vincent et al., 1993], while the D2 family is composed of three subtypes: D_2, D_3, and D_4 [Bunzow et al., 1988; Monsma et al., 1989; O'Malley et al., 1992]. The effects produced by activation of each DA receptor subtype are varied, although a large body of evidence supports a functional synergy between the two DA receptor families [La Hoste et al., 1993] in which the D1 family receptors must be activated for the full effect of D2 family receptor responses to be realized. At other times, activation of each family produces antagonistic effects [Nestler, 1994]. Interestingly, the D1/D2 receptor synergy dissolves in altered experimental conditions such as DA depletion or DA receptor blockade [Gerfen et al., 1990; La Hoste et al., 1996]. It is becoming increasingly clear that responses of NS neurons to the release of glutamate and DA are determined by multiple, interacting receptors. This cellular integration allows considerable plasticity in a neuronal response to synaptic input and also offers potential opportunities for modulation which can serve as a basis for therapeutic intervention in conditions under which receptors become dysfunctional or abnormal.

The present review will concentrate on glutamate-DA interactions, in particular the NMDA-DA receptor interaction. Although several excellent reviews dealing with glutamate and DA have been published [Carlsson and Carlsson, 1990; Di Chiara et al., 1994; Greenamyre, 1993; Kötter, 1994; Lange et al., 1997; Lovinger and Tyler, 1996; Starr, 1995], recent electrophysiological data necessitate an update and there is to our knowledge no review focusing on DA-NMDA receptor interactions from an electrophysiological viewpoint.

Historical Perspective of the Actions of DA on NS Neurons

The following review is not exhaustive. We apologize for omitting many important studies, but because of space limitations we chose to cite studies representing points we wished to emphasize. Our goal in this section is to highlight aspects of DA-glutamate neurophysiology indicating that a clear-cut answer to questions concerning the physiological role of DA has always been problematic.

Historically, and even now, the primary approach has been to view DA as a classic neurotransmitter, very much like the excitatory and inhibitory amino acids or acetylcholine at the neuromuscular junction. Once two families of DA receptors were identified, a new level of complexity was added, but each of the families was often viewed as either excitatory or inhibitory. Thus, most experimental investigations of the actions of DA attempted to force DA into an excitatory or inhibitory role by trying to fit the function of DA into the rigid scheme of classical neurotransmission. At the time, this approach represented state-of-the-art thinking. However, the complexity of the action of DA precluded any real agreement among experimental investigations. In addition to two families of DA receptors, there are a number of variables that potentially contribute to determining the actions of DA. Among these are local concentration, which could contribute to differential activation of receptor subtypes with higher or lower affinities, multiple sites of localization of DA receptors on the pre- or postsynaptic neuron, multiple types of neurons and whether or not they are capable of expressing all or only some DA receptors, and the mode of DA application. As we review the electrophysiological actions of DA, we will point out how these variables have influenced interpretation of outcomes.

As expected, the earliest attempts to elucidate the effects of DA on NS cell electrophysiology reached no unanimous agreement. Pioneering studies in the 1960s, using extracellular recordings, showed that DA decreased spontaneous or glutamate-induced firing in anesthetized animals [Bloom et al., 1965; Hertz and Zieglgänsberger, 1968; McLennan and York, 1967; York, 1967]. Although the balance leaned towards inhibition, excitatory or mixed effects of DA were reported [Bevan et al., 1975;

Hirata et al., 1984; Nisenbaum and Berger, 1992; Norcross and Spehlmann, 1978; Ohno et al., 1987; Siggins, 1978; Spencer and Havlicek, 1974]. Surprisingly, in a recent review of the electrophysiological actions of DA, these excitatory effects have been minimized or ignored [see Calabresi et al., 1997b]. Different hypotheses were generated to explain the excitatory and inhibitory actions of DA. Among these were opposing pre- and postsynaptic effects, or alternatively, excitation and inhibition mediated by different receptor subtypes with differing affinities for DA [Norcross and Spehlmann, 1978] leading to the idea that local concentration of DA might be the important variable. For example, dose-response curves showed that excitation was obtained with ejection currents several times weaker than those required to produce inhibition [Norcross and Spehlmann, 1978]. This idea has found considerable support [Chiodo and Berger, 1986; Hu et al., 1990; Hu and White, 1997]. Chiodo and Berger [1986] accounted for both excitatory and inhibitory effects by demonstrating that DA could increase or decrease glutamate-induced cell firing depending on its concentration (or at least the intensity of the iontophoretic current used for ejection of DA). Again, low iontophoretic currents of DA increased, whereas higher currents decreased firing. More recently, the cooperation of both DA receptor subtypes in producing these effects in normal conditions has been emphasized in determining whether DA can produce excitatory or inhibitory actions [Hu et al., 1990; Hu and White, 1997].

More recent work has concentrated on analyzing the actions of DA in awake, unrestrained preparations. DA alters spontaneous or glutamate-induced activity of NS cells. Interestingly, motor-related NS neurons are excited by DA, whereas nonmotor-related neurons respond with inhibition. Furthermore, motor-related neurons respond to the co-administration of glutamate and DA with synergistic increases in firing rate, and the ability of DA to enhance glutamate-induced responses is more pronounced in neurons displaying moderate levels of activity [Pierce and Rebec, 1995]. These findings led to the hypothesis that, by exerting a slight inhibitory action on basal activity, DA sets the stage for a relative amplification of the glutamate signal [Kiyatkin and Rebec, 1996], a concept that we will return to later in this review.

Additional insights into DA's actions have been gained from intracellular studies in vivo. Stimulation of inputs from the substantia nigra, presumably releasing DA, induce monosynaptic or polysynaptic excitatory postsynaptic potentials [Hull et al., 1970; Kitai et al., 1975]. Furthermore, iontophoretic application of DA depolarized NS neurons [Kitai et al., 1976]. These studies reinforced the idea that some of the actions of DA are excitatory. In order to explain the differences in findings between extracellular and intracellular studies, the suggestion was made that the inhibition observed primarily in the extracellular recordings was due to excitation of inhibitory neurons. In later studies, however, iontophoretic application of DA inhibited spontaneous or glutamate-induced cell firing but depolarized NS neuronal membranes concomitantly [Bernardi et al., 1978; Herrling and Hull, 1980]. The fact that DA was able to depolarize the membrane but inhibit action potentials provided some clues into the complex nature of its actions. Based on intracellular in vivo recording studies, if frequency of firing is viewed as the sole indicator of DA actions, then DA could be considered mainly inhibitory. However, if membrane depolarization is assumed to reflect increased excitability, then DA actions would be excitatory. A methodological variable appeared to be involved, at least partly, in some of these effects. This variable concerned the proximity of the iontophoretic pipette to different parts of the cell. Iontophoretic applications of DA distant from the soma consistently induced membrane depolarizations, whereas closer applications produced an initial hyperpolarization followed by depolarization in some neurons [Herrling and Hull, 1980]. Since these intracellular recording studies used in vivo preparations, it was difficult to analyze further the mechanisms of the complex actions of DA.

In vitro preparations provide the main avenue for mechanistic analyses. Early studies using in vitro preparations showed that most actions of DA were inhibitory [Calabresi et al., 1987a]. To explain the decrease in cell firing, DA was proposed to inhibit action potentials by reducing a tetrodotoxin-sensitive inward rectification. However, this mechanism alone could not account for the observation that high concentrations of DA produce membrane depolarizations (in at least 50% of the cells tested at these concentrations). Another study showed that DA could induce bidirectional effects depending on its concentration [Akaike et al., 1987], reinforcing hypotheses generated by extracellular recording experiments [Norcross and Spehlmann, 1978; Chiodo and Berger, 1986]. Low concentrations of DA in the bath produced depolarization and increased spontaneous firing. Higher concentrations inhibited firing without changing the membrane potential. These effects were explained by suggesting that excitatory actions were mediated by activation of D2 receptors, whereas inhibitory effects were mediated by activation of D1 receptors. Another study provided additional evidence for dual actions of ionto-

phoretically applied DA in slices [Rutherford et al., 1988]. DA reduced the number of action potentials evoked by short depolarizing pulses and inhibited the afterhyperpolarization that followed trains of action potentials, resulting in an increased number of spikes per pulse. By this dual action, DA could exert both a facilitatory and an inhibitory role on cell firing. These findings were used to explain how amphetamine and DA produce an increase in activity of NS neurons in vitro [Trulson and Atasteh, 1986]. Interestingly, the effect of DA on the afterhyperpolarization may be mediated by D1 receptors [Rutherford et al., 1988]. Compelling evidence for bidirectional actions of DA came recently with the demonstration that D1 receptor agonists inhibit NS cells at hyperpolarized membrane potentials (–80 mV), but at depolarized potentials (around –55 mV), they enhance evoked activity [Hernández-Lopez et al., 1997]. Taken together, the findings emphasizing dual actions begin to reconcile the multiple effects of DA observed in in vitro and in vivo studies.

Whether studies are carried out using in vivo or in vitro preparations has affected interpretations of DA actions. In general, experiments using freely moving animals indicate that DA has excitatory actions [Pierce and Rebec, 1995]. In contrast, in vitro studies demonstrate mainly inhibitory effects [Calabresi et al., 1987a]. Membrane depolarizations are observed after iontophoretic application in vivo [Bernardi et al., 1978; Herrling and Hull, 1980]; however, these effects are rather exceptional in vitro [Cepeda et al., 1993], implying that intact circuitry may be necessary to observe the depolarization. Alternatively, this difference could be explained by the fact that in vivo NS neurons are more depolarized than in vitro [Wilson, 1990]. In vivo, the more depolarized membrane potentials could lead to DA-induced activation of specific Ca^{2+} conductances [Cepeda et al., 1998; Hernández-Lopez et al., 1997] which would increase membrane depolarization. We will return to this point later. NS plasticity induced by tetanic stimulation can also differ depending on the experimental conditions. In vitro stimulation usually induces long-term depression (LTD) [Calabresi et al., 1992; Lovinger et al., 1993; Walsh, 1993]. However, in vivo stimulation can cause long-term potentiation (LTP) [Charpier and Deniau, 1997].

Some of the inconsistencies with regard to the effects of DA can be attributed also to methodological differences in the mode of application. Conclusions based on the utilization of only one mode of application should be viewed with caution. Bath application of drugs is the easiest and most widely used approach in in vitro studies. However, this technique is not without drawbacks. Since usually several minutes are required to observe drug effects, receptor desensitization may occur. Furthermore, the effects of bath application are diffuse, potentially altering many types of cells throughout the slice. A clearer picture of the actions of DA will be obtained only after careful examination of the results obtained using different techniques. Results obtained from several approaches should not be considered mutually exclusive, but complementary.

The effect of mode of application in producing conflicting outcomes is exemplified in recent publications concerning the actions of DA in altering corticostriatal synaptic plasticity [Calabresi et al., 1996; Wickens et al., 1996]. Under normal conditions, activation of both non-NMDA and DA receptors appears to be required to produce LTD. This outcome is derived from evidence obtained by bath application of DA receptor agonists and from inferences on the role of endogenous DA based on depletions induced by substantia nigra lesions [Calabresi et al., 1996]. In contrast, DA applied in a pulsatile manner reverses the depression of synaptic activity that follows tetanic stimulation and produces potentiation [Wickens et al., 1996]. One possible explanation of these divergent results is the difference in the method of DA application. Pulsatile application was intended to replicate the transient increases in DA concentration which occur naturally and have been associated with rewarding stimulation [Mirenowicz and Schultz, 1994]. Functional differences between tonic and phasic release of DA have been emphasized previously as well [Grace, 1991; Grace and Bunney, 1984]. There are two important points to be gleaned from these studies. First, they demonstrate the importance of the mode of DA application (pulsatile and localized versus tonic and diffuse). Second, under special circumstances (which appear to replicate a more physiological situation), DA is capable of potentiating corticostriatal synaptic transmission.

There is further support for the importance of mode of application in determining the effects of DA [Gonon, 1997; Gonon and Sundstrom, 1996]. In anesthetized rats, electrical stimulation of the medial forebrain bundle mimicking the spontaneous activity of DA neurons results in DA overflow and a delayed increase in discharge activity that appears mediated by activation of D1 receptors in a subpopulation of NS neurons [Gonon, 1997]. This effect was interpreted as DA facilitating the activity of NS neurons receiving other excitatory inputs. Interestingly, microinjections of NMDA in the ventral tegmentum also facilitate discharge activity of most target neurons in the nucleus accumbens [Gonon and Sundstrom,

1996]. The importance of these findings, as we will see later, is that potential enhancing effects for DA can be demonstrated and these enhancements appear to involve an interaction of NMDA and D1 receptors.

At this point it is clear that attempts to force the effects of DA into the classic neurotransmitter mold have failed to provide a viable framework within which to understand its actions. The effects of DA are very heterogeneous and there are multiple variables that contribute to its actions. A more viable and productive approach would be to fit the actions of DA into a neuromodulatory role in which it acts to alter the effects of classic neurotransmitters like the excitatory and inhibitory amino acids. The definition of a neuromodulator is a substance that, per se, is neither inhibitory nor excitatory, so that when applied alone it has little effect, but when applied in conjunction with other substances it has the ability to alter their actions. In fact, in many of the early studies examining the actions of DA on NS cells using extracellular recording, DA was applied to alter glutamate-, GABA- or acetylcholine-induced responses. DA had little or no effect when applied alone. Unfortunately, its actions were interpreted as those of a classic neurotransmitter. When DA is viewed as a neuromodulator, its effects become more explicable and frameworks can be derived within which to generate theories of its functions [Cepeda et al., 1993; Chiodo and Berger, 1986; Reader et al., 1979]. Not surprisingly, the localization of DA receptors conforms to this type of view. DA synapses are localized most frequently to the necks of spines and shafts of dendrites of NS spiny neurons postsynaptically [Freund et al., 1984], a position from which they would be capable of altering responses induced by activation of the glutamate-containing synapses localized on spine heads. Similarly, DA may have a modulatory role presynaptically since there is evidence that DA is capable of altering glutamate release, probably via D2 receptors [Kornhuber and Kornhuber, 1986; Mitchell and Doggett, 1980; Rowlands and Roberts, 1980; Yamamoto and Davy, 1992].

If DA is considered a neuromodulator, it becomes possible to understand and predict more accurately its actions. One prediction would be that DA should alter the excitatory postsynaptic potentials induced by corticostriatal stimulation. In vivo [Herrling and Hull, 1980; Mercuri et al., 1985] and in vitro experiments [Calabresi et al., 1987a] indicate that DA consistently reduces responses evoked by corticostriatal stimulation. This action of DA has withstood the test of time, but unfortunately there remains debate regarding the specific role of D1 and D2 receptors in mediating the attenuation of the cortical response. Calabresi et al. [1987a] suggested attenuation is mediated postsynaptically by activation of D1 receptors. D2 receptor-mediated effects did not occur under normal physiological conditions, but could be uncovered only after D2 receptors were rendered hypersensitive [Calabresi et al., 1988]. However, other studies demonstrate potential D2-mediated attenuation of cortically evoked responses under normal conditions [Brown and Arbuthnott, 1983; Cepeda et al., 1994; Flores-Hernández et al., 1997; Garcia-Muñoz et al., 1991; Hsu et al., 1995; Jiang and North, 1991; Levine et al., 1996b]. As we will discuss later, this inhibitory action of DA is highly dependent on which receptor subtypes are activated.

Although modulatory actions of DA leading to attenuation of excitatory responses of NS neurons cannot be disputed, there is an impressive body of behavioral, pharmacological and early-gene induction studies, indicating that DA receptor activation has potentiating effects as well [Cameron and Williams, 1993; Girault et al., 1986; Konradi et al., 1996; Starr, 1995]. At the electrophysiological level, there is now significant evidence that under specific conditions, activation of D1 DA receptors potentiates excitatory responses [Cepeda et al., 1993; Galarraga et al., 1997; Harvey and Lacey, 1997; Hernández-Lopez et al., 1997; Levine et al., 1996b].

DA-Glutamate Interactions: Importance of Receptor Subtype

The complex modulatory actions of DA can be better understood if a scheme or framework is devised within which to structure the modulation. Over the past several years we have begun to develop such a scheme, based on receptor subtype. While it does not explain all of the modulatory actions of DA, it provides a reasonable approach from which hypotheses can be derived and tested.

There is considerable evidence that the different pharmacologically defined glutamate receptor subtypes, NMDA, AMPA and KA are colocalized on the great majority of medium-sized neurons [Albin et al., 1992; Ariano et al., 1997; Tallaksen-Greene et al., 1992; Standaert et al., 1994]. There has been, however, considerable controversy regarding colocalization of DA receptors to specific subtypes of medium-sized spiny cells [Gerfen et al., 1990; Le Moine and Bloch, 1995; Lester et al., 1993; Surmeier et al., 1993]. For example, one view is that D_{1A} receptors are localized primarily to medium-sized spiny cells that project to the substantia nigra, while D_2 receptors are localized to cells projecting to the globus pallidus

[Gerfen et al., 1990]. An opposing view is that there are varying degrees of colocalization of D_{1A} and D_2 receptors in the two output pathways [Ariano et al., 1992; Surmeier et al., 1992, 1993]. Based on colocalization with peptides, this latter view has been altered to indicate that D_{1A} and D_3 receptors and D_2 and D_{1B} receptors are more segregated to striatonigral and striatopallidal pathways, respectively [Surmeier et al., 1996]. More recent work has demonstrated that NMDA and AMPA receptor subunits are coexpressed to a high degree with D_{1A} and D_2 receptor subtypes in a majority of medium-sized neurons, providing a very broad framework for functional interactions to occur [Ariano et al., 1997]. In contrast to these studies, there seems to be good agreement that electrophysiologically, most NS cells respond to activation of D1 and D2 families, probably because specific pharmacological agonists and antagonists for the D1 and D2 families cannot easily differentiate effects mediated by D_{1A} versus D_{1B} or among D_2, D_3 and D_4 subtypes. Thus, from a functional perspective there appears to be strong evidence that medium-sized spiny cells have the potential of colocalizing all ionotropic glutamate receptors as well as subtypes of both D1 and D2 families. This would imply that this cell type has the potential of responding to activation of all combinations of glutamate and DA receptors, but perhaps with different types of responses depending upon the degree of activation of each receptor subtype.

NS neurons in vitro are typically hyperpolarized [Calabresi et al., 1987b], although this may partially depend on extracellular K^+ concentration [Bargas et al., 1988]. This implies that NMDA receptor activation is unlikely in this preparation, due to Mg^{2+} blockade [Mayer et al., 1984; Nowak et al., 1984]. However, in vivo NS neurons display spontaneous membrane depolarizations [Cepeda et al., 1989; Calabresi et al., 1990; Cowan and Wilson, 1994; Wilson and Kawaguchi, 1996], allowing partial relief of Mg^{2+} blockade [Kita, 1996] indicating that components of responses mediated by NMDA receptors may occur. For example, although it is generally believed that corticostriatal excitatory synaptic transmission is mediated by non-NMDA receptors [Herrling, 1985], an NMDA receptor-mediated component can be disclosed when the cell membrane is depolarized [Cherubini et al., 1988]. NMDA receptor activation can also be produced at resting membrane potentials by iontophoretic application of selective agonists. The responses induced by iontophoretic application of excitatory amino acid (EAA) receptor agonists in the NS are heterogeneous [Herrling et al., 1983]. Glutamate, AMPA and quisqualate generally induce a rapidly occurring depolarization and repetitive single action potentials [Cepeda et al., 1993]. In contrast, NMDA receptor agonists induce slow membrane depolarizations and bursts of action potentials [Cepeda et al., 1993]. In about one third of rat NS neurons [Cepeda et al., 1993], two-thirds of cat caudate nucleus neurons [Herrling et al., 1983], and almost all human caudate nucleus neurons [Cepeda et al., 1991], NMDA induces complex rhythmic oscillations consisting of a burst of fast action potentials followed by a plateau depolarization and small, putative Ca^{2+} spikes. This depolarization is ended abruptly by an afterhyperpolarization, probably mediated by a Ca^{2+}-activated K^+ conductance.

When we studied the effects of DA on glutamate-evoked excitation in slices, we also demonstrated that DA inhibits action potentials induced by iontophoretic application of glutamate and reduces the amplitude of the evoked depolarization [Cepeda et al., 1992, 1993]. However, when we investigated the effects of DA on excitation induced by selective activation of NMDA receptors, we found instead that DA enhanced these excitations. Since at resting membrane potentials in the slice glutamate activates almost exclusively the non-NMDA receptor subtypes, we hypothesized that DA produces a differential modulation of glutamate-evoked responses depending on which EAA receptor subtype it activates. Confirming this assumption, we found that DA reduces non-NMDA-induced excitations. DA, of course, activates both D1 and D2 receptor families. To examine which receptor subtype mediated each effect we used specific agonists and antagonists and showed that the enhancement of NMDA responses is mediated by activation of D1 receptors and blocked by D1 antagonists. In contrast, activation of D2 receptors decreased or did not affect responses to NMDA [Cepeda et al., 1993]. Activation of D2 receptors almost always attenuated responses mediated by activation of non-NMDA receptors.

Three additional pieces of evidence confirmed our initial observations. First, we used pharmacological tools to dissect the electrically evoked excitatory postsynaptic potential into non-NMDA and NMDA components. When these components were examined in isolation we found that the NMDA component was enhanced by DA and D1 receptor agonists. In contrast, the non-NMDA receptor-mediated component was reduced by DA and D2 receptor agonists [Levine et al., 1996b]. Second, mutant mice that lack the D_{1A} receptor subtype display reduced enhancements of NMDA-mediated responses [Levine et al., 1996a]. Third, we recently investigated the DA-NMDA receptor interactions in visually identified medium-sized neurons using infrared videomicroscopy and whole-cell

patch clamp techniques in NS slices of young rats (12–18 days old). We showed that DA applied iontophoretically or in the bath enhances NMDA currents. Activation of D1 receptors by bath application of agonists (SKF 38393 or A 77636) consistently enhanced NMDA currents. Quinpirole, a D2 receptor agonist, produced inconsistent effects [Cepeda et al., 1998].

These results clearly demonstrate that the receptor subtype activated can determine the direction of the modulatory effects of DA. If the subtype of receptor activated can be controlled, under two conditions it is possible with considerable accuracy to predict the direction of DA modulation. When NMDA and D1 receptors are activated, the modulatory effect is potentiation while when non-NMDA and D2 receptors are activated, the modulatory effect is attenuation. Prediction of the direction of modulation is not as clear when NMDA and D2 receptors are activated or when non-NMDA and D1 receptors are activated. With these latter combinations, both attenuation and potentiation can occur.

DA-EAA Receptor Interactions: Potential Mechanisms

We will devote the remainder of this review to a discussion of the potential mechanisms underlying DA modulation of responses induced by activation of EAA receptors and their functional implications. It is not clear why specific combinations of receptor subtype interactions lead to very predictable outcomes but others do not. Possibilities may be that there are either spatial or mechanistic couplings of specific receptor subtypes. For example, EAA and DA receptor subtypes may be located in close proximity on the same spine, dendrite or cell [Yung et al., 1995]. Unfortunately, there are few data on precise ultrastructural colocalization of EAA receptor subunits and DA receptor subtypes. Another possibility is that specific subtypes of DA receptors tap into the same transduction systems as specific subtypes of EAA receptors. It is well known that D1 DA receptor activation also produces increases in cAMP [Stoof and Kebabian, 1981]. As we will point out, activation of the cAMP-PKA transduction system also can enhance NMDA-induced responses. There are considerable data on the ionic bases of DA modulation, the relationship of EAA receptors to transduction systems and more recently on how alterations in transduction systems contribute to DA-EAA receptor interactions. We will examine these issues in more detail in the following sections.

There are multiple routes by which DA can modulate responses of NS cells. DA can modulate excitability of NS cells by altering voltage-dependent conductances, and/or modulate responses by directly changing excitability of ligand-gated channels, probably through transduction systems or changes in intracellular ion concentrations. These actions are not mutually exclusive and are probably not the only routes by which DA can achieve its effects. However, they serve as reasonable starting points to assess mechanisms underlying the modulatory role of DA.

DA and Modulation of Excitability

In voltage-clamp experiments, the effects of DA and its receptor agonists on specific voltage-gated conductances have been teased apart pharmacologically and experimentally. DA reduces most of the voltage-activated inward and outward currents in NS neurons either in dissociated cell preparations or slices [Cepeda et al., 1995a; Schiffmann et al., 1995; Surmeier and Kitai, 1993] and these reductions will have complex effects on cell excitability. For example, D1 receptor agonists reduce the amplitude of evoked Na^+ currents in the vast majority of cells. D2 agonists reduce these currents in more than half the cells, but in about 20% they increase their amplitude [Surmeier and Kitai, 1993]. D1 agonists also reduce a slowly-inactivating K^+ current (favoring the transition to a depolarized membrane potential), whereas D2 agonists enhance this current. D2 agonists induce K^+ channel openings as well [Freedman and Weight, 1988; Greif et al., 1995]. Most medium-sized NS neurons express high-voltage activated (HVA) Ca^{2+} currents almost exclusively [Bargas et al., 1994], although low-voltage activated (LVA) currents have also been reported [Hoehn et al., 1993]. D1 receptor activation can produce differential effects on HVA currents depending on the specific type of current activated. D1 agonists reversibly reduce N- and P-type HVA currents, probably via the cAMP-PKA transduction cascade. However in a subset of neurons, D1 receptor-mediated activation enhances L-type HVA current [Surmeier et al., 1995]. This work confirmed current clamp studies indicating that D1 receptor activation consistently increased the plateau potentials induced in tetraethylammonium, a K^+ channel blocker [Hernández-Lopez et al., 1997; Surmeier et al., 1995]. These potentials were assumed to be mediated by L-type Ca^{2+} channels because they are facilitated by Bay K 8644 (an L-type channel agonist) [Cherubini and Lanfumey, 1987a].

This wide range of actions of DA and its receptor subtypes on voltage-dependent currents can provide the ionic framework to explain the variety of actions produced by

DA at the macroscopic level. For example, DA-induced reduction of postsynaptic responses evoked by cortical stimulation could depend on the decrement of HVA N- and P-type Ca^{2+} conductances [Surmeier et al., 1995]. In addition, our studies support the view that DA could attenuate postsynaptic potentials by decreasing a persistent Na^+ conductance [Cepeda et al., 1995a]. Alternatively, the presence of D2 receptors on presynaptic terminals provides a basis for DA modulation of Ca^{2+} conductances. For example, N-type Ca^{2+} channels play a crucial role at corticostriatal synapses [Lovinger et al., 1994]. By the same token, studies describing the potentiating actions of DA could be explained by facilitation of Ca^{2+} conductances [Bergmann-Erb et al., 1988], specifically L-type conductances [Cepeda et al., 1998; Galarraga et al., 1997; Hernández-Lopez et al., 1997].

In a series of experiments aimed at elucidating the possible ionic mechanisms involved in the enhancement of NMDA currents by DA, we examined the role of different voltage-gated conductances [Cepeda et al., 1998]. Specific Na^+ and K^+ conductances did not appear to play a major role in this aspect of DA modulation [see also Altemus and Levine, 1996]. Since it had been shown that the L-type Ca^{2+} conductance was enhanced by DA receptor activation [Surmeier et al., 1995], we blocked this conductance and demonstrated that the enhancement of NMDA currents by DA was greatly reduced, but not eliminated. Furthermore, the L-type Ca^{2+} channel agonist Bay K 8644 increased NMDA currents. These findings imply that enhancement of L-type Ca^{2+} current has an important role in DA enhancement of NMDA currents.

One possible mechanism by which DA receptor activation alters voltage- and ligand-gated conductances to enhance NMDA currents may involve unclamped voltages on dendrites. Accurate voltage control in cells with extended processes is precluded as a result of space clamp limitations [Armstrong and Gilly, 1992]. Thus, it is very likely that unclamped voltages, due to activation of voltage-dependent, intrinsic Ca^{2+} conductances on dendrites, contributed to DA potentiation of NMDA currents. This fact may be thought of as a drawback of voltage-clamp technique applied in the slice preparation. Of more importance, it underscores the active role of the voltage-dependent conductances in dendrites in the integration of synaptic signals [Eilers and Konnerth, 1997].

Additional possibilities exist to account for the contribution of L-type Ca^{2+} conductances. Specific Ca^{2+} conductances can be activated at membrane potentials more negative than those normally required to activate HVA currents. For example, there is evidence that a population of dihydropyridine-sensitive channels are active at resting membrane potentials. These channels appear to be present throughout the neuron and are concentrated in the proximal dendrites [Magee et al., 1996]. There is also evidence for a novel dihydropyridine-sensitive Ca^{2+} LVA conductance that is active at negative membrane potentials [Ferroni et al., 1996].

The increase in NMDA responses may not be accounted for solely by unclamped voltages in distal processes since blockade of L-type Ca^{2+} channels decreased but did not totally eliminate DA potentiation of NMDA currents. Accordingly, we think that the enhancement of NMDA currents by DA may involve at least two mechanisms. First, DA may enhance NMDA currents by facilitating a voltage-dependent Ca^{2+} current (probably an L-type current) either directly or through phosphorylation and up-regulation of Ca^{2+} channels. Second, DA can enhance NMDA currents by phosphorylation of NMDA receptors. These two mechanisms are not mutually exclusive and both may contribute to the enhancement of NMDA currents.

DA and Ca^{2+} Conductances

Using different preparations, there is an impressive literature concerning the effects of DA and its receptor agonists on Ca^{2+} conductances. The picture that emerges from these studies is that differential effects largely depend on the DA receptor subtype activated as well as the specific Ca^{2+} conductance examined [Brown and Seabrook, 1995; Lukyanetz and Kostyuk, 1996; Williams et al., 1990]. For example, DA via activation of D1 receptors and cAMP-dependent protein kinase produces a differential modulation of T- and L-type Ca^{2+} currents, decreasing the transient current while increasing the sustained current [Pfeiffer-Linn and Lasater, 1993]. In addition, D1 receptor activation recruits dihydropyridine-sensitive Ca^{2+} channels that are normally quiescent but can be activated by repetitive depolarizations, depolarizing prepulses, or by agents that raise cAMP [Artalejo et al., 1990]. There is considerable overlap between facilitation of Ca^{2+} currents by membrane depolarization and cAMP-dependent phosphorylation [Dolphin, 1996]. This situation is similar to that observed in the NS in which Ca^{2+} conductances are modulated differentially by D1 receptor activation. D1 agonists via the cAMP-PKA cascade reversibly reduce N- and P-type but enhance L-type currents [Surmeier et al., 1995]. Interestingly, L-type channels also display voltage-dependent facilitation in NS neurons [Song and Surmeier, 1996].

Other potential mechanisms involving Ca^{2+} can be envisaged. DA, as well as D1 receptor agonists (but not

D2 agonists), induce inward currents in *Xenopus* oocytes injected with mRNA from rat NS. These currents are consistent with activation of Ca^{2+}-dependent Cl^- channels. DA also stimulates inositol phosphate production and release of Ca^{2+} from intracellular stores [Mahan et al., 1990].

DA and EAA-Gated Conductances

Direct or indirect (via Ca^{2+} conductances) effects of DA and the cAMP dependent protein kinase cascade on EAA ligand-gated currents have also been demonstrated. In teleost retinal horizontal cells, exposure to DA augments the responsiveness to glutamate or KA. DA appears to modulate the kinetics of ion channels gated by EAAs. Although DA does not alter the number of glutamate-gated channels or their unitary conductance, it increases the frequency of channel openings and to a lesser extent the open time [Knapp et al., 1990]. In hippocampal neurons, a cAMP-dependent PKA cascade enhances glutamate and KA responses [Greengard et al., 1991]. Calcimycin (a Ca^{2+} ionophore) potentiates responses to NMDA but not to quisqualate in rat hippocampal slices [Markram and Segal, 1991]. In cultured NS and cortical neurons, DA via D1 receptor activation enhances NMDA-induced currents [Fraser and MacVicar, 1994]. Preliminary data in dissociated hippocampal and NS neurons indicate that DA produces differential effects, enhancing NMDA while decreasing AMPA currents [K. Hsu, pers. commun.; Hsu, 1996]. In nucleus accumbens slices D1 receptor activation potentiates NMDA currents [Harvey and Lacey, 1997]. In conclusion, there is strong evidence that DA or D1 receptor agonists can modulate EAA-gated currents. A component of this modulation might involve direct or indirect contributions of voltage-gated Ca^{2+} currents.

In contrast to a growing body of evidence that DA can modulate EAA-induced responses, Calabresi et al. [1995a] did not observe DA modulation of AMPA or NMDA-evoked responses in current or voltage clamp conditions. This is somewhat puzzling since the same authors showed that DA modulates the AMPA-mediated component of the synaptic response in current clamp conditions and suggested a postsynaptic site of action [Calabresi et al., 1987a]. Several factors may account for this discrepancy. The mode of DA application and its local concentration play important roles. Of possibly more relevance, the same authors showed that DA does not affect the excitatory postsynaptic potential at very hyperpolarized membrane levels (about −85 to −90 mV). At these potentials, voltage-dependent conductances may not be available for modulation [Hernández-Lopez et al., 1997; Cepeda et al., 1998].

DA and Phosphorylation of EAA Receptors

There is also emerging evidence for direct regulation of excitatory and inhibitory ligand-gated channels by protein phosphorylation. Protein kinases and phosphatases can be activated by multiple receptors, particularly those belonging to the G-protein family, allowing 'receptor crosstalk' [Smart, 1997]. Although it was believed that NMDA receptors were only regulated by PKC, more recent studies indicate that the cAMP-PKA cascade is also involved [Leonard and Hell, 1997]. In agreement, using current clamp recordings we have shown that activation of the cAMP-PKA cascade is capable of potentiating NMDA responses in NS neurons [Colwell and Levine, 1995]. In nucleus accumbens slices, forskolin, DA, or D1 receptor agonists (but not D2 agonists) increase phosphorylation of the NMDA-R1 subunit. DA-induced phosphorylation of NMDA-R1 was blocked by an inhibitor of PKA. Moreover, the ability of DA to phosphorylate NMDA-R1 was attenuated in mice lacking the gene for DARPP-32 [Snyder et al., 1996]. The role of protein phosphorylation in modulating NMDA channels was explored in *Xenopus* oocytes injected with mRNA from rat NS and hippocampus [Blank et al., 1996]. Both PKA and PKC activation potentiated NMDA-mediated responses in the NS, but only PKC in the hippocampus. A cAMP analog also enhanced NMDA responses. PKA-mediated enhancement of NMDA responses in NS was prevented by an inhibitor of protein phosphatases. Furthermore, an important role for the phosphoprotein DARPP-32 was suggested. Phosphorylation of this protein by PKA may inhibit dephosphorylation of NMDA receptors via inhibition of endogenous protein phosphatases, thus enhancing NMDA responses [Blank et al., 1997]. Interestingly, it has been shown recently that DA exerts a bidirectional control on the state of phosphorylation of DARPP-32. D1-like receptor agonists increase, whereas D2-like agonists decrease protein phosphorylation [Nishi et al., 1997].

DA and Ionic Pumps

Although it appears that Ca^{2+} conductances and phosphorylation of NMDA receptors are likely involved in the enhancement of NMDA responses, other potential mechanisms have to be considered. The presence of a ouabain-sensitive hyperpolarization has been described in rat NS neurons [Cherubini and Lanfumey, 1987a]. In the presence of K^+ channel blockers, long-lasting plateau potentials were followed by a voltage-independent hyperpolari-

zation. This hyperpolarization was irreversibly blocked by ouabain, indicating that it may result from the activation of an Na^+/K^+ ATPase electrogenic pump. An ATP-sensitive K^+ channel also has been identified in medium-sized spiny neurons [Schwanstecher and Panten, 1994]. It is important to indicate that one of the known effects of DA is inhibition of Na^+/K^+ ATPase activity in isolated NS neurons [Bertorello et al., 1990]. This inhibitory effect of DA is mediated by activation of the PKA pathway and DARPP-32 also plays an essential role in the regulation of Na^+/K^+ ATPase activity [Nishi et al., 1996]. Drugs that interfere with this ionic pump enhance the membrane depolarizations and inward currents induced by subcritical concentrations of EAAs [Calabresi et al., 1995a]. Thus, some of the effects of DA receptor activation may be due to alterations in ionic pumps.

Functional Implications

DA, via activation of D1 receptors and the cAMP-PKA cascade, can increase the excitability of NS neurons. In particular, DA can enhance L-type Ca^{2+} conductances, induce membrane depolarizations (at least in vivo), and potentiate NMDA-receptor mediated responses. The mechanisms underlying these effects are not fully understood, but a complex interaction between modulation of voltage- and ligand-gated channels, receptor phosphorylation and, to a lesser extent, modulation of ionic pumps, may be involved. What are the functional implications of these effects of DA? We will emphasize several areas in which these interactions can have marked functional consequences.

Setting Membrane Potentials

DA modulation of Ca^{2+} conductances can have marked effects on biasing membrane potentials. For example, in chromaffin cells, DA facilitation of Ca^{2+} channels may form the basis of a positive feedback loop for catecholamine secretion [Artalejo et al., 1990]. Such rapid secretion may have physiological importance in response to danger or stress. DA-induced enhancement of L-type current in the retina would increase the amount of Ca^{2+} that enters the cell and play a role in maintaining the membrane potential of horizontal cells at depolarized membrane levels in the dark [Pfeiffer-Linn and Lasater, 1993]. Such membrane potential shifts are essential for maintaining a long depolarized plateau in response to a brief exogenous glutamate pulse [Lasater and Dowling, 1982] or to an injected current pulse [Shingai and Christensen, 1986; Sullivan and Lasater, 1990]. DA by increasing the intracellular Ca^{2+} level in the cell maintains depolarization and reduces the amount of neurotransmitter required to maintain the dark resting potential. Increases in intracellular Ca^{2+} also can activate enzyme systems that control protein phosphorylation, resulting in ion channel regulation [Ewald and Levitan, 1987], and cell plasticity [Nicoll, 1988].

Hull et al. [1970] were the first to report long-lasting depolarizations in NS neurons after high-frequency stimulation (>30 Hz) of the substantia nigra. They hypothesized that these poststimulus depolarizations could function to 'set' the membrane level close to firing threshold for fairly long periods of time so that excitatory inputs ordinarily ineffective in firing a cell might more easily do so. Similarly, iontophoretic application of DA in vivo inhibits Na^+ action potentials but depolarizes the cell membrane concomitantly [Bernardi et al., 1978; Herrling and Hull, 1980]. Although the ionic mechanism of this membrane depolarization is not known, it is possible that, in vivo, activation of L-type channels is more likely to occur, particularly when membrane oscillations evoked by activation of ligand-gated channels bring the membrane to a more depolarized state. Enhancement of Ca^{2+} influx by D1 receptor activation would depolarize the membrane further which, in turn, would recruit more Ca^{2+} channels. This would form the basis for a positive feedback mechanism. By analogy with the retina, it is tempting to speculate that one function of DA in the NS is to maintain the cell at depolarized membrane potentials for long time periods.

DA, Signal-to-Noise Ratio and Synaptic Plasticity

One consequence of DA-induced membrane depolarization is the removal of Mg^{2+} blockade of NMDA receptors. By enhancing NMDA and reducing non-NMDA-receptor-mediated responses, DA could select NS inputs. This mechanism by which relevant (or salient) information is integrated, while less relevant inputs are screened out, could then be considered a filtering device that effectively increases the signal-to-noise ratio [Cepeda et al., 1992, 1993]. The elegant work by Mirenowicz and Schultz [1996] and Schultz et al. [1997] has amply demonstrated that the DA system is extremely important for extracting inputs with high adaptive value.

Sustained membrane depolarizations induced by DA may act as a signal amplifier. Action potential generation back-propagates to the dendrites and regulates Ca^{2+} signaling [Stuart and Sakmann, 1994, 1995; Jaffe et al., 1992]. Such a mechanism is used to amplify excitatory inputs arriving coincidentally at the cell membrane and

may be involved in Hebbian learning [Koch, 1997; Zador et al., 1990]. In hippocampal neurons, pairing subthreshold excitatory postsynaptic potentials with back-propagating action potentials results in amplification of dendritic action potentials and evokes Ca^{2+} influx near the site of synaptic input, causing robust LTP [Magee and Johnston, 1997]. Since one effect of DA in NS is inhibition of Na^{+} action potentials, this mechanism of amplification and coincidence detection would be obliterated. Considering that most of the excitatory input to NS neurons occurs at dendritic spines and shafts, loci at which D1 receptors are concentrated [Bergson et al., 1995; Hersch et al., 1995], it is possible that DA-induced membrane depolarization, and the consequent increase in Ca^{2+} influx through L-type channels, would provide a compensatory device for signal amplification.

DA effects leading to or enhancing excitation in NS neurons may have important implications for normal and abnormal NS function. One of these involves short- and long-term plasticity in corticostriatal synaptic transmission. For example, endogenous DA and coactivation of D1 and D2 receptors are required to induce LTD at corticostriatal synapses [Calabresi et al., 1992]. LTD induction also requires membrane depolarization and Ca^{2+} influx through L-type channels [Calabresi et al., 1994; Choi and Lovinger, 1997]. However, it is uncertain how this sustained depolarization is brought about, particularly under physiological conditions. According to Lovinger and Tyler [1996], it is still unclear whether activation of AMPA/KA receptors is involved. Certainly, high-frequency stimulation of corticostriatal terminals will activate these receptors. However, a concomitant increase in DA release [see Cheramy et al., 1986; Calabresi et al., 1995b] should attenuate responses due to activation of non-NMDA receptors. Another likely possibility is that release of DA and activation of D1 receptors induces membrane depolarization and activation of L-type Ca^{2+} channels [Choi and Lovinger, 1997]. This may explain why D1 receptor activation is also necessary for LTD induction [Calabresi et al. 1992; however see Altemus et al., 1997].

One prediction from our studies is that synaptic plasticity will vary depending on which EAA and DA receptor subtypes are preferentially activated. Similar stimulation paradigms used to elicit LTD produce short-term potentiation or LTP if NMDA receptors are unmasked by removal of Mg^{2+} [Calabresi et al., 1992; Walsh, 1991; Walsh and Dunia, 1993]. The mechanisms underlying LTP induction in NS have not been extensively studied. Presumably, DA released by high-frequency stimulation is an important variable for LTP induction, although there is at present little direct evidence for its involvement. Wickens et al. [1996] demonstrated in vitro that pulsatile application of DA at the time of the tetanizing cortical stimulation produces LTP. It is probable that DA, released by tetanic stimulation, will depolarize the membrane, increase Ca^{2+} influx, and unmask NMDA receptors. It is somewhat surprising why LTP is not seen more frequently in vitro. Differences in the mode of DA application [Wickens et al., 1996; Arbuthnott and Wickens, 1996] or use of different tetanic stimulation protocols may account for this. Furthermore, there may be a regional gradient of synaptic plasticity in the NS. Medial corticostriatal synapses tend to exhibit LTP after high-frequency stimulation, whereas lateral synapses tend to exhibit LTD [Musleh et al., 1997]. Interestingly, there is a differential distribution of D2 receptors in the NS. Fewer positively labeled cells are seen in the medial compared to the lateral regions [Joyce et al., 1985; Szele et al., 1991].

Differences between in vitro and in vivo conditions in the elicitation of synaptic changes have been reported in hippocampus and, more recently, also in the NS. Charpier and Deniau [1997] described LTP after tetanic stimulation of the corticostriatal pathway in vivo. Furthermore, LTP was dependent on membrane depolarization and Ca^{2+} influx. Very recent preliminary experiments also show that tetanic stimulation of the substantia nigra can induce LTP [Wickens et al., 1997].

The expression of one or the other form of synaptic plasticity may depend also on the relative distribution, presence or absence, of different DA receptor subtypes. It has been shown that mice lacking D_2 receptors express NMDA-dependent LTP instead of LTD implying that D_2 receptors play a critical role in controlling the direction of NS synaptic plasticity [Calabresi et al., 1997c]. The conclusion that D_2 receptors might exert a negative control on the mechanisms activated by sustained stimulation of NMDA receptors is accounted for within our receptor subtype hypothesis [Cepeda et al., 1993]. Interestingly, studies of synaptic plasticity in the hippocampus have shown that D1 receptor activation produces enhancement of LTP by increasing cAMP [Kusuki et al., 1997; Otmakhova and Lisman, 1996] and perfusion with D1 receptor agonists without tetanic stimulation can induce LTP [Huang and Kandel, 1995]. Besides DA, it is possible that acetylcholine modulates synaptic plasticity in the NS. It has been shown that muscarinic antagonists increase the amplitude of LTD, indicating that an endogenous cholinergic tone exerts a negative control on the expression of LTD in NS [Calabresi et al., 1992]. It will be important to explore the possibility that increasing cholinergic activity

may, in fact, favor the emergence of LTP. Preliminary studies in our laboratory indicate that acetylcholine enhances NMDA-receptor-mediated responses [Buchwald et al., 1997; see also Calabresi et al., 1997a].

In rat visual cortex, it has been shown that the same tetanic stimulation can induce either LTP or LTD depending on the level of depolarization of the postsynaptic neuron. The level required to evoke LTD is lower than the threshold for LTP induction [Artola et al., 1990; Artola and Singer, 1993]. It is likely that NS neurons are able to express both LTD and LTP in physiological conditions and that both are important for NS function. Although it was suggested previously that LTP only occurs in conditions of energy failure [Calabresi et al., 1996], available evidence demonstrates that it can also occur in more physiological conditions [Charpier and Deniau, 1997]. Both processes may be important in motor function. For example, the expression of LTD in the NS may represent a mechanism for extinction of unrewarded behavior, and LTP may be a mechanism for reinforcement of rewarded behavior [Arbuthnott and Wickens, 1996]. Removal of tonic DA inputs, as occurs in Parkinson's disease, would be equivalent to a permanent error signal in the NS which might extinguish movement and could provide a model of akinesia [Arbuthnott and Wickens, 1996].

Other processes in which DA-NMDA receptor interactions may play a significant role are in the presynaptic attenuation of glutamatergic input and in the induction of gene expression. First in nucleus accumbens slices, D1 receptor activation enhances postsynaptic NMDA receptor-mediated currents [Harvey and Lacey, 1997]. Interestingly, this potentiation promotes adenosine release which, in turn, acts as a retrograde messenger that inhibits glutamate release via activation of presynaptic A_1 receptors. It will be important to determine whether this effect also occurs in the dorsal NS since there is evidence that adenosine receptors play a role in the initiation of short-term synaptic depression [Lovinger and Choi, 1995]. Second, induction of gene expression in NS neurons by amphetamine, as well as other pharmacological and electrophysiological manipulations, depends on activation of postsynaptic D1 and NMDA receptors. These two receptor systems interact at the intracellular level, probably through cAMP-PKA-dependent phosphorylation [Das et al., 1997; Konradi et al., 1996; Liste et al., 1995].

DA and Neurotoxicity

D1 receptor activation, L-type Ca^{2+} conductances and NMDA-receptor-mediated responses may be involved in excitotoxic events. It is well known that excess Ca^{2+} is deleterious to cells. If DA, via D1 receptor activation, enhances NMDA-evoked responses and L-type conductances, there is a risk that Ca^{2+} will accumulate inside the cell. To address this question, we studied DA-NMDA receptor interactions using a cell swelling assay [Dodt et al., 1993]. Cell swelling is one early sign of excitotoxicity produced as a consequence of excessive NMDA receptor stimulation. Changes in somatic area can be visualized in NS slices using differential interference contrast and infrared videomicroscopy [Dodt et al., 1993]. D1 receptor activation enhanced NMDA-induced cell swelling [Cepeda et al., 1995b]. In contrast, D2 receptor activation reduced cell swelling. We also have demonstrated, using Ca^{2+} imaging techniques, that application of DA or a D1 agonist increases NMDA-induced intracellular Ca^{2+} in cultured cortical and acutely dissociated NS cells [Levine et al., 1997]. Thus, D1 receptor stimulation may be deleterious for NS neurons. Fortunately, in normal conditions, excessive accumulations of Ca^{2+} do not represent a risk because activation of D1 and D2 receptors reduces Ca^{2+} influx through other types of channels. Furthermore, activation of metabotropic glutamate receptors [Colwell et al., 1996; however see Pisani et al., 1997] or D2 receptors confers protection against NMDA challenge.

In Huntington's disease, it has been hypothesized that because of energy failure, medium-sized NS neurons become more vulnerable to excitotoxic damage resulting from glutamate receptor activation [Beal et al., 1993]. Accordingly, impairment of neuronal energy metabolism results in reduced levels of ATP, and defective repolarization which leads to prolonged activation of Ca^{2+} channels and enhanced Ca^{2+} influx through NMDA channels. DA application reproduces effects reminiscent of conditions of energy failure. DA is also a potent reversible inhibitor of mitochondrial respiration [Ben-Shachar et al., 1995]. DA, via D1 receptors, potentiates the toxicity induced by other mitochondrial inhibitors, such as malonate [McLaughlin et al., 1997]. This implies that DA itself may be implicated in neural damage [Filloux and Wamsley, 1991]. There is evidence that DA-induced neurotoxicity can occur under conditions of increased DA availability and decreased antioxidant capacity [Hastings and Zigmond, 1997; Hoyt et al., 1997] and activation of D1 receptors may induce neuropathological damage in the NS [Kelly et al., 1990]. There is additional evidence that DA modulates neurotoxicity in the NS. For example, lesions of the substantia nigra reduce the damage produced by EAAs [Buisson et al., 1991; Chapman et al., 1989] and protect against neurotoxicity induced by cerebral ischemia [Globus et al., 1987, 1988].

DA and NMDA in Development and Aging

DA modulation of NMDA responses appears to develop during the third postnatal week in the rat. Enhancements of NMDA currents were not observed in rat pups younger than 12–15 days. Two weeks of age in the rat is a period of intense morphological change. Synapse formation increases considerably and dendritic spines develop [Misgeld et al., 1986]. D1 and D2 receptor binding, which is very low at birth, progressively increases and reaches adult levels between days 14 and 21 [Schambra et al., 1994]. Furthermore, the preponderance of D1 compared to D2 receptors in the NS emerges around 15 days of age [Gelbard et al., 1989]. Electrophysiologically, NMDA currents reach their peak around 14–21 days [Cepeda et al., 1996a]. In addition, Ca^{2+} conductances mature concomitantly [De Fazio and Walsh, 1995]. The convergence of these maturational factors allows the expression of DA modulation of NMDA currents.

At the other end of the age spectrum, DA function is reduced. This may lead to motor deficits which can be partially reversed by administration of DA agonists [Marshall and Berrios, 1979]. We have studied the effects of aging on DA-glutamate interactions. We found that some aged neurons are less responsive to NMDA but more importantly, that in a population of cells the modulation by DA is reduced [Cepeda et al., 1996a].

One of the most consistent findings during aging is that the number and density of D2 receptors are significantly reduced [Joyce et al., 1996; Merchant et al., 1993; Mesco et al., 1993; Morgan et al., 1987]. One possible consequence of this change, considering that D2 receptors exert a negative regulation of glutamate-receptor-mediated responses, is to make NS cells more vulnerable to excitotoxic damage. In Huntington's disease, an age-related pathology, loss of D2 receptors along with increased potentiation of NMDA responses (coupled with energy failure) can lead to neuronal death.

Conclusions

This review emphasizes the complexity of the actions of DA. Clearly, a great deal of work will be necessary to explain the vast body of contradictory data in the literature. We believe, however, that there is enough evidence to provide a model as a tentative working hypothesis of the action of DA in the NS. Primary to the model is the assumption that DA is a neuromodulator and its actions are not unidirectional. The existence of different glutamate and DA receptor subtypes provides the framework for the model. Complex synergistic and antagonistic actions of DA on voltage- and ligand-gated conductances are the basis for functional diversity. The modulatory effects of DA will depend on the DA and glutamate receptor subtype preferentially activated, on its concentration, on the mode of application and probably a number of other factors that we have failed to include. DA is released tonically and phasically. Tonic release will attenuate responses of NS medium-sized spiny cells, probably through a combination of presynaptic inhibition of glutamate release via D2 receptors and reduction of postsynaptic Na^+ and N- and P-type Ca^{2+} conductances via activation of both D1 and D2 receptors. Strong K^+ conductances keep the membrane hyperpolarized. Activation of D2 receptors enhances these conductances. In these conditions, non-NMDA receptors will be activated preferentially and DA will attenuate responses. Phasic release of DA (presumably induced by bursting of substantia nigra neurons), evokes membrane depolarization and activation of L-type Ca^{2+} conductances. D1 receptor activation, which also decreases slowly inactivating K^+ currents, facilitates the transition to the depolarized state. NMDA receptors are unmasked and DA, via D1 receptors and activation of the cAMP-PKA cascade, potentiates NMDA responses either by enhancement of L-type currents and/or phosphorylation of NMDA receptors.

We believe that this model has considerable empirical content and encompasses an already significant amount of electrophysiological, pharmacological and behavioral data that could not be explained were we restricted to consider DA as a purely excitatory or inhibitory neurotransmitter. Paraphrasing Schultz in a recent review [1997], it can be said that recent reports [Cepeda et al., 1993; Gonon, 1997; Harvey and Lacey, 1997; Hernández-Lopez et al., 1997] are prominent examples on how the actions of DA, separated according to an action via D1- and D2-type receptors, might be resolved after more than 20 years of inconsistent results.

Acknowledgments

The authors thank Drs. M.F. Chesselet, K.L. Altemus, R. Hurst and J.P. Walsh for providing valuable comments and criticisms of earlier versions of the manuscript and Chris Calvert and Ahrin Koppel for helping to organize the bibliography. This work was supported by USPHS Grants NS33533 and NS35649.

References

Akaike A, Ohno Y, Sasa M, Takaori S (1987) Excitatory and inhibitory effects of dopamine on neuronal activity of the caudate nucleus neurons in vitro. Brain Res 418:262–272.

Albin RL, Makowiec RL, Hollingsworth ZR, Dure LS, Penney JB, Young AB (1992) Excitatory amino acid binding sites in the basal ganglia of the rat: A quantitative autoradiographic study. Neuroscience 46:35–48.

Altemus KL, Levine MS (1996) Potassium channel blockade does not alter the modulatory effects of dopamine in neostriatal slices. Brain Res 718:212–216.

Altemus KL, Zhang M, Yu Q, Watson IB, Drago I, Sibley DR, Levine MS (1997) Long-term plasticity in the dopamine D1A-receptor deficient mutant mouse. Soc Neurosci Abstr 23:189.

Arbuthnott GW, Wickens JR (1996) Dopamine cells are neurones too! Trends Neurosci 19: 279–280.

Ariano MA, Larson ER, Noblett KL, Sibley DR, Levine MS (1997) Coexpression of striatal dopamine receptor subtypes and excitatory amino acid subunits. Synapse 26:400–414.

Ariano MA, Stromski CJ, Smyk-Randall EM, Sibley DR (1992) D2 dopamine receptor localization on striatonigral neurons. Neurosci Lett 144:215–220.

Armstrong CM, Gilly WF (1992) Access resistance and space clamp problems associated with whole-cell patch clamping. Methods Enzymol 207:100–122.

Artalejo CR, Ariano MA, Perlman RL, Fox AP (1990) Activation of facilitation calcium channels in chromaffin cells by D1 dopamine receptors through a cAMP/protein kinase A-dependent mechanism. Nature 348:239–242.

Artola A, Brocher S, Singer W (1990) Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature 347: 69–72.

Artola A, Singer W (1993) Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosci 16:480–487.

Bargas J, Galarraga E, Aceves J (1988) Electrotonic properties of neostriatal neurons are modulated by extracellular potassium. Exp Brain Res 72:390–398.

Bargas J, Howe A, Eberwine J, Cao Y, Surmeier DJ (1994) Cellular and molecular characterization of Ca^{2+} currents in acutely isolated, adult rat neostriatal neurons. J Neurosci 14:6667–6686.

Beal MF, Hyman BT, Koroshetz W (1993) Do defects in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases? Trends Neurosci 16:125–131.

Ben-Shachar D, Zuk R, Glinka Y (1995) Dopamine neurotoxicity: Inhibition of mitochondrial respiration. J Neurochem 64:718–723.

Bergmann-Erb D, Engberg I, ten Bruggencate G (1988) Biogenic amines facilitate N-methyl-*DL*-aspartate responses in the guinea-pig neocortex in vitro. Pflügers Arch Suppl 411:R127.

Bergson C, Mrzljak L, Smiley JF, Pappy M, Levenson R, Goldman-Rakic PS (1995) Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. J Neurosci 15:7821–7836.

Bernardi G, Marciani MG, Morocutti C, Pavone F, Stanzione P (1978) The action of dopamine on rat caudate neurones intracellularly recorded. Neurosci Lett 8:235–240.

Bertorello AM, Hopfield JF, Aperia A, Greengard P (1990) Inhibition by dopamine of (Na(+)+K+)ATPase activity in neostriatal neurons through D1 and D2 dopamine receptor synergism. Nature 347:386–388.

Bevan P, Bradshaw CM, Szabadi E (1975) Effects of desipramine on neuronal responses to dopamine, noradrenaline, 5-hydroxytryptamine and acetylcholine in the caudate nucleus of the rat. Br J Pharmacol 54:285–293.

Blank T, Nijholt I, Behrsing H, Spiess J (1996) Modulation of NMDA-receptor function in the rat striatum-interplay of kinases and phosphatases. Soc Neurosci Abstr 22:380.

Blank T, Nijholt I, Teichert U, Kugler H, Spiess J (1997) PKA-dependent modulation of NMDA responses: Putative role of the phosphoprotein DARPP-32. Soc Neurosci Abstr 23:707.

Bloom FE, Costa E, Salmoiraghi GC (1965) Anesthesia and the responsiveness of individual neurons of the caudate nucleus of the cat to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis. J Pharmacol Exp Ther 150:244–252.

Brown JR, Arbuthnott GW (1983) The electrophysiology of dopamine (D2) receptors: A study of the actions of dopamine on corticostriatal transmission. Neuroscience 10:349–355.

Brown NA, Seabrook GR (1995) Phosphorylation- and voltage-dependent inhibition of neuronal calcium currents by activation of human D2(short) dopamine receptors. Br J Pharmacol 115:459–466.

Buchwald NA, Altemus KL, Cepeda C, Levine MS (1997) Cholinergic modulation of neostriatal synaptic responses mediated by activation of glutamate receptors. Soc Neurosci Abstr 23:189.

Buisson A, Pateau V, Plotkine M, Boulu RG (1991) Nigrostriatal pathway modulates striatum vulnerability to quinolinic acid. Neurosci Lett 131:257–259.

Bunzow JR, Van Van Tol HH, Grandy DK, Albert P, Salon J, Christie M, Machida CA, Neve KA, Civelli O (1988) Cloning and expression of a rat D2 dopamine receptor cDNA. Nature 336: 783–787.

Calabresi P, Benedetti M, Mercuri NB, Bernardi G (1988) Endogenous dopamine and dopaminergic agonists modulate synaptic excitation in neostriatum: Intracellular studies from naive and catecholamine-depleted rats. Neuroscience 27:145–157.

Calabresi P, Centonze D, Pisani A, Gubellini P, Marfia G, Bernardi G (1997a) Endogenous acetylcholine increases NMDA responses recorded from striatal spiny neurons. Soc Neurosci Abstr 23:2022.

Calabresi P, De Murtas M, Pisani A, Stefani A, Sancesario G, Mercuri NB, Bernardi G (1995a) Vulnerability of medium spiny striatal neurons to glutamate: Role of Na+/K+ ATPase. Eur J Neurosci 7:1674–1683.

Calabresi P, Fedele E, Pisani A, Fontana G, Mercuri NB, Bernardi G, Raiteri M (1995b) Transmitter release associated with long-term synaptic depression in rat corticostriatal slices. Eur J Neurosci 7:1889–1894.

Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G (1992) Long-term synaptic depression in the striatum: Physiological and pharmacological characterization. J Neurosci 12:4424–4233.

Calabresi P, Mercuri N, Stanzioni P, Stefani A, Bernardi G (1987a) Intracellular studies on the dopamine-induced firing inhibition of neostriatal neurons in vitro: Evidence for D1 receptor involvement. Neuroscience 20:757–771.

Calabresi P, Mercuri NB, Stefani A, Bernardi G (1990) Synaptic and intrinsic control of membrane excitability of neostriatal neurons. I. An in vivo analysis. J Neurophysiol 63:651–662.

Calabresi P, Misgeld U, Dodt HU (1987b) Intrinsic membrane properties of neostriatal neurons can account for their low level of spontaneous activity. Neuroscience 20:293–303.

Calabresi P, Pisani A, Centonze D, Bernardi G (1997b) Synaptic plasticity and physiological interactions between dopamine and glutamate in the striatum. Neurosci Biobehav Rev 21: 519–523.

Calabresi P, Pisani A, Mercuri NB, Bernardi G (1996) The corticostriatal projection: From synaptic plasticity to dysfunctions of the basal ganglia. Trends Neurosci 19:19–24.

Calabresi P, Pisani A, Mercuri NB, Bernardi G (1994) Post-receptor mechanisms underlying striatal long-term depression. J Neurosci 14: 4871–4881.

Calabresi P, Saiardi A, Pisani A, Baik JH, Centonze D, Mercuri NB, Bernardi G, Borrelli E (1997c) Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors. J Neurosci 17:4536–4544.

Cameron DL, Williams JT (1993) Dopamine D1 receptors facilitate transmitter release. Nature 336:344–347.

Carlsson M, Carlsson A (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia-implications for schizophrenia and Parkinson's disease. Trends Neurosci 13:272–276.

Cepeda C, Buchwald NA, Levine MS (1993) Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. Proc Natl Acad Sci USA 90:9576–9580.

Cepeda C, Chandler SH, Shumate LW, Levine MS (1995a) Persistent Na^+ conductance in medium-sized neostriatal neurons: Characterization using infrared videomicroscopy and whole cell patch-clamp recordings. J Neurophysiol 74:1343–1348.

Cepeda C, Colwell CS, Itri JN, Chandler SH, Levine MS (1998) Dopaminergic modulation of NMDA-induced whole-cell currents in neostriatal neurons in slice: Contribution of calcium conductances. J Neurophysiol 79:82–94.

Cepeda C, Li Z, Levine MS (1996a) Aging reduces neostriatal responsiveness to N-methyl-*D*-aspartate and dopamine: An in vitro electrophysiological study. Neuroscience 73:733–750.

Cepeda C, Peacook W, Levine MS, Buchwald NA (1991) Iontophoretic application of NMDA produces different types of excitatory responses in developing human cortical and caudate neurons. Neurosci Lett 126:167–171.

Cepeda C, Radisavljevic Z, Peacock W, Levine MS, Buchwald NA (1992) Differential modulation by dopamine of responses evoked by excitatory amino acids in human cortex. Synapse 11:330–341.

Cepeda C, Shumate L, Colwell CS, Levine MS (1996b) NMDA-receptor development in neostriatum: II. Whole-cell voltage clamp analysis of currents in visually identified cells. Soc Neurosci Abstr 22:408.

Cepeda C, Walsh JP, Hull CD, Buchwald NA, Levine MS (1989) Intracellular neurophysiological analysis reveals alterations in excitation in striatal neurons in aged rats. Brain Res 494: 215–226.

Cepeda C, Walsh JP, Peacock W, Buchwald NA, Levine MS (1994) Neurophysiological, pharmacological and morphological properties of human caudate neurons recorded in vitro. Neuroscience 59:89–103.

Cepeda C, Yu Q, Colwell CS, Buchwald NA, Levine MS (1995b) NMDA-induced excitotoxicity in visually identified neostriatal neurons in slices. Modulation by dopamine. Soc Neurosci Abstr 21:912.

Chapman AG, Durmuller N, Lees GJ, Meldrum BS (1989) Excitotoxicity of NMDA and kainic acid is modulated by nigrostriatal dopaminergic fibres. Neurosci Lett 107:256–260.

Charpier S, Deniau JM (1997) In vivo activity-dependent plasticity at cortco-striatal connections. Evidence for physiological long-term potentiation. Proc Natl Acad Sci USA 94:7036–7040.

Cheramy A, Romo R, Godeheu G, Baruch P, Glowinski J (1986) In vivo presynaptic control of dopamine release in the cat caudate nucleus. II. Facilitatory or inhibitory influence of *L*-glutamate. Neuroscience 19:1081–1090.

Cherubini E, Herrling PL, Lanfumey L, Stanzione P (1988) Excitatory amino acids in synaptic excitation of rat striatal neurones in vitro. J Physiol (Lond) 400:677–690.

Cherubini E, Lanfumey L (1987a) A ouabain-sensitive hyperpolarization in rat striatal neurones in vitro. Neurosci Lett 78:338–342.

Cherubini E, Lanfumey L (1987b) An inward calcium current underlying regenerative calcium potentials in rat striatal neurons in vitro enhanced by Bay K 8644. Neuroscience 21:997–1005.

Chesselet MF, Delfs JM (1996) Basal ganglia and movement disorders: An update. Trends Neurosci 19:417–422.

Chiodo LA, Berger TW (1986) Interactions between dopamine and amino acid-induced excitation and inhibition in the striatum. Brain Res 375:198–203.

Choi S, Lovinger DM (1997) Decreased probability of neurotransmitter release underlies striatal long-term depression and postnatal development of corticostriatal synapses. Proc Natl Acad Sci USA 94:2665–2670.

Civelli O, Bunzow JR, Grandy DK (1993) Molecular diversity of the dopamine receptors. Annu Rev Pharmacol Toxicol 33:281–307.

Colwell CS, Altemus KL, Cepeda C, Levine MS (1996) Regulation of N-methyl-*D*-aspartate-induced toxicity in the neostriatum: A role for metabotropic glutamate receptors? Proc Natl Acad Sci USA 93:1200–1204.

Colwell CS, Levine MS (1995) Excitatory synaptic transmission in neostriatal neurons: Regulation by cyclic AMP-dependent mechanisms. J Neurosci 15:1704–1713.

Colwell CS, Levine MS (1996) Glutamate receptor-induced toxicity in neostriatal cells. Brain Res 724:205–212.

Cowan RL, Wilson CJ (1994) Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex. J Neurophysiol 71:17–32.

Das S, Grunert M, Williams L, Vincent SR (1997) NMDA and D1 receptors regulate the phosphorylation of CREB and the induction of c-fos in striatal neurons in primary culture. Synapse 25:227–233.

De Fazio T, Walsh JP (1995) Differential ontogeny of calcium currents in the rat nigrostriatal system. Soc Neurosci Abstr 25:1577.

Di Chiara G, Morelli M, Consolo S (1994) Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions. Trends Neurosci 17:228–233.

Di Figlia M (1990) Excitotoxic injury of the neostriatum: A Model for Huntington's disease. Trends Neurosci 13:286–289.

Dodt HU, Hager G, Zieglgänsberger W (1993) Direct observation of neurotoxicity in brain slices with infrared videomicroscopy. J Neurosci Methods 50:165–171.

Dolphin AC (1996) Facilitation of Ca^{2+} current in excitable cells. Trends Neurosci 19:35–43.

Eilers J, Konnerth A (1997) Dendritic signal integration. Curr Opin Neurobiol 7:385–390.

Ewald DA, Levitan IB (1987) Ion channels regulated by calcium; in Kaczmarek LK, Levitan IB (eds): Neuromodulation. New York, Oxford University Press, pp 138–158.

Ferroni A, Galli A, Mazzanti M (1996) Functional role of low-voltage-activated dihydropyridine-sensitive Ca^{2+} channels during the action potential in adult rat sensory neurones. Pflügers Arch 431:954–963.

Filloux F, Wamsley JK (1991) Dopaminergic modulation of excitotoxicity in rat striatum: Evidence from nigrostriatal lesions. Synapse 8: 281–288.

Flores-Hernández J, Galarraga E, Bargas J (1994) Dopamine selects glutamatergic inputs to neostriatal neurons. Synapse 25:185–195.

Fraser DD, MacVicar BA (1994) Dopamine modulates NMDA-activated currents in striatal and cortical neurons. Soc Neurosci Abstr 20:481.

Freedman JE, Weight FF (1988) Single K^+ channels activated by D2 dopamine receptors in acutely dissociated neurons from rat corpus striatum. Proc Natl Acad Sci USA 85:3618–3622.

Freund TF, Powell JF, Smith AD (1984) Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience 13:1189–1215.

Galarraga E, Hernández-Lopez S, Reyes A, Barral J, Bargas J (1997) Dopamine facilitates striatal EPSPs through an L-type Ca^{2+} conductance. Neuroreport 8:2183–2186.

Garcia-Muñoz M, Young SJ, Groves PM (1991) Terminal excitability of the corticostriatal pathway. I. Regulation by dopamine receptor stimulation. Brain Res 551:195–206.

Gelbard HA, Teicher MH, Faedda G, Baldessarini RJ (1989) Postnatal development of dopamine D1 and D2 receptor sites in rat striatum. Brain Res Dev Brain Res 49:123–130.

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ, Sibley DR (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250:1429–1432.

Girault JA, Spampinato U, Glowinski J, Besson MJ (1986) In vivo release of [^{3}H]gamma-aminobutyric acid in the rat neostriatum. II. Opposing effects of D1 and D2 dopamine receptor stimulation in the dorsal caudate putamen. Neuroscience 19:1109–1117.

Globus MY, Busto R, Dietrich WD, Martinez E, Valdes I, Ginsberg MD (1988) Intra-ischemic extracellular release of dopamine and glutamate is associated with striatal vulnerability to ischemia. Neurosci Lett 91:36–40.

Globus MY, Ginsberg MD, Dietrich WD, Busto R, Scheinberg P (1987) Substantia nigra lesion protects against ischemic damage in the striatum. Neurosci Lett 80:251–256.

Gonon F (1997) Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. J Neurosci 17:5972–5978.

Gonon F, Sundstrom L (1996) Excitatory effects of dopamine released by impulse flow in the rat nucleus accumbens in vivo. Neuroscience 75: 13–18.

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24.

Grace AA, Bunney BS (1984) The control of firing pattern in nigral dopamine neurons: Burst firing. J Neurosci 4:2877–2890.

Graybiel AM (1995) The basal ganglia. Trends Neurosci 18:60–62.

Greenamyre JT (1993) Glutamate-dopamine interactions in the basal ganglia: Relationship to Parkinson's disease. J Neural Transm Gen Sect 91:225–269.
Greengard P, Jen J, Nairn AC, Stevens CF (1991) Enhancement of the glutamate response by cAMP-dependent protein kinase in hippocampal neurons. Science 253:1135–1138.
Greif GJ, Lin YJ, Liu JC, Freedman JE (1995) Dopamine-modulated potassium channels on rat striatal neurons: Specific activation and cellular expression. J Neurosci 15:4533–4544.
Harvey J, Lacey MG (1997) A postsynaptic interaction between dopamine D1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. J Neurosci 17:5271–5280.
Hastings TG, Zigmond MJ (1997) Loss of dopaminergic neurons in parkinsonism: Possible role of reactive dopamine metabolites. J Neural Transm Suppl 49:103–110.
Hernández-Lopez S, Bargas J, Surmeier DJ, Reyes A, Galarraga E (1997) D1 receptor activation enhances evoked discharge in striatal medium spiny neurons by modulating an L-type Ca^{2+} conductance. J Neurosci 17:3334–3342.
Herrling PL (1985) Pharmacology of the corticocaudate excitatory postsynpatic potential in the cat: Evidence for its mediation by quisqualate- or kainate receptors. Neuroscience 14:417–426.
Herrling PL, Hull CD (1980) Iontophoretically applied dopamine depolarizes and hyperpolarizes the membrane of cat caudate neurons. Brain Res 192;441–462.
Herrling PL, Morris R, Salt TE (1983) Effects of excitatory amino acids and their antagonists on membrane and action potentials of cat caudate neurones. J Physiol (Lond) 339:207–222.
Hersch SM, Ciliax BJ, Gutekunst CA, Rees HD, Heilman CJ, Yung KK, Bolam JP, Ince E, Yi H, Levey AI (1995) Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. J Neurosci 15:5222–5237.
Hertz A, Zieglgänsberger W (1968) The influence of microelectrophoretically applied biogenic amines, cholinomimetics and procaine on synaptic excitation in the corpus striatum. Int J Neuropharmacol 7:221–230.
Hirata K, Yim CY, Mogenson GJ (1984) Excitatory input from sensory motor cortex to neostriatum and its modification by conditioning stimulation of the substantia nigra. Brain Res 321: 1–8.
Hoehn K, Watson TW, MacVicar BA (1993) Multiple types of calcium channels in acutely isolated rat neostriatal neurons. J Neurosci 13: 1244–1257.
Hollmann M, Heinemann S (1994) Cloned glutamate receptors. Annu Rev Neurosci 17:31–108.
Hoyt KR, Reynolds IJ, Hastings TG (1997) Mechanisms of dopamine-induced cell death in cultured rat forebrain neurons: Interactions with and differences from glutamate-induced cell death. Exp Neurol 143:269–281.
Hsu KS (1996) Characterization of dopamine receptors mediating inhibition of excitatory synaptic transmission in the rat hippocampal slice. J Neurophysiol 76:1887–1895.
Hsu KS, Huang CC, Yang CH, Gean PW (1995) Presynaptic D2 dopaminergic receptors mediate inhibition of excitatory synaptic transmission in rat neostriatum. Brain Res 690: 264–268.
Hu XT, Wachtel SR, Galloway MP, White FJ (1990) Lesions of the nigrostriatal dopamine projection increase the inhibitory effects of D1 and D2 dopamine agonists on caudate-putamen neurons and relieve D2 receptors from the necessity of D1 receptor stimulation. J Neurosci 10:2318–2329.
Hu XT, White FJ (1997) Dopamine enhances glutamate-induced excitation of rat striatal neurons by cooperative activation of D1 and D2 class receptors. Neurosci Lett 224:61–65.
Huang YY, Kandel ER (1995) D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. Proc Natl Acad Sci USA 92:2446–2450.
Hull CD, Bernardi G, Buchwald NA (1970) Intracellular responses of caudate neurons to brain stem stimulation. Brain Res 22:163–179.
Jaffe DB, Johnston D, Lasser-Ross N, Lisman JE, Miyakawa H, Ross WN (1992) The spread of Na^+ spikes determines the pattern of dendritic Ca^{2+} entry into hippocampal neurons. Nature 357:244–246.
Jiang ZG, North RA (1991) Membrane properties and synaptic responses of rat striatal neurones in vitro. J Physiol (Lond) 443:533–553.
Joyce JN, Loeschen SK, Marshall JF (1985) Dopamine D-2 receptors in rat caudate-putamen: The lateral to medial gradient does not correspond to dopaminergic innervation. Brain Res 338:209–218.
Joyce JN, Loeschen SK, Sapp DW, Marshall JF (1986) Age-related regional loss of caudate-putamen dopamine receptors revealed by quantitative autoradiography. Brain Res 378: 158–163.
Kelly AE, Delfs JM, Chu B (1990) Neurotoxicity induced by the D-1 agonist SKF 38393 following microinjection into rat brain. Brain Res 532:342–346.
Kita H (1996) Glutamatergic and GABAergic postsynaptic responses of striatal spiny neurons to intrastriatal and cortical stimulation recorded in slice preparations. Neuroscience 70:925–940.
Kitai ST, Sugimori M, Kocsis JD (1976) Excitatory nature of dopamine in the nigro-caudate pathway. Exp Brain Res 24:351–363.
Kitai ST, Wagner A, Precht W, Ono T (1975) Nigro-caudate and caudato-nigral relationship: An electrophysiological study. Brain Res 85: 44–48.
Kiyatkin EA, Rebec GV (1996) Dopaminergic modulation of glutamate-induced excitations of neurons in the neostriatum and nucleus accumbens of awake, unrestrained rats. J Neurophysiol 75:142–153.
Knapp AG, Schmidt KF, Dowling JE (1990) Dopamine modulates the kinetics of ion channels gated by excitatory amino acids in retinal horizontal cells. Proc Natl Acad Sci USA 87:767–771.
Koch C (1997) Computation and the single neuron. Nature 385:207–210.
Konradi C, Leveque JC, Hyman SE (1996) Amphetamine and dopamine-induced immediate early gene expression in striatal neurons depends on postsynaptic NMDA receptors and calcium. J Neurosci 16:4231–4239.
Kornhuber J, Kornhuber ME (1986) Presynaptic dopaminergic modulation of cortical input to the striatum. Life Sci 39:699–674.
Kötter R (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. Prog Neurobiol 44:163–196.
Kusuki T, Imahori Y, Ueda S, Inokuchi K (1997) Dopaminergic modulation of LTP induction in the dentate gyrus of intact brain. Neuroreport 8:2037–2040.
La Hoste GJ, Ruskin DN, Marshall JF (1996) Cerebrocortical Fos expression following dopaminergic stimulation: D1/D2 synergism and its breakdown. Brain Res 728:97–104.
La Hoste GJ, Yu J, Marshall JF (1993) Striatal Fos expression is indicative of dopamine D1/D2 synergism and receptor supersensitivity. Proc Natl Acad Sci USA 90:7451–7455.
Lange KW, Kornhuber J, Riederer P (1997) Dopamine/glutamate interactions in Parkinson's disease. Neurosci Biobehav Rev 21:393–400.
Lasater EM, Dowling JE (1982) Carp horizontal cells in culture respond selectively to *L*-glutamate and its agonists. Proc Natl Acad Sci USA 79:936–940.
Le Moine C, Bloch B (1995) D1 and D2 dopamine receptor gene expression in the rat striatum: Sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. J Comp Neurol 355:418–426.
Leonard AS, Hell JW (1997) Cyclic AMP-dependent protein kinase and protein kinase C phosphorylate N-methyl-*D*-aspartate receptors at different sites. J Biol Chem 272:12107–12115.
Lester J, Fink S, Aronin N, Di Figlia M (1993) Colocalization of D1 and D2 dopamine receptor mRNAs in striatal neurons. Brain Res 621: 106–110.
Levine MS, Altemus KL, Cepeda C, Cromwell HC, Crawford C, Ariano MA, Drago J, Sibley DR, Westphal H (1996a) Modulatory actions of dopamine on NMDA receptor-mediated responses are reduced in D1A-deficient mutant mice. J Neurosci 16:5870–5882.
Levine MS, De Fazio T, Espinosa de los Monteros A, DeVellis J (1997) Dopamine modulation of NMDA-induced calcium transients in fetal neocortical cultures and dissociated neostriatal neurons. Soc Neurosci Abstr 23:1192.
Levine MS, Li Z, Cepeda C, Cromwell HC, Altemus KL (1996b) Neuromodulatory actions of dopamine on synaptically-evoked neostriatal responses in slices. Synapse 24:65–78.

Liste I, Rozas G, Guerra MJ, Labandeira-Garcia JL (1995) Cortical stimulation induces Fos expression in striatal neurons via NMDA glutamate and dopamine receptors. Brain Res 700: 1–12.
Lovinger DM, Choi S (1995) Activation of adenosine A1 receptors initiates short-term synaptic depression in rat striatum. Neurosci Lett 199: 9–12.
Lovinger DM, Merritt A, Reyes D (1994) Involvement of N- and non-N-type calcium channels in synaptic transmission at corticostriatal synapses. Neuroscience 62:31–40.
Lovinger DM, Tyler E (1996) Synaptic transmission and modulation in the neostriatum. Int Rev Neurobiol 39:77–111.
Lovinger DM, Tyler Ec, Merritt A (1993) Short- and long-term synaptic depression in rat neostriatum. J Neurophysiol 70:1937–1949.
Lukyanetz EA, Kostyuk PG (1996) Two distinct receptors operate the cAMP cascade to up-regulate L-type Ca^{2+} channels. Pflügers Arch 432: 174–181.
Magee JC, Avery RB, Christie BR, Johnston D (1996) Dihydropyridine-sensitive, voltage-gated Ca^{2+} channels contribute to the resting intracellular Ca^{2+} concentration of hippocampal CA1 pyramidal neurons. J Neurophysiol 76: 3460–3470.
Magee JC, Johnston D (1997) A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 275:209–213.
Mahan LC, Burch RM, Monsma FJ, Sibley DR (1990) Expression of striatal D1 dopamine receptors coupled to inositol phosphate production and Ca^{2+} mobilization in Xenopus oocytes. Proc Natl Acad Sci USA 87:2196–2200.
Markram H, Segal M (1991) Calcimycin potentiates responses of rat hippocampal neurons to N-methyl-*D*-aspartate. Brain Res 540:322–324.
Marshall JF, Berrios N (1979) Movement disorders of aged rats: Reversal by dopamine receptor stimulation. Science 206:477–479.
Mayer ML, Westbrook GL, Guthrie PB (1984) Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. Nature 309: 261–263.
McLaughlin BA, Nelson D, Erecinska M, Chesselet MF (1997) Dopamine potentiates the toxicity of mitochondrial inhibition in vitro. Soc Neurosci Abstr 23:271.
McLennan H, York DH (1967) The action of dopamine on neurones of the caudate nucleus. J Physiol (Lond) 189:393–402.
Merchant KM, Dobie DJ, Dorsa DM (1993) Differential loss of dopamine D2 receptor mRNA isoforms during aging in Fischer-344 rats. Neurosci Lett 154:163–167.
Mercuri N, Bernardi G, Calabresi P, Cotugno A, Levi G, Stanzione P (1985) Dopamine decreases cell excitability in rat striatal neurons by pre- and postsynaptic mechanisms. Brain Res 358:110–121.
Mesco ER, Carlson SG, Joseph JA, Roth GS (1993) Decreased striatal D2 dopamine receptor mRNA synthesis during aging. Brain Res Mol Brain Res 17:160–162.
Mirenowicz J, Schultz W (1996) Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. Nature 379: 449–451.
Mirenowicz J, Schultz W (1994) Importance of unpredictability for reward resonses in primate dopamine neurons. J Neurophysiol 72:1024–1027.
Misgeld U, Dodt HU, Frotscher M (1986) Late development of intrinsic excitation in the rat neostriatum: An in vitro study. Brain Res 392: 59–67.
Mitchell PR, Doggett NS (1980) Modulation of striatal [^{3}H]-glutamic acid release by dopaminergic drugs. Life Sci 26:2073–2081.
Monaghan DT, Bridges RJ, Cotman CW (1989) The excitatory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system. Annu Rev Pharmacol Toxicol 29:365–402.
Monsma FJ, Mahan LC, McVittie LD, Gerfen CR, Sibley DR (1990) Molecular cloning and expression of a D1 dopamine receptor linked to adenylyl cyclase activation. Proc Natl Acad Sci USA 87:6723–6727.
Monsma FJ, McVittie LD, Gerfen CR, Mahan LC, Sibley DR (1989) Multiple D2 dopamine receptors produced by alternative RNA splicing. Nature 342:926–929.
Morgan DG, Marcusson JO, Nyberg P, Wester P, Winblad B, Gordon MN, Finch CE (1987) Divergent changes in D-1 and D-2 dopamine binding sites in human brain during aging. Neurobiol Aging 8:195–201.
Musleh W, Akopian G, Walsh JP (1997) Novel medial to lateral differences in the expression of short- and long-term synaptic plasticity in the rat striatum. Soc Neurosci Abstr 23:1281.
Nestler EJ (1994) Hard target: Understanding dopaminergic neurotransmission. Cell 79:923–926.
Nicoll RA (1988) The coupling of neurotransmitter receptors to ion channels in the brain. Science 241:545–551.
Nisenbaum ES, Berger TW (1992) Functionally distinct subpopulations of striatal neurons are differentially regulated by GABAergic and dopaminergic inputs. I. In vivo analysis. Neuroscience 48:561–578.
Nishi A, Snyder GL, Fienberg A, Allen P, Fisone G, Nairn AC, Aperia A, Greengard P (1996) Role of DARPP-32 in the regulation of Na+, K+-ATPase activity in striatal neurons. Soc Neurosci Abstr 22:380.
Nishi A, Snyder GL, Greengard P (1997) Bidirectional control of DARPP-32 phosphorylation by dopamine. J Neurosci 17:8147–8155.
Nocross K, Spehlmann R (1978) A quantitative analysis of the excitatory and depressant effects of dopamine on the firing of caudatal neurons: Electrophysiological support for the existence of two distinct dopamine-sensitive receptors. Brain Res 156:168–174.
Nowak I, Bregestovski P, Ascher P, Herbet A, Prochiantz A (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307:462–465.
O'Malley KL, Harmon S, Tang L, Todd RD (1992) The rat dopamine D4 receptor: Sequence, gene structure, and demonstration of expression in the cardiovascular system. New Biol 4:137–146.
Ohno Y, Sasa M, Takaori S (1987) Coexistence of inhibitory dopamine D-1 and excitatory D-2 receptors on the same caudate nucleus neurons. Life Sci 40:1937–1945.
Otmakhova NA, Lisman JE (1996) D1/D5 dopamine receptor activation increases the magnitude of early long-term potentiation at CA1 hippocampal synapses. J Neurosci 16:7478–7486.
Pfeiffer-Linn C, Lasater EM (1993) Dopamine modulates in a differential fashion T- and L-type calcium currents in bass retinal horizontal cells. J Gen Physiol 102:277–294.
Pierce RC, Rebec GV (1995) Iontophoresis in the neostriatum of awake, unrestrained rats: Differential effects of dopamine, glutamate and ascorbate on motor- and nonmotor-related neurons. Neuroscience 67:313–324.
Pisani A, Calabresi P, Centonze D, Bernardi G (1997) Enhancement of NMDA responses by group I metabotropic glutamate receptor activation in striatal neurones. Br J Pharmacol 120:1007–1014.
Reader TA, Ferron A, Descarries L, Jasper HH (1979) Modulatory role for biogenic amines in the cerebral cortex. Microiontophoretic studies. Brain Res 160:217–229.
Rolls ET (1994) Neurophysiology and cognitive functions of the striatum. Rev Neurol (Paris) 150:648–660.
Rowlands GF, Roberts PJ (1980) Activation of dopamine receptors inhibits calcium-dependent glutamate release from cortico-striatal terminals in vitro. Eur J Pharmacol 62:241–242.
Rutherford A, Garcia-Muñoz M, Arbuthnott GW (1988) An afterhyperpolarization recorded in striatal 'in vitro': Effect of dopamine administration. Exp Brain Res 71:399–405.
Schambra UB, Duncan GE, Breese GR, Fornaretto MG, Caron MG, Fremeau RT Jr (1994) Ontogeny of D1A and D2 dopamine receptor subtypes in rat brain using in situ hybridization and receptor binding. Neuroscience 62:65–85.
Schiffmann SN, Lledo PM, Vincent JD (1995) Dopamine D1 receptor modulates the voltage-gated sodium current in rat striatal neurones through a protein kinase A. J Physiol (Lond) 483:95–107.
Schultz W (1997) Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol 7: 191–197.
Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593–1599.
Schwanstecher C, Panten U (1994) Identification of an ATP-sensitive K^+ channel in spiny neurons of rat caudate nucleus. Pflügers Arch 427: 187–189.
Shingai R, Christensen BN (1986) Excitable properties and voltage-sensitive ion conductances of horizontal cells isolated from catfish *(Ictalurus punctatus)* retina. J Neurophysiol 56:32–49.

Sibley DR, Monsma FJ (1992) Molecular biology of dopamine receptors. Trends Pharmacol Sci 13:61–69.
Siggins GR (1978) Electrophysiological role of dopamine in striatum: Excitatory or inhibitory? In Lipton MA, DiMasco A, Killam KF (eds): Psychopharmacology: A Generation of Progress. New York, Raven Press, pp 143–157.
Smart TG (1997) Regulation of excitatory and inhibitory neurotransmitter-gated ion channels by protein phosphorylation. Curr Opin Neurobiol 7:358–367.
Smith AD, Bolam JP (1990) The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends Neurosci 13:259–265.
Snyder G, Fienberg A, Dulubova I, Nairn AC, Greengard P (1996) Dopamine-mediated phosphorylation of NMDA-R1 in the rat nucleus accumbens. Soc Neurosci Abstr 22:380.
Song WJ, Surmeier DJ (1996) Voltage-dependent facilitation of calcium channels in rat neostriatal neurons. J Neurophysiol 76:2290–2306.
Spencer HJ, Havlicek V (1974) Alterations by anesthetic agents of the responses of rat striatal neurons to iontophoretically applied amphetamine, acetylcholine, noradrenaline, and dopamine. Can J Physiol Pharmacol 52:808–813.
Standaert DG, Testa CM, Young AB, Penney JB (1994) Organization of N-methyl-*D*-aspartate glutamate receptor gene expression in the basal ganglia of the rat. J Comp Neurol 343:1–16.
Starr MS (1995) Glutamate/dopamine D1/D2 balance in the basal ganglia and its relevance to Parkinson's disease. Synapse 19:264–293.
Stoof JC, Kebabian JW (1981) Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 294: 366–368.
Stuart G, Sakmann B (1995) Amplification of EPSPs by axosomatic sodium channels in neocortical pyramidal neurons. Neuron 15:1065–1076.
Stuart GJ, Sakmann B (1994) Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature 467:69–72.
Sullivan JM, Lasater EM (1990) An unusually small potassium current that is well-suited to a retinal neuron which is chronically depolarized. Brain Res 528:130–132.
Surmeier DJ, Bargas J, Hemmings HC, Nairn AC, Greengard P (1995) Modulation of calcium currents by a D1 dopaminergic protein kinase/phosphatase cascade in rat neostriatal neurons. Neuron 14:385–397.
Surmeier DJ, Eberwine J, Wilson CJ, Cao Y, Stefani A, Kitai ST (1992) Dopamine receptor subtypes colocalize in rat striatonigral neurons. Proc Natl Acad Sci USA 89:10178–10182.
Surmeier DJ, Kitai ST (1993) D1 and D2 dopamine receptor modulation of sodium and potassium currents in rat neostriatal neurons. Prog Brain Res 99:309–324.
Surmeier DJ, Reiner A, Levine MS, Ariano MA (1993) Are neostriatal dopamine receptors colocalized? Trends Neurosci 16:299–305.
Surmeier DJ, Song WJ, Yan Z (1996) Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. J Neurosci 16:6579–6591.
Szele FG, Artymyshyn R, Molinoff PB, Chesselet MF (1991) Heterogeneous distribution of dopamine D2 receptor mRNA in the rat striatum: A quantitative analysis with in situ hybridization histochemistry. Anat Rec 231:548–558.
Tallaksen-Greene SJ, Wiley RG, Albin RL (1992) Localization of striatal excitatory amino acid binding site subtypes to striatonigral projection neurons. Brain Res 594:165–170.
Trulson ME, Atasteh K (1986) Effects of dopamine and amphetamine on mouse caudate neurons recorded in vitro. Eur J Pharmacol 124:161–165.
Vincent SL, Khan Y, Benes FM (1993) Cellular distribution of dopamine D1 and D2 receptors in rat medial prefrontal cortex. J Neurosci 13: 2551–2564.
Walsh JP (1991) Long-term potentiation (LTP) of excitatory synaptic input to medium spiny neurons of the rat striatum. Soc Neurosci Abstr 17: 852.
Walsh JP (1993) Depression of excitatory synaptic input in rat striatal neurons. Brain Res 608: 123–128.
Walsh JP, Dunia R (1993) Synaptic activation of N-methyl-*D*-aspartate receptors induces short-term potentiation at excitatory synapses in the striatum of the rat. Neuroscience 57:241–248.
Watkins JC, Krogsgaard-Larsen P, Honore T (1990) Structure-activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonists. Trends Pharmacol Sci 11:25–33.
Wickens JR, Begg AJ, Arbuthnott GW (1996) Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex in vitro. Neuroscience 70:1–5.
Wickens JR, Reynolds JNJ (1997) Synaptic plasticity in the rat neostriatum in vivo. Soc Neurosci Abstr 23:1281.
Williams PJ, MacVicar BA, Pittman QJ (1990) Synaptic modulation by dopamine of calcium currents in rat pars intermedia. J Neurosci 10: 757–763.
Wilson CJ (1990) Basal ganglia; in Shepard GM (ed): The synaptic organization of the brain. New York, Oxford University Press, pp 279–316.
Wilson CJ, Kawaguchi Y (1996) The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. J Neurosci 16:2397–2410.
Yamamoto BK, Davy S (1992) Dopaminergic modulation of glutamate release in striatum as measured by microdialysis. J Neurochem 58: 1736–1742.
York DH (1967) The inhibitory action of dopamine on neurones of the caudate nucleus. Brain Res 5:263–266.
Yung KK, Bolam JP, Smith AD, Hersch SM, Ciliax BJ, Levey AI (1995) Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: Light and electron microscopy. Neuroscience 65:709–730.
Zador A, Koch C, Brown TH (1990) Biophysical model of a Hebbian synapse. Proc Natl Acad Sci USA 87:6718–6722.