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Review

Dopaminergic Modulation of Synaptic Transmission in Cortex and Striatum

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Among the many neuromodulators used by the mammalian brain to regulate circuit function and plasticity, dopamine (DA) stands out as one of the most behaviorally powerful. Perturbations of DA signaling are implicated in the pathogenesis or exploited in the treatment of many neuropsychiatric diseases, including Parkinson's disease (PD), addiction, schizophrenia, obsessive compulsive disorder, and Tourette's syndrome. Although the precise mechanisms employed by DA to exert its control over behavior are not fully understood, DA is known to regulate many electrical and biochemical aspects of neuronal function including excitability, synaptic transmission, integration and plasticity, protein trafficking, and gene transcription. In this Review, we discuss the actions of DA on ionic and synaptic signaling in neurons of the prefrontal cortex and striatum, brain areas in which dopaminergic dysfunction is thought to be central to disease.

Introduction

Dopamine (DA) is a catecholamine (CA) that was initially identified as the metabolic precursor of the neurotransmitter norepinephrine (NE). Pioneering studies by Arvid Carlsson in the late 1950s first lent support to the idea that DA does not merely serve as an intermediate for NE biosynthesis, but rather functions as a transmitter in the mammalian CNS in its own right (Carlsson et al., 1957, 1958; Carlsson, 1959). Since that time, neuroscientists have sought to elucidate the influence that DA exerts on behavior and neural circuits and to uncover the underlying cellular and molecular underpinnings of such effects. Interest in the actions of this molecule is further stimulated by the recognition of its involvement in several neurological and psychiatric disorders, including Parkinson's disease (PD), addiction, schizophrenia, obsessive compulsive disorder, and Tourette's syndrome. DA plays an important role in the control of fine motor actions and higher cognitive functions such as learning, working memory, attention, decision making, and appetitive and consummatory aspects of reward. However, the precise mechanisms employed by DA to mediate these effects remain largely unknown owing to the multiplicity and complexity of its actions. DA signaling involves a plethora of molecules including kinases, phosphatases, transcription factors, ion channels, and membrane receptors. Moreover, DA's actions have largely defied interpretation because they vary greatly between cell types, depend on the strength and duration of receptor stimulation, are influenced by current and past cellular states, and compete with other neuromodulatory systems impinging on similar pathways. Thus, despite extensive investigation, there is no unified view of dopamine's actions in the CNS, and many studies have yielded contradictory conclusions. Here, we discuss dopamine's ability to rapidly influence synaptic transmission, dendritic integration, and membrane excitability.

The search for neurons that produce DA started in the early 1960s, after the remarkable finding that catecholamine-containing neurons could be visualized in tissue after chemical conversion of CAs into fluorescent molecules with formaldehyde (Carlsson et al., 1962; Falck et al., 1982). Using this method, seventeen groups of CA cells (designated A1–A17) were initially identified in the CNS. Specific identification of DA-producing cells is complex even with modern techniques. Firmly establishing a dopaminergic identity necessitates the analysis of multiple cellular markers and ideally the demonstration of stimulus-evoked DA release from genetically defined neurons such as by combining optogenetics and carbon fiber voltammetry (e.g., Stuber et al., 2010; Tecuapetla et al., 2010). Collectively, the available data support the existence of ten DA-producing nuclei in the mammalian brain (A8–A17). Neurons within each field can differ significantly with respect to axonal projection areas, electrophysiological properties, and the expression of synthetic enzymes, membrane and vesicular transporters, neuropeptides, and other amino acid transmitters (Björklund and Dunnett, 2007; Hnasko et al., 2010; Lammel et al., 2011).

Midbrain DA neurons in the substantia nigra pars compacta (SNc; field A9) and ventral tegmental area (VTA; field A10) are perhaps the best studied of these because of their central roles in the pathology of PD and in reward signaling and reinforcement, respectively. These two centers provide the bulk of DA to the basal ganglia and forebrain and contain the vast majority of DA neurons in the CNS. In the rat, VTA and SNc each contain ~20,000 neurons bilaterally (German and Manaye, 1993). Given their small numbers and powerful impact on many aspects of behavior, each midbrain DA neuron must exert influence over large brain areas and many cells. Indeed, individual SNc neurons extend impressive axons of half a meter in total length that densely ramify throughout up to 1 mm^3 of tissue (Matsuda et al., 2009). Furthermore, midbrain DA neurons are spontaneously active at low frequencies, suggesting that each neuron provides a basal DA tone to many target neurons that is rapidly adjusted by either phasic bursts or transient pauses of activity.

Some of the first electrophysiological investigations of DA's influence in the 1970s and 1980s utilized in vivo and in vitro extracellular and intracellular recordings and examined the effects of electrical stimulation of DA centers or local application of

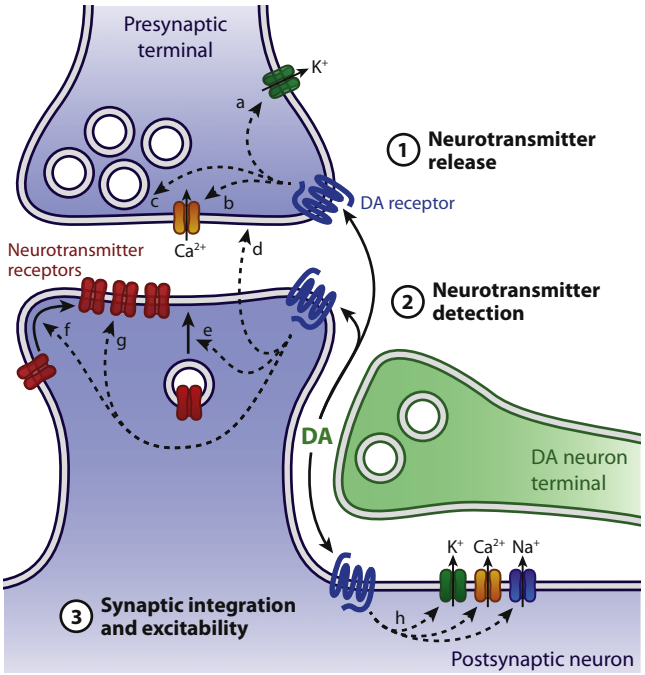

Figure 1. Potential Sites of Modulation of Synaptic Transmission by DA

DA may affect neurotransmitter release by modulating axon terminal excitability (a), Ca^{2+} influx (b), or vesicular release machinery (c). This can occur directly, through activation of presynaptic DA receptors, or indirectly, after the recruitment of postsynaptic DA receptors and liberation of retrograde signaling molecules (d). Postsynaptic DA receptors may influence neurotransmitter detection by modulating the membrane insertion (e), synaptic recruitment (f), or properties (g) of neurotransmitter receptors. In addition, DA alters synaptic integration and the excitability of pre- and postsynaptic membranes by modulating ion channels that control resting potential, Ca^{2+} influx, and action potential threshold and waveform (h).

exogenous DA. These studies invariably reported complex, variable, and often contradictory findings (see Nicola et al., 2000; Seamans and Yang, 2004 for review). Some of these disparities probably arose because, as discussed below, DA activates multiple classes of receptors that are heterogeneously distributed and engage different intracellular signaling cascades.

Neuromodulators affect several distinct steps of synaptic transmission, including the probability of neurotransmitter release, the postsynaptic sensitivity to neurotransmitter, and the membrane excitability of the pre- and postsynaptic cells (Figure 1). These neuromodulatory targets are expected to alter synaptic communication in different ways and should be considered separately. First, the excitability of presynaptic neurons directly determines the frequency of activation of synapses by controlling the rate of action potential invasion of presynaptic boutons. Such changes may fall under the general category of ''gain-control'' mechanisms, which linearly transform the input-output relationship of a circuit. Modulation of the excitability of interneurons that mediate feedback and feedforward inhibition can additionally introduce time-dependent transformations that alter circuit activity in complex ways. Second, neuromodulators directly regulate the probability of action potential-evoked vesicular neurotransmitter release from presynaptic boutons by altering the size and properties of the vesicle pool or of the state of active zone proteins. DA also has indirect effects on release probability due to its impact on ion channels that determine action potential-evoked Ca^{2+} influx. Alterations in release probability have complex effects on the time dependence of neurotransmitter release that can profoundly alter the dynamics of action potential firing. Third, neuromodulators control the number, classes, and properties of neurotransmitter receptors in the synapse, thereby regulating the biochemical and electrical postsynaptic response. In the simplest cases, changing the number of synaptic ionotropic receptors is analogous to gain control—e.g., increasing the number of synaptic AMPA-type glutamate receptors enlarges the excitatory postsynaptic potential (EPSP), thus altering the gain in the transformation from pre- to postsynaptic activity. However, more subtle modes of regulation are possible with specific changes to subsets of neurotransmitter receptors. Downstream of neurotransmitter receptor activation, regulation of postsynaptic ion channels can have profound effects on the generation of synaptic potentials, Ca^{2+} influx, synaptic integration, plasticity, and action potential firing.

This Review will dissect the reported effects of DA on each of three steps that broadly define synaptic transmission: presynaptic neurotransmitter release, postsynaptic neurotransmitter detection, and membrane excitability and synaptic integration. Given space constraints, we restrict our analysis to prefrontal cortex (PFC) and striatum, as they are the major targets of the largest group of DA neurons in the mammalian brain and perturbations of DA in these brain regions are implicated in the pathogenesis of numerous neurological diseases. We limit our presentation to studies in which pharmacological, biochemical, or electrophysiological assays were used to specifically assign (to the extent possible) the regulatory targets of DA to each of these three synaptic transmission steps. We also restrict our discussion to studies of rodents because they constitute the model of choice for the majority of in vitro electrophysiological studies and have significantly contributed to our understanding of DA signaling in recent years with the application of molecular, genetic, and optogenetic techniques.

Intracellular Signaling by DA Receptors

Once released from presynaptic terminals, DA mediates its effects by interacting with members of a family of GPCRs (D1–D5 receptors). These distinct but closely related DA receptors are commonly segregated in two major classes based on their structural, pharmacological, and signaling properties: D1 and D5 receptors belong to the subfamily of D1-like receptors, whereas D2, D3, and D4 receptors are grouped into the D2-like receptor class (Table 1). The D2-like receptors are alternatively spliced, giving rise to isoforms with distinct physiological properties and subcellular localization, with the best characterized of these isoforms being the short and long variants of D2 receptors (D2S and D2L, respectively). Several variants of D3 and D4 receptors have also been described (Callier et al., 2003; Rankin et al., 2010). By contrast, the genes encoding D1-like receptors consist of a single exon and therefore do not generate splice variants. At the protein level, receptors within the D1- and D2-like receptor classes share a high level of

Table 1. Basic Characteristics of DA Receptors

	D1-like Family		D2-like Family		
DA receptor subtype	D1	D5	D2	D3	D4
Gene name	*Drd1a*	*Drd5*	*Drd2*	*Drd3*	*Drd4*
Number of introns	0	0	6	5	3
Splice variants	No	No	Yes (D2S, D2L)	Yes	Yes
Affinity for DA (μM)*	1.0–5.0	0.2–2.0	0.2–2.0	0.02–0.2	0.01–0.1
G protein coupling	$G\alpha_s$, $G\alpha_{olf}$	$G\alpha_s$, $G\alpha_q$	$G\alpha_i$, $G\alpha_0$	$G\alpha_i$, $G\alpha_0$	$G\alpha_i$, $G\alpha_0$
Common family-specific agonists	SKF-38393, SKF-81297		(−) Quinpirole, Cabergoline		
Common family-specific antagonists	SCH-23390, SKF-83566		(−) Sulpiride, Spiperone, Nemonapride		

*RKi ranges for cloned human DA receptors obtained from the NIMH Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu) and the International Union of Basic and Clinical Pharmacology.

homology and display similar pharmacological properties. Pharmacological agonists and antagonists of DA receptors can readily distinguish between receptor families, but less so between individual subtypes within a family. The affinity of D2-like receptors for DA is generally reported to be 10- to 100-fold greater than that of D1-like receptors, with D3 and D4 receptors displaying the highest sensitivity for DA and D1 receptors the lowest (Beaulieu and Gainetdinov, 2011). However, given that these measurements rely on displacement of radiolabeled antagonists from heterologously expressed DA receptors and do not capture the coupling efficacy to downstream signaling cascades, it is difficult to infer whether D2-like receptors are preferentially activated by basal extracellular levels of DA in vivo. Moreover, D1 and D2 receptors can exist in both high and low affinity states and have similar nanomolar affinities for DA in their high affinity states (reviewed in Wickens and Arbuthnott, 2005). Finally, the D1- and D2-like receptor classes differ functionally in the intracellular signaling pathways they modulate. As GPCRs, all DA receptors activate heterotrimeric G proteins, but the second messenger pathways and effector proteins activated by both receptor classes vary greatly and often mediate opposite effects (Figure 2). These signaling cascades are described in detail elsewhere (see Beaulieu and Gainetdinov, 2011; Fisone, 2010; Neve et al., 2004 and references within); only a brief overview is presented here.

D1-like receptors stimulate the heterotrimeric G proteins $G\alpha_s$ and $G\alpha_{olf}$, which are positively coupled to adenylyl cyclase (AC), leading to the production of cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A (PKA). By contrast, D2-like receptors activate $G\alpha_i$ and $G\alpha_o$ proteins, which inhibit AC and limit PKA activation. PKA mediates most of the effects of D1-like receptors by phosphorylating and regulating the function of a wide array of cellular substrates such as voltage-gated K^+, Na^+ and Ca^{2+} channels, ionotropic glutamate, and GABA receptors and transcription factors. One of the major targets of PKA is the DA and cAMP-regulated phosphoprotein DARPP-32, which is highly expressed in DA-responsive striatal and cortical neurons and plays a critical role in the regulation of downstream signal transduction pathways. DARPP-32 integrates signals from several neurotransmitters to bidirectionally modulate PKA activity. When phosphorylated by PKA, DARPP-32 amplifies PKA signaling by inhibiting protein phosphatase 1 (PP1), which counteracts PKA's actions. By contrast, dephosphorylation by the calmodulin-dependent protein phosphatase 2B (PP2B) upon D2-like receptor stimulation helps convert DARPP-32 into a potent inhibitor of PKA signaling.

DA receptors can also signal independently of cAMP/PKA to modulate intracellular Ca^{2+} levels and regulate ligand- and voltage-gated ion channels. This is particularly true for $G\alpha_{i/0}$-coupled receptors, such as members of the D2-like family, which target several effector proteins through liberation of the $G\beta\gamma$ subunit of heterotrimeric G proteins upon receptor activation. Membrane-bound $G\beta\gamma$ subunits can diffuse along the plasma membrane to directly activate ion channels or second messengers. The best example is the gating of G protein-activated inward-rectifier K^+ channels ($K_{ir}3$) in D2 receptor-expressing midbrain DA neurons (Beckstead et al., 2004). Release of $G\beta\gamma$ subunits after D2-like receptor stimulation can also decrease $Ca_V2.2$ (N-type) and Ca_V1 (L-type) Ca^{2+} currents directly or indirectly via activation of phospholipase C (PLC). There is also evidence that D1-class receptors can activate PLC by coupling to $G\alpha_q$ heterotrimeric G proteins; but this property may be limited to cells expressing D5 receptors or D1/D2 heterodimers (Lee et al., 2004; Sahu et al., 2009). In addition to their effects on G protein-regulated pathways, D1 and D2 receptors can alter membrane trafficking of $Ca_V2.2$ channels as well as NMDA and $GABA_A$ receptors through direct protein-protein interactions or downstream of tyrosine kinase activation.

DA Receptor Distribution in Forebrain

DA receptors are broadly expressed in the CNS, with their distribution and expression levels largely mirroring the density of innervating DA fibers (see Bentivoglio and Morelli, 2005; Callier et al., 2003 and references within). D1 and D2 receptors are the two most abundant receptor subtypes expressed in the brain, with D1 receptors displaying the most widespread distribution and highest expression levels. D1 and D2 receptors are most prominently found in dorsal striatum, ventral striatum (nucleus accumbens), and olfactory tubercle, which constitute the principal recipient structures of midbrain DA axons. D1 and D2 receptor mRNA is also found in other forebrain structures, including cortex. The expression of D3, D4, and D5 receptors

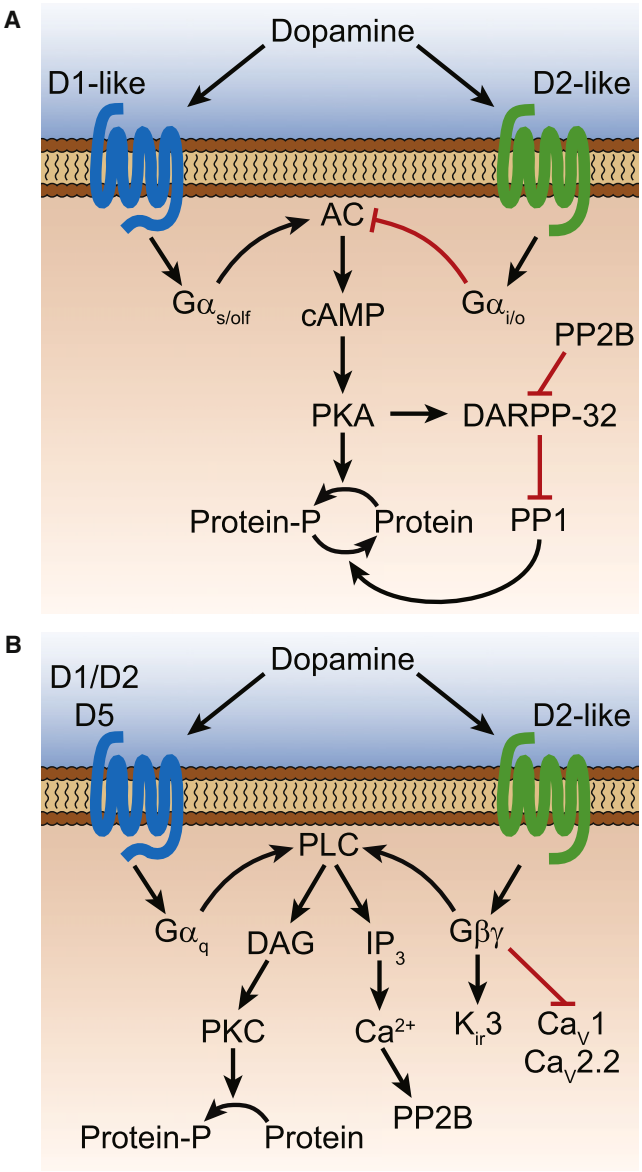

Figure 2. Intracellular DA Signaling Pathways
Schematic of cAMP/PKA-dependent (A) and -independent (B) pathways recruited by DA receptors. D1- and D2-like receptors are depicted in the same cell for illustrative purposes. Note that some of the targets of Gβγ are ion channels ($K_{ir}3$, Ca_V1, and $Ca_V2.2$). Black and red arrows depict activation and inhibition, respectively. IP_3, inositol triphosphate; DAG, diacylglycerol.

in the brain is considerably more restricted and weaker than that of D1 and D2 receptors. D1- and D2-like receptors are expressed in both striatal projection neurons (SPNs) and interneurons, as well as in subpopulations of pyramidal neurons, interneurons, and glial cells in cortex (Table 2). In these brain regions and others, D1- and D2-like receptors are localized presynaptically in nerve terminals and axonal varicosities, as well as postsynaptically in dendritic shafts and spines (Bentivoglio and Morelli, 2005). Thus, no simple and general division of labor exists between D1 and D2 receptor families with respect to receptor distribution in projection versus locally projecting neurons or pre- versus postsynaptic membrane specializations.

Striatum is almost entirely populated by two equally sized groups of GABAergic SPNs that extend axons either to basal ganglia output nuclei (the striatonigral or so-called direct pathway SPNs, denoted dSPNs) or to the external segment of the globus pallidus (GPe) (the striatopallidal or indirect pathway SPNs, denoted iSPNs). Anatomical, pharmacological, and single-cell RT-PCR studies determined that dSPNs express high levels of D1 receptors along with the peptides neurotransmitter substance P and dynorphin, whereas iSPNs express D2 receptors as well as the neurotransmitter enkephalin (Gerfen, 1992; Gerfen and Surmeier, 2011). This dichotomy was recapitulated in transgenic mice using bacterial artificial chromosomes (BACs) that express Cre recombinase or fluorescent proteins such as enhanced green fluorescent protein (EGFP) or tdTomato under control of the promoter region for D1 or D2 receptor genes (Ade et al., 2011; Gong et al., 2003, 2007). In these mice, transgenes driven by D1 and D2 receptor promoters are almost exclusively segregated into striatonigral and striatopallidal populations, respectively, although a small number of D1 receptor-containing dSPNs additionally extend axon collaterals in GPe (Valjent et al., 2009), consistent with earlier anatomical studies of single biocytin-filled cells. Moreover, molecular profiling studies in iSPNs and dSPNs support the selective enrichment of D1 and D2 receptors in distinct SPN populations (Heiman et al., 2008; Lobo et al., 2010). However, some controversy persists as to whether the segregation of DA receptor families in SPNs is absolute and whether subpopulations of SPNs potentially coexpressing both receptor types underlie the synergistic actions of D1 and D2 receptor agonists observed in some experimental preparations (Perreault et al., 2011). Indeed, in situ hybridization and single-cell RT-PCR experiments have revealed that D1 and D2 receptors can both be detected in a subset of SPNs in striatum and that dSPNs and iSPNs also express low levels of D3, D4, and D5 receptor mRNA (Lester et al., 1993; Surmeier et al., 1992, 1996). It is unclear whether these low-abundance transcripts significantly contribute to SPN function and whether the apparent cooperative effects of D1- and D2-like receptors observed in some studies instead arise from complex network interactions.

By virtue of the fact that dSPNs and iSPNs share largely similar morphological and physiological properties, they represent an ideal system to compare the differential neuromodulatory effects of D1 and D2 receptors on synaptic transmission and intrinsic excitability. However, despite this seeming simplicity, electrophysiological characterizations of DA's actions have been complicated by the fact that striatal interneurons also express DA receptors, as do the synaptic terminals of striatal afferents. In dorsal striatum, there are at least five distinct subtypes of GABAergic interneurons (Tepper et al., 2010) and one population of large aspiny cholinergic interneurons. Although these interneurons collectively account for only 5%–10% of all striatal neurons, they exert a powerful influence on behavior (Gittis et al., 2011; Witten et al., 2010). Striatal GABAergic interneurons can be distinguished based on the expression of neuropeptides, synthetic enzymes, and calcium binding proteins (e.g., parvalbumin [PV]-expressing fast-spiking

Table 2. Cellular Distribution of DA Receptors in the Cortex and Striatum of Rodents

	D1	D2	D3	D4	D5
Striatum					
dSPNs	+++ (>90%)	–	+ (50%)	+ (<10%)	–
iSPNs	+ (<10%)	+++ (>90%)	+ (<10%)	+ (<10%)	+ (<10%)
Cholinergic interneurons	+ (<20%)	++ (>80%)	–	–	++ (>80%)
PV^+ interneurons					+ (>70%)
NPY/SOM/NO^+ interneurons	+ (<10%)				+ (>70%)
CR^+ interneurons					+ (50%)
Cortex					
L2/3 pyramidal neurons	++ (<20%)	+ (<10%)		+	+
L5/6 pyramidal neurons	++ (20%–40%)	+ (25%)		+	+
L2–L6 interneurons	++ (30%–60%)*	+ (20%)*	+	+	+

This table reports semiquantitative expression levels of various DA receptor subtypes (+++, highest expression; +, low expression; –, mRNA not detected) and their relative cellular distribution (in parentheses) within defined cortical and striatal neuronal populations.
*For the most part, PV+ interneurons.

[FS] interneurons, neuropeptide Y [NPY]/somatostatin [SOM]/nitric oxide synthase [NOS]-coexpressing low-threshold spiking [LTS] interneurons, NPY only expressing neurogliaform, TH-expressing interneurons, and calretinin [CR]-expressing interneurons). Cholinergic interneurons mainly coexpress D2 and D5 receptors, whereas PV^+, CR^+, and NPY/SOM/NOS^+ interneurons express D5 receptors (Rivera et al., 2002; Yan and Surmeier, 1997). It is currently unknown whether NPY-neurogliaform and TH^+ interneurons express DA receptors. In addition, D2 receptors adorn the presynaptic terminals of DA afferents (Sesack et al., 1994), glutamatergic cortical and thalamic afferents that innervate SPNs and interneurons (Wang and Pickel, 2002), as well as GABAergic pallidostriatal neurons (Hoover and Marshall, 2004), which mostly terminate on PV^+ interneurons and SPNs (Mallet et al., 2012). D1 receptors have also been observed in a small number of presynaptic glutamatergic terminals in striatum (Dumartin et al., 2007). Lastly, SPNs provide lateral inhibition onto each other through recurrent axon collaterals that contain D1 or D2 receptors, depending on SPN subtype (Guzmán et al., 2003; Taverna et al., 2005; Tecuapetla et al., 2009). Thus, DA probably initiates a complex cascade of modulatory events in striatum that has the potential to vary dynamically depending on the recruitment of distinct striatal circuits.

In cerebral cortex, the cellular distribution of DA receptors is not as well delineated. The distribution and density of mesocortical DA fibers and cortical DA receptors varies between species, as well as between and within cortical areas in a given species (Bentivoglio and Morelli, 2005), limiting the ability to extract general DA signaling principles. Most studies have focused on PFC, which is the principal cortical recipient of DA afferents. During the past two decades, a large number of histological studies have confirmed that D1 receptors are the most widespread and strongly expressed DA receptors in PFC. D1 and D2 receptors distribute to both pyramidal neurons and interneurons throughout layers (L) 2 to 6, but most prominently in deep cortical layers (Bentivoglio and Morelli, 2005; Santana et al., 2009), where DA innervation is densest. In PFC pyramidal neurons, D1 receptor mRNA is expressed in approximately 20% of layer L2/3 and L5 and in 40% of L6 pyramidal cells (Table 2). By contrast, D2 receptor mRNA is only sparsely detected in superficial layer pyramidal neurons (5% in L2/3) and in 25% and 13% of L5 and L6 pyramidal cells, respectively (Santana et al., 2009). The cellular distribution of D5 receptors in pyramidal neurons overlaps with that of D1 receptors (Bergson et al., 1995), and D3 and D4 receptors mostly distribute to GABAergic interneurons (Khan et al., 1998). Therefore, unlike striatum, DA receptors in PFC may only be expressed in a fraction of projection neurons, indicating that a considerable number of pyramidal cells may not be subject to direct modulation by DA. Moreover, DA receptor expression in PFC pyramidal neurons does not delineate a functionally homogeneous group of cells, as only a small proportion of corticostriatal (6%–11%), corticothalamic (~25%), and corticocortical (4%–10%) neurons expressed D1 or D2 receptors (Gaspar et al., 1995).

Although the total number of DA receptor-expressing pyramidal neurons exceeds that of interneurons, DA receptors are proportionally more widespread and homogeneously expressed within local interneuron populations. D1 receptor mRNA is present in 30%–60% of all GABA-containing cortical interneurons across cortical layers in rat (Le Moine and Gaspar, 1998; Santana et al., 2009). The vast majority of these cells are PV^+ FS interneurons and calbindin (CB)-expressing LTS interneurons but only rarely CR^+ interneurons; it is estimated that up to 60% of PV^+, 25% of CB^+, and <10% of CR^+ interneurons express D1 receptors (Le Moine and Gaspar, 1998). The fraction of interneurons expressing D1-like receptors may be larger, as D5 receptors complement the expression pattern of D1 receptors, labeling mostly CR^+ interneurons, and less so PV^+ interneurons (Glausier et al., 2009). By contrast, D2 receptors distribute to a comparatively smaller fraction of cortical GABAergic interneurons: only 5%–17% of interneurons contain D2 receptor mRNA (Santana et al., 2009), the majority of which consist of PV^+ interneurons (Le Moine and Gaspar, 1998). Although D3 and D4 receptors may complement the expression of D2 receptors in cortical interneurons, their overall distribution

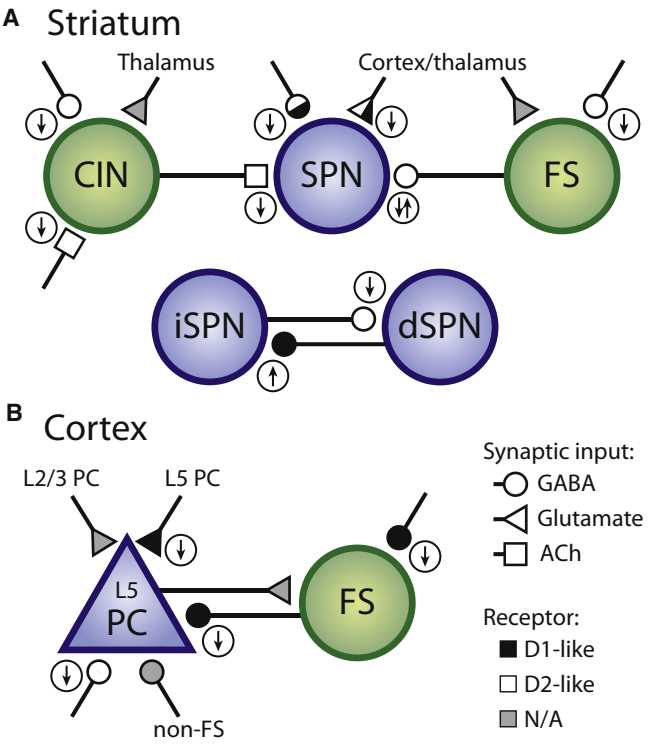

Figure 3. DA Modulation of Neurotransmitter Release
Summary of modulatory effects of DA on transmitter release (small circled arrows) in striatum (A) and cortex (B). Principal cells are depicted in blue and interneurons in green. Glutamatergic, GABAergic, and cholinergic synaptic inputs are represented as triangles, circles, and squares shaded to reflect modulation by D1-class (black) or D2-class (white) receptors. Lack of presynaptic modulation by DA is shown in gray. The identity of the presynaptic cell (inferred or deducted from paired recordings) is indicated where possible. Note that some modulatory changes only apply to striatal subdivisions (dorsal versus ventral) and that inconsistencies exist (e.g., DA modulation of GABAergic inputs onto L5 PCs). CIN, cholinergic interneuron; PC, pyramidal cell.

is limited (Khan et al., 1998), indicating that D2-like receptors are unlikely to distribute to a large proportion of GABAergic interneurons.

Transgenic mice have the potential to help identify cortical cells with transcriptionally active DA receptor genes. However, currently available transgenic lines for D1 and D2 receptors were selected based on the fidelity of transgene expression in striatal neurons (Valjent et al., 2009). Comparatively little is known in cortex regarding the penetrance and specificity of these transgenes in D1 and D2 receptor-expressing neurons. A recent study by Zhang et al. (2010) determined that *Drd2*-EGFP/*Drd1a*-tdTomato BAC transgenic mice express EGFP in over 90% of PFC pyramidal neurons and tdTomato in 16%–25% of pyramidal cells, most of which coexpress EGFP, without any region or layer-specific differences. This distribution stands in stark contrast to that described previously (Bentivoglio and Morelli, 2005). In another recent study (Gee et al., 2012), PFC pyramidal neurons identified in *Drd2*-EGFP and *Drd2*-Cre BAC transgenic mice were found to project to thalamus but not contralateral cortex, unlike previous descriptions using in situ hybridization (Gaspar et al., 1995). These discrepancies probably speak to the weaknesses of both histological and transgenic approaches. BAC transgenes are generated by nonspecific integration into the target genome and are not immune to positional effects, requiring phenotypic characterization of several transgenic lines before identifying the ones that most closely recapitulate endogenous gene expression patterns. Moreover, transgenic reporter and effector proteins are not subject to the same posttranscriptional and homeostatic regulatory mechanisms that control GPCR expression and may therefore highlight cells that do not functionally detect DA under normal conditions. Conversely, low-abundance GPCR transcripts may be functionally relevant but below the detection limit of conventional histological methods. Therefore, more functional studies like the one recently performed on L5 PFC pyramidal neurons in *Drd1a*-TdTomato mice (Seong and Carter, 2012) are needed to determine whether BAC transgene expression in brain areas other than striatum accurately identifies neurons that are directly modulated by DA.

DA Modulation of Neurotransmitter Release

One of the many ways neuromodulators influence synaptic transmission is by regulating release of neurotransmitters. Neuromodulators can initiate changes in release probability ($P_{release}$) either by activating presynaptic receptors or by eliciting the liberation of retrograde signaling molecules from the postsynaptic membrane. Thus, modulation of $P_{release}$ by DA cannot simply be inferred based on presynaptic localization of DA receptors, nor can it be excluded in their absence. For the purposes of this Review, we focus on electrophysiological studies in acute brain slices that clearly identify a presynaptic modulatory effect of DA either through analysis of tetrodotoxin (TTX)-resistant "miniature" excitatory or inhibitory postsynaptic currents (mEPSCs or mIPSCs), paired-pulse ratios, or evoked excitatory or inhibitory postsynaptic currents (EPSCs or IPSCs) when postsynaptic changes in neurotransmitter receptor composition have been excluded.

DA acting through both D1 and D2 receptor families has been implicated in heterosynaptic regulation of $P_{release}$ at glutamatergic, GABAergic, and cholinergic terminals (Figure 3). Specifically, D2-like receptor activation decreases release of glutamate onto SPNs in dorsal and ventral striatum (Bamford et al., 2004; Higley and Sabatini, 2010; Salgado et al., 2005; Wang et al., 2012). D2-like receptors also decrease $P_{release}$ of GABA onto PFC pyramidal neurons (Chiu et al., 2010; Seamans et al., 2001b; Xu and Yao, 2010), SPNs (Delgado et al., 2000; Guzmán et al., 2003; Kohnomi et al., 2012; Taverna et al., 2005; Tecuapetla et al., 2009), and striatal interneurons (Bracci et al., 2002; Centonze et al., 2003; Momiyama and Koga, 2001; Pisani et al., 2000). In addition, D2-like receptors depress release of acetylcholine (Ach) onto striatal cholinergic interneurons (Pisani et al., 2000). D1-like receptor stimulation decreases release of glutamate onto L5 pyramidal cells in PFC (Gao et al., 2001; Gao and Goldman-Rakic, 2003; Gonzalez-Islas and Hablitz, 2003; Seamans et al., 2001a) and SPNs in ventral striatum (Harvey and Lacey, 1997; Nicola and Malenka, 1997; Pennartz et al., 1992; Wang et al., 2012) but not dorsal striatum (Nicola and Malenka, 1998). Moreover, DA-mediated activation of

D1-like receptors reduces GABA release onto cortical FS interneurons (Towers and Hestrin, 2008), L2–L5 PFC pyramidal neurons (Gao et al., 2003; Gonzalez-Islas and Hablitz, 2001), and SPNs in ventral striatum only (Nicola and Malenka, 1997, 1998; Pennartz et al., 1992; Taverna et al., 2005). Thus, at synapses responsive to DA modulation, DA typically acts to decrease $P_{release}$.

There are, however, some notable exceptions to this simple view. DA and D1-like receptor agonists enhance GABA release from dSPN axon collaterals (Guzmán et al., 2003). Such D1-like receptor-induced facilitation of transmitter release is consistent with the previously reported presynaptic enhancement of neurotransmission by cAMP and PKA at hippocampal and cerebellar synapses (Chen and Regehr, 1997; Trudeau et al., 1996). In addition, the D2-like receptor agonist quinpirole was reported to increase GABA release in a third of synaptic connections formed by FS interneurons onto SPNs in nucleus accumbens and to decrease it in another third (Kohnomi et al., 2012). The variable or inconsistent nature of some of these observations may arise from cell type or synaptic heterogeneity or from the recruitment of other neuromodulatory systems that in turn influence release probability. In cortex, DA differentially influences GABAergic transmission from FS and non-FS interneurons onto pyramidal neurons: it depresses GABA release from FS interneurons and potentiates inhibitory postsynaptic potentials initiated by non-FS cells without affecting electrophysiological measures of $P_{release}$ (Gao et al., 2003). In striatum, anatomical studies indicate that presynaptic D1 and D2 receptors are only expressed in a small fraction of glutamatergic synapses (Dumartin et al., 2007; Wang and Pickel, 2002), in agreement with reports of sparse DA receptor expression in a subset of striatum-projecting L5 pyramidal neurons (Gaspar et al., 1995). This observation is corroborated by functional imaging studies of vesicular release from corticostriatal afferents, in which DA modulation is limited to only a small number of terminals (Bamford et al., 2004; Wang et al., 2012). Moreover, DA modulates the activity of cholinergic interneurons (Aosaki et al., 1998; Pisani et al., 2000) and can promote the postsynaptic liberation of adenosine and endocannabinoids from SPNs, which independently influence transmitter exocytosis through the activation of presynaptic GPCRs (Harvey and Lacey, 1997; Oldenburg and Ding, 2011; Wang et al., 2012).

Molecular Substrates of Presynaptic DA Modulation

The molecular mechanisms of DA's action on presynaptic terminals remain poorly understood due to technical difficulties associated with probing presynaptic intracellular signal cascades. D1- and D2-like receptor agonists inhibit somatic $Ca_V2.1$ (P/Q-type) and $Ca_V2.2$ channels (Salgado et al., 2005; Surmeier et al., 1995; Yan et al., 1997), which are primarily responsible for initiating neurotransmission in the CNS. These Ca^{2+} channels therefore constitute a likely substrate for the presynaptic modulatory effect of DA. Indeed, inhibition of $Ca_V2.2$ underlies the D2 receptor-induced reduction of GABA release onto striatal cholinergic interneurons (Momiyama and Koga, 2001; Pisani et al., 2000), and the D2 receptor-evoked depression of GABA release from SPN axon collaterals depends on modulation of $Ca_V2.1$ or $Ca_V2.2$ depending on age (Salgado et al., 2005). However, DA's effects on neurotransmitter release are not exclusively mediated through presynaptic modulation of Ca^{2+} channels; in ventral striatum, DA acting on D1-like receptors depresses excitatory transmission independently of presynaptic Ca^{2+} influx (Nicola and Malenka, 1997).

Pre- and Postsynaptic Regulation of Transmitter Release by DA

While there are good reasons to believe that DA modulates transmitter release by directly activating presynaptic DA receptors, experimental evidence formally excluding the involvement of postsynaptic receptors is rare, especially at synapses in which DA receptors are expressed both pre- and postsynaptically. Using paired recordings from synaptically connected SPNs, Tecuapetla et al. (2009) showed that DA acting on D2 but not D1 receptors depresses GABA release from iSPNs (expressing D2 receptors) onto dSPNs (expressing D1 receptors), providing compelling evidence for a direct presynaptic locus of action. In striatum, activation of D2 receptors diminishes presynaptic release of glutamate from corticostriatal afferents (Bamford et al., 2004; Higley and Sabatini, 2010; Salgado et al., 2005; Wang et al., 2012). Although commonly attributed to activation of presynaptic D2 receptors, DA and D2 receptor agonists have small (Wang et al., 2012) or negligible effects on mEPSCs (André et al., 2010; Nicola and Malenka, 1998), the reduction in evoked glutamate release scales with afferent stimulation frequency (Bamford et al., 2004; Yin and Lovinger, 2006) and is prevented by postsynaptic Ca^{2+} buffering as well as pharmacological and genetic blockade of metabotropic glutamate and endocannabinoid receptors (Tozzi et al., 2011; Wang et al., 2012; Yin and Lovinger, 2006). While these studies do not exclude a role for presynaptic D2 receptors, they suggest that under conditions of elevated synaptic activity, DA and glutamate interact postsynaptically to decrease synaptic drive through the synthesis of endocannabinoid retrograde messengers. A similar inhibitory feedback pathway relying on postsynaptic release of adenosine has been proposed downstream of D1-like and NMDA receptors in ventral striatum (Harvey and Lacey, 1997; Wang et al., 2012), though this has not been universally observed (Nicola and Malenka, 1997).

Using optical imaging of exocytic events and electrophysiological recordings from EGFP-labeled dSPNs and iSPNs in BAC transgenic mice, Wang et al. (2012) recently dissected the presumed pre- and postsynaptic effects of D1 and D2 receptors on glutamate release from corticoaccumbal afferents. Under conditions of minimal synaptic activity (i.e., in TTX), their studies revealed slight presynaptic excitatory and inhibitory effects of D1- and D2-like receptor agonists on glutamate release, respectively. Under conditions of moderate to high corticoaccumbal activity (spontaneous and evoked EPSCs), stimulation of D1- and D2-like receptors both evoked a more pronounced decrease in glutamate release that originated postsynaptically and occluded presynaptic contributions. The D1 receptor-mediated downregulation of glutamate release required AMPA and NMDA receptors and resulted from activation of presynaptic adenosine A1 receptors after postsynaptic liberation of adenosine. By contrast, D2 receptors interacted postsynaptically with metabotropic glutamate receptors to stimulate endocannabinoid production. This same pathway is known to be required for long-term depression of glutamate release onto iSPNs in

dorsal striatum (Kreitzer and Malenka, 2007). The effects of DA on transmitter release are therefore complex, context-dependent, and not limited to the action of presynaptically localized DA receptors. The observation that other neuromodulatory systems can independently be engaged by DA further complicates analyses of the mechanisms employed by endogenous DA to modulate transmitter release.

DA Modulation of Postsynaptic Neurotransmitter Receptors

Postsynaptic neurotransmitter receptors are likely targets for the neuromodulatory effects of DA. During the past two decades, in vitro studies demonstrating rapid DA receptor-mediated modulation of ionotropic glutamate and GABA receptor function and trafficking have abounded, leaving little doubt as to the ability of DA to regulate them. However, the nature and consequences of these interactions are complex and controversial, owing to differences in DA's actions across brain areas, cell types, and experimental conditions.

DA Modulation of NMDA Receptors

It is generally accepted that DA acting on D1-like receptors potentiates currents, membrane depolarization, and cytosolic Ca^{2+} levels evoked by ionotophoretic or bath application of NMDA receptor agonists in acutely dissociated neurons (André et al., 2010; Chen et al., 2004; Flores-Hernández et al., 2002; Jocoy et al., 2011) or slice preparations from PFC and striatum (Cepeda et al., 1998; Levine et al., 1996a; Tseng and O'Donnell, 2004; Zheng et al., 1999). Neuronal glutamate receptors distribute to both synaptic and nonsynaptic membranes, but the receptors that populate these membrane domains are distinct with respect to subunit composition, trafficking regulatory mechanisms and function (Gladding and Raymond, 2011; Shepherd and Huganir, 2007). By virtue of the fact that exogenous application of agonists preferentially targets somatic and extrasynaptic receptors, these studies collectively indicate that D1 receptor stimulation can potentiate extrasynaptic NMDA receptor function. Several mechanisms have been proposed to underlie this potentiation, most of which implicate NMDA receptor phosphorylation and membrane trafficking, although the intracellular effectors involved are a matter of debate (Braithwaite et al., 2006; Flores-Hernández et al., 2002; Gao and Wolf, 2008; Hallett et al., 2006). Importantly, many of the studies reporting enhancements of NMDA receptor function in slices either measured membrane potential or recorded membrane currents under conditions that do not minimize errors associated with the inability to adequately voltage clamp distal dendrites. This is particularly problematic when investigating functional contributions of NMDA receptors, for which gating is voltage dependent. Indeed, DA modulation of dendritic voltage-gated Ca^{2+} channels has been shown to contribute indirectly to NMDA receptor potentiation, possibly by helping relieve Mg^{2+} block (Cepeda et al., 1998).

It has been comparatively more difficult to establish whether D1 receptors also affect synaptically localized NMDA receptors, as synaptic stimulation experiments require conditions that additionally exclude contributions from DA's actions on local interneurons and presynaptic release. Nevertheless, activation of D1-like receptors potentiates miniature and electrically evoked NMDA receptor EPSCs through postsynaptic signaling involving PKA and protein kinase C (PKC) in PFC (Gonzalez-Islas and Hablitz, 2003; Li et al., 2010; Seamans et al., 2001a). In striatum, synaptically evoked NMDA receptor EPSCs are potentiated by D1-like receptor stimulation in some studies (Jocoy et al., 2011; Levine et al., 1996b) but remain unaffected by DA in others (Beurrier and Malenka, 2002; Nicola and Malenka, 1998).

Several studies have also presented evidence that currents evoked by exogenous NMDA application can be attenuated by stimulation of D1-like (Castro et al., 1999; Lee et al., 2002; Lin et al., 2003; Tong and Gibb, 2008) or D2-like (André et al., 2010; Flores-Hernández et al., 2002; Jocoy et al., 2011; Kotecha et al., 2002; Li et al., 2009; Liu et al., 2006; Wang et al., 2003; Zheng et al., 1999) receptors. One concern associated with some electrophysiological experiments showing depressing effects of D1-like receptor agonists is that they may have been confounded by direct, nonspecific effects of these agents on NMDA receptors; high concentrations of DA or SKF38393, a D1-like receptor agonist, promote rapid, reversible, and voltage-dependent blockade of NMDA receptor currents in cultured hippocampal, striatal, and thalamic neurons (Castro et al., 1999; Kotecha et al., 2002). With few exceptions (Wang et al., 2003), most reports of decreased NMDA receptor function by DA point to mechanisms independent of G protein signaling, resulting either from direct protein-protein interactions between NMDA receptors and D1 and D2 receptors (Lee et al., 2002; Liu et al., 2006) or from the activation of intracellular tyrosine kinases (Kotecha et al., 2002; Li et al., 2009; Tong and Gibb, 2008). However, few studies have revealed diminished function of synaptic NMDA receptors after DA application. In striatum, postsynaptic NMDA receptor currents evoked by electrical stimulation or two-photon glutamate uncaging are unperturbed by D2 receptor agonists (Higley and Sabatini, 2010; Levine et al., 1996b). Interestingly, a PKA-dependent decrease in Ca^{2+} influx through NMDA receptors was observed in iSPNs upon D2 receptor activation, indicating that while D2 receptors do not directly modulate the depolarizing currents contributed by NMDA receptors, they can limit the activation of Ca^{2+}-dependent pathways downstream of NMDA receptors (Higley and Sabatini, 2010), an effect likely due to the regulation of NMDA receptor Ca^{2+} permeability by PKA phosphorylation of the channel (Chalifoux and Carter, 2010; Skeberdis et al., 2006). Likewise, the D2-like receptor agonist quinpirole did not significantly affect NMDA receptor EPSCs in L2/3 PFC pyramidal neurons (Gonzalez-Islas and Hablitz, 2003). By contrast, selective pharmacological activation of D4 receptors suppresses synaptically evoked NMDA receptor EPSCs in cortex through PKA-dependent NMDA receptor internalization (Wang et al., 2003). Thus, DA has the capacity to bidirectionally modulate synaptic NMDA receptors through D1- and D2-class receptors, but the susceptibility of individual synapses across brain areas and the intracellular pathways recruited vary greatly.

DA Modulation of AMPA Receptors

As for NMDA receptors, there is a large body of evidence showing that DA bidirectionally modulates the function and membrane trafficking of AMPA receptors. Biochemical studies have demonstrated that D1 receptor agonists and D2 receptor

antagonists promote PKA-dependent phosphorylation of AMPA receptors, whereas D2 receptor agonists diminish it by favoring PP1 activity (Håkansson et al., 2006; Snyder et al., 2000). PKA phosphorylation increases AMPA receptor peak open probability and extrasynaptic membrane expression (Shepherd and Huganir, 2007). Consistent with this, D1 receptors acting through PKA increase surface AMPA receptors in neuronal cultures prepared from nucleus accumbens (Sun et al., 2008) and PFC (Sun et al., 2005), whereas D2 receptor agonists decrease surface AMPA receptor levels (Sun et al., 2005). Moreover, membrane currents and potentials evoked by local application of AMPA receptor agonists in striatal and cortical neurons are depressed by D2 receptor stimulation (André et al., 2010; Hernández-Echeagaray et al., 2004; Levine et al., 1996a) and are either unaffected (Calabresi et al., 1995; Seamans et al., 2001a; Zheng et al., 1999) or potentiated (André et al., 2010; Levine et al., 1996a; Lin et al., 2003; Yan et al., 1999) by D1 receptor agonists. Importantly, DA receptor signaling is not sufficient to recruit AMPA receptors to postsynaptic terminals (Sun et al., 2005, 2008), probably because AMPA receptor surface expression and synaptic targeting by lateral diffusion constitute two independent and separately regulated trafficking steps (Shepherd and Huganir, 2007). Thus, modifications of AMPA receptor surface expression at extrasynaptic membranes by DA may not necessarily extend to synaptic sites. Indeed, very few studies have reported increased or decreased postsynaptic AMPA receptor currents in response stimulation of D1- or D2-class receptors, respectively (Gonzalez-Islas and Hablitz, 2003; Levine et al., 1996b). In most cases, postsynaptic AMPA receptor function was unaltered by DA or D1 receptor agonists in PFC (Gao et al., 2001; Gao and Goldman-Rakic, 2003; Seamans et al., 2001a; Zhou and Hablitz, 1999) and striatum (Bracci et al., 2002; Levine et al., 1996b; Nicola and Malenka, 1997, 1998). Likewise, D2 receptor agonists do not significantly alter synaptically evoked AMPA receptor EPSCs in cortex or striatum using electrical stimulation (Gonzalez-Islas and Hablitz, 2003; Pisani et al., 2000), two-photon glutamate uncaging (Higley and Sabatini, 2010), or paired recordings (Gao et al., 2001). Together, these studies indicate that activation of DA receptors is not sufficient to modify the number or conductance of synaptic AMPA receptors. Instead, DA might need to work in concert with other signaling molecules to promote synaptic AMPA receptor incorporation.

DA Modulation of $GABA_A$ Receptors

Despite widespread reports of $GABA_A$ receptor phosphorylation and current modulation by PKA and PKC (reviewed in Kittler and Moss, 2003), comparatively few studies have observed DA modulation of $GABA_A$ receptor function. In deep layer PFC pyramidal neurons, DA reduces postsynaptic $GABA_A$ receptor currents at synaptic and extrasynaptic sites through D4 receptor-mediated downregulation of surface receptors (Graziane et al., 2009; Seamans et al., 2001b; Wang et al., 2002). In striatum, D1 and D5 receptors respectively decrease and enhance $GABA_A$ receptor currents evoked by local application of GABA on the somata of acutely dissociated SPNs (Flores-Hernandez et al., 2000) and cholinergic interneurons (Yan and Surmeier, 1997). Aside from these, most studies investigating DA modulation of synaptic GABAergic transmission either failed to detect changes in postsynaptic inhibitory currents or potentials or assigned them to presynaptic modifications in GABA release or postsynaptic membrane properties in PFC (Gao et al., 2003; Gonzalez-Islas and Hablitz, 2001; Gulledge and Jaffe, 2001; Kröner et al., 2007; Towers and Hestrin, 2008; Zhou and Hablitz, 1999) and striatum (Bracci et al., 2002; Centonze et al., 2003; Delgado et al., 2000; Kohnomi et al., 2012; Nicola and Malenka, 1997, 1998; Pisani et al., 2000; Taverna et al., 2005; Tecuapetla et al., 2009).

DA Modulation of Postsynaptic Excitability and Synaptic Integration

Striatal Projection Neurons

During the past two and a half decades, evidence has accumulated that DA exerts a powerful influence on SPN intrinsic excitability. Early electrophysiological studies in slice indicated that DA can both enhance and reduce SPN spiking evoked by intracellular current injection (reviewed in Nicola et al., 2000). Not surprisingly, the polarity and magnitude of these alterations depended in large part on the type of DA receptor activated. However, the picture that arose initially is opposite of the one that constitutes our current understanding of DA's effects on intrinsic excitability. It was determined that activation of D1 receptors diminishes SPN excitability, whereas D2 receptor signaling promotes excitation (Nicola et al., 2000). The advent of improved methodologies to identify and record from dSPNs and iSPNs in situ, combined with a greater understanding of the contribution of individual ionic conductances to the overall behavior of SPNs, have reversed this view to the one originally advanced by anatomists and pathologists some 20 years ago, namely that DA favors the activation of dSPNs and reduces the excitability of iSPNs (Gerfen and Surmeier, 2011).

Under basal conditions, dSPNs and iSPNs exhibit small but significant differences in dendritic morphology and membrane properties that translate into greater excitability of iSPNs over dSPNs. Although the cell types do not differ with regards to input resistance and resting membrane potential, the action potential discharge rate of iSPNs is twice that of dSPNs in response to somatic current injection (Gertler et al., 2008; Kreitzer and Malenka, 2007). Morphologically, the dendrites of dSPNs and iSPNs are studded with a similarly high density of spines, but iSPNs possess more primary dendrites compared to dSPNs, resulting in a functionally greater number of excitatory synaptic contacts onto these cells (Day et al., 2006; Gertler et al., 2008; Kreitzer and Malenka, 2007). The dendrites of iSPNs are also more excitable than those of dSPNs (Day et al., 2008). While some of the differential effects of DA on SPN excitability admittedly originate from circuit-level interactions between striatal cells, DA directly influences SPN excitability by modulating ion channels, several of which have been defined. Modulation of any of these channels has the potential to significantly alter SPN excitability, although the relative impact of these changes critically depends on membrane potential, as the array of voltage-gated ion channels engaged at different potentials varies considerably.

DA does not significantly alter SPN excitability by modulating leak conductances as DA receptor agonists exert little or no influence on SPN resting membrane potential or input

resistance. Instead, most of DA's reported effects on intrinsic excitability and synaptic integration involve PKA-dependent modulation of voltage-gated K^+, Na^+, and Ca^{2+} channels. In both dorsal and ventral striatum, studies of pharmacologically isolated currents have revealed that D1 receptors facilitate inward rectifier K^+ channels belonging to the $K_{ir}2$ family (Pacheco-Cano et al., 1996; Uchimura and North, 1990) and decrease slowly inactivating A-type K^+ currents attributed to K_V4 channels (Kitai and Surmeier, 1993). These changes are predicted to impede synaptically driven transitions from the hyperpolarized resting potential (so-called down state) to a more depolarized, sustained potential near spike threshold (up state), while enhancing action potential firing during up states (Wickens and Arbuthnott, 2005). In addition, D1 receptor stimulation increases Ca_V1 currents (Hernández-López et al., 1997; Song and Surmeier, 1996; Surmeier et al., 1995), which potentiate up state transitions, excitatory synaptic potentials, and action potential discharge (Plotkin et al., 2011; Vergara et al., 2003), and suppresses currents carried by $Ca_V2.1$ and $Ca_V2.2$ (Surmeier et al., 1995; Zhang et al., 2002), which limit repetitive action potential firing by activating small (SK)- and large (BK)-conductance Ca^{2+}-dependent K^+ channels (Hopf et al., 2010; Vilchis et al., 2000). Interestingly, activation of D1 receptors was recently shown to prolong "up state-like" potentials evoked by repetitive glutamate uncaging on distal SPN dendrites (Plotkin et al., 2011). Generation of these regenerative plateau potentials required NMDA receptors and low-threshold Ca_V3 channels, which are enriched in distal dendrites and spines (Carter and Sabatini, 2004; Carter et al., 2007; Day et al., 2006), but it is currently unclear whether the D1 receptor-evoked enhancement is mediated by direct modulation of NMDA receptors or dendritic K^+ and Ca^{2+} conductances or both. Thus, through its actions on voltage-gated K^+ and Ca^{2+} channels, D1 receptors promote synaptic integration and spike discharge during up states while increasing the threshold for upward transitions, effectively acting to enhance contrast between up and down states. However, this relatively simple and consistent view of DA's action on dSPNs is complicated by the reported effects on voltage-gated Na^+ currents, which are reduced in amplitude by DA and D1-like receptor agonists (Cepeda et al., 1995; Schiffmann et al., 1995; Surmeier et al., 1992; Zhang et al., 1998). This observation is largely responsible for the initial conclusion that D1 receptors exert a net inhibitory action on SPN excitability (Nicola et al., 2000). The apparently conflicting actions of DA on various ionic conductances reflect some of the difficulties associated with extrapolating overall neuromodulatory effects of DA from changes in isolated conductances. Given the importance of subthreshold membrane potential fluctuations to SPN function and the inability of somatic current injection protocols to engage distal dendritic conductances (Day et al., 2008) and to evoke state transitions in acute slices (Wilson, 2004), analyses of spike discharge modulation upon somatic depolarization may not adequately capture DA's influence on synaptic integration and intrinsic excitability. Nevertheless, although the spike-promoting effects of D1 receptors on K^+ and Ca^{2+} channels may be moderated by reduced Na^+ channel availability, most of the evidence accrued to date favors models in which D1 receptors promote dSPN intrinsic excitability (Gerfen and Surmeier, 2011; Wickens and Arbuthnott, 2005).

The reported effects of D2 receptor activation on isolated ionic conductances and up state potentials in SPNs largely oppose those of D1 receptors. Through their inhibitory action on PKA, D2 receptors suppress currents attributable to $K_{ir}2$ channels but enhance depolarization-activated and ATP-sensitive K^+ channels (Greif et al., 1995; Perez et al., 2006; Sun et al., 2000; Surmeier and Kitai, 1993), indicating that D2 receptor activation may facilitate up state transitions but stunt their duration and the depolarization achieved. D2 receptors further limit somatic excitability by decreasing Ca^{2+} influx through somatic Ca_V1 channels (Hernandez-Lopez et al., 2000; Salgado et al., 2005). In dendritic shafts and spines, D2 receptor stimulation mainly decreases Ca^{2+} currents carried by $Ca_V2.3$, which gate dendritic SK channels (Higley and Sabatini, 2010), although synaptic potentials evoked by glutamate uncaging remain unaffected by quinpirole (Higley and Sabatini, 2010), perhaps due to concurrent potentiation of dendritic K_V4 channels (Day et al., 2008). Moreover, D2 receptors shorten regenerative plateau potentials evoked by glutamate uncaging on the distal dendrites of iSPNs (Plotkin et al., 2011), possibly by decreasing Ca^{2+} influx through NMDA receptors or voltage-gated Ca^{2+} channels (Day et al., 2008; Higley and Sabatini, 2010). Unlike D1 receptors, the effects of D2 receptors on Na^+ channels are inconsistent: they were found to enhance, suppress, or have no effects in subpopulations of SPNs in ventral and dorsal striatum (Hu et al., 2005; Surmeier et al., 1992; Zhang et al., 1998). Together, this body of work depicts a relatively coherent model of modulation by D2 receptors, in which DA suppresses iSPN synaptic integration and spiking output by diminishing the potential and duration of up states and by limiting the spread and depolarization of synaptic potentials.

Striatal Interneurons

Among the six populations of striatal interneurons characterized to date, the modulatory actions of DA have been investigated only in cholinergic, FS, and LTS interneurons. The latter possess wide axonal arbors that innervate a large number of SPNs, and DA depolarizes these cells by activating D5 receptors (Centonze et al., 2002; Tepper et al., 2010). FS interneurons integrate glutamatergic inputs from cortex and establish strong GABAergic synapses on the somata of surrounding SPNs, forming a potent feedforward inhibitory circuit that preferentially targets dSPNs over iSPNs (Tepper et al., 2010). FS interneurons also receive a GABAergic projection from GPe (Mallet et al., 2012). Studies in striatal slices have revealed that DA directly and dose dependently depolarizes the membrane of FS interneurons via D5 receptors, possibly by promoting the closure of a K^+ conductance (Bracci et al., 2002; Centonze et al., 2003). In combination with the D2 receptor-mediated selective decrease of GABAergic (but not glutamatergic) inputs onto these cells, DA is believed to limit the influence of GPe afferents and local interneurons, while promoting corticostriatal feedforward inhibition of SPNs.

The DA and cholinergic systems dynamically and reciprocally influence each other in numerous ways, many of which continue to be unraveled (Cragg, 2006; Threlfell et al., 2012). Cholinergic interneurons are tonically active in vivo and respond to

behaviorally salient stimuli with a brief pause in activity that can be preceded or followed by a transient increase in firing (Cragg, 2006). Experiments in vivo have suggested that this pause is dependent on DA (Aosaki et al., 1994), and several in vitro studies have since revealed potential cellular and molecular substrates for this interaction (reviewed in Goldberg and Reynolds, 2011). Cholinergic interneurons express D2 and D5 receptors (Rivera et al., 2002; Yan and Surmeier, 1997) and pharmacological studies have reported both excitatory and inhibitory modulatory changes by DA. In slice, DA and D5 receptor stimulation depolarize cholinergic interneurons and promote spiking through cAMP-dependent suppression of a K^+ conductance and opening of an undefined cation channel (Aosaki et al., 1998; Centonze et al., 2003; Pisani et al., 2000). By contrast, application of DA together with a D1-like receptor antagonist reveals a hyperpolarizing current (Aosaki et al., 1998), indicating that D5 and D2 receptors both influence the membrane potential of cholinergic interneurons. In agreement with this, direct activation of D2 receptors evokes a dose-dependent depolarization and action potential firing (Maurice et al., 2004; Tozzi et al., 2011; but see Pisani et al., 2000, 2006). The effect of D2 receptors has been proposed to be mediated by reductions in a persistent Na^+ current and a hyperpolarization-activated, cyclic-nucleotide-gated (HCN) cation current that controls pacemaking (Deng et al., 2007; Maurice et al., 2004). In addition, D2 receptor stimulation reduces $Ca_V2.2$ currents in dissociated cholinergic interneurons (Pisani et al., 2006; Yan et al., 1997) and in striatal slices (Ding et al., 2006), which may underlie the D2 receptor-mediated depression of presynaptic Ach release (Pisani et al., 2000). Because $Ca_V2.2$ channels are functionally coupled to somatodendritic SK channels, which contribute to spike afterhyperpolarizing potentials (Goldberg and Wilson, 2005), downregulation of $Ca_V2.2$ by D2 receptors is expected to disrupt autonomous pacemaking and promote a transition to burst firing (Goldberg and Wilson, 2005). Endogenous activation of D5 receptors using electrical stimulation quickly and transiently prolongs interspike intervals by augmenting spike afterhyperpolarization (Bennett and Wilson, 1998), which stands in contrast to the increase in firing observed with bath application of DA or D1-like receptor agonists (Aosaki et al., 1998). Thus, although the net effect of DA on the intrinsic excitability of cholinergic interneurons appears to be excitatory (Aosaki et al., 1998; Centonze et al., 2003; Pisani et al., 2000), signaling through D2 and D5 receptors exert opposite effects and the specific conductances that underlie DA's actions remain to be defined. Given that DA presynaptically inhibits GABAergic but not glutamatergic inputs onto cholinergic interneurons (Momiyama and Koga, 2001; Pisani et al., 2000) and that excitatory inputs precisely regulate spike timing in these cells (Bennett and Wilson, 1998), DA may promote the synchronous activation of cholinergic interneurons, engendering a complex cascade of signaling events resulting in further DA release and inhibition of SPN output (English et al., 2012; Threlfell et al., 2012; Witten et al., 2010).

Prefrontal Cortex Pyramidal Neurons

The prefrontal cortex is the major cortical recipient of DA inputs and DA is believed to play a critical role in several cognitive processes conducted by PFC networks, including working memory, attention, and decision making. Although considerable efforts have been invested during the past several decades in elucidating the cellular mechanisms by which DA modulates PFC function, the actions of DA and the underlying receptors and signaling pathways involved remain controversial. What is clear is that DA modulates the intrinsic excitability of both pyramidal neurons and local interneurons and that DA's actions on the latter has historically confounded in vivo and in vitro investigations of its effects on the former (reviewed in Seamans and Yang, 2004). In addition, PFC is composed of several functionally distinct pyramidal and nonpyramidal cell types that receive variable dopaminergic innervation along their dendritic trees and express different levels and combinations of DA receptors across cortical layers (Wang et al., 2006). Finally, the functional implications of modulatory effects on isolated currents are often unclear due to the large number of ionic conductances that shape synaptic potentials and spike output, the dependence of these processes on membrane potential, and the complexity of the network in which these cells are embedded.

In the majority of in vitro studies in which synaptic contributions are pharmacologically excluded, DA enhances the intrinsic excitability of deep layer PFC pyramidal neurons by elevating the resting membrane potential or promoting a slow but long-lasting increase in the number of action potentials evoked by somatic depolarization (Ceci et al., 1999; Gao and Goldman-Rakic, 2003; Gulledge and Jaffe, 2001; Gulledge and Stuart, 2003; Kroener et al., 2009; Lavin and Grace, 2001; Moore et al., 2011; Penit-Soria et al., 1987; Shi et al., 1997; Wang and Goldman-Rakic, 2004; Yang and Seamans, 1996). In most cases, DA's actions are selectively abolished by D1-like receptor antagonists and mimicked by D1-like agonists (Chen et al., 2007; Gao and Goldman-Rakic, 2003; Gulledge and Jaffe, 2001; Gulledge and Stuart, 2003; Kroener et al., 2009; Lavin and Grace, 2001; Penit-Soria et al., 1987; Seong and Carter, 2012; Shi et al., 1997; Tseng and O'Donnell, 2004; Witkowski et al., 2008; Yang and Seamans, 1996), implicating signaling through D1-class receptors. Moreover, some studies have indicated that D2-like receptors actively oppose D1 receptor-mediated excitation by directly suppressing intrinsic neuronal excitability (Gulledge and Jaffe, 1998; Tseng and O'Donnell, 2004). However, several other studies have assigned DA-induced increased excitability to D2-class receptors in deep layer pyramidal neurons (Ceci et al., 1999; Gee et al., 2012; Moore et al., 2011; Wang and Goldman-Rakic, 2004) and have reported a net inhibitory effect of D1-class receptors on spike output (Moore et al., 2011; Rotaru et al., 2007). In L2/3 PFC pyramidal neurons, DA was shown to promote (Henze et al., 2000) or leave unaffected action potential firing evoked by somatic current injection (Gonzalez-Islas and Hablitz, 2001; Zhou and Hablitz, 1999).

Regulation of several voltage-gated conductances may contribute to these diverse effects. In PFC pyramidal neurons, activation of D1 receptors reduces K^+ currents carried by inward-rectifying (Dong et al., 2004; Witkowski et al., 2008) and voltage-activated (Dong and White, 2003; Dong et al., 2004, 2005; Yang and Seamans, 1996) K^+ channels, which are respectively expected to facilitate transitions to up states and help sustain them once achieved. D1 receptor activation has been shown to increase (Gorelova and Yang, 2000; Yang and

Seamans, 1996), suppress (Geijo-Barrientos and Pastore, 1995; Gulledge and Jaffe, 2001; Rotaru et al., 2007), or exert no effect (Maurice et al., 2001) on the amplitude of persistent voltage-activated Na^+ currents. This diversity may result in part from the voltage dependence of this modulation (Gorelova and Yang, 2000). In addition, D1 receptor agonists inhibit transient voltage-sensitive Na^+ currents (Maurice et al., 2001; Peterson et al., 2006; but see Gulledge and Jaffe, 2001; Gulledge and Stuart, 2003). Some of these effects are consistent with the differential modulation of transient and persistent Na^+ currents by PKA and PKC (Chen et al., 2006; Franceschetti et al., 2000), which are both engaged by D1-like receptors in PFC neurons and together exert a net positive influence on membrane excitability (Franceschetti et al., 2000). Modulation of Na^+ channels can not only influence action potential initiation and discharge rate, but also the amplitude of synaptic potentials and their active propagation along dendrites (Rotaru et al., 2007). Electrophysiological and Ca^{2+} imaging experiments in deep layer pyramidal neurons also revealed that D1-like receptor agonists suppress dendritic Ca^{2+} influx through Ca_V1, $Ca_V2.2$, and possibly $Ca_V2.1$ via PKC or direct protein interaction (Kisilevsky et al., 2008; Yang and Seamans, 1996; Young and Yang, 2004; Zhou and Antic, 2012). However, other studies failed to detect any DA modulation of dendritic Ca^{2+} transients evoked by back-propagating action potentials (Gulledge and Stuart, 2003) or reported PKA-dependent potentiation of Ca_V1 currents evoked by subthreshold somatic current injection (Young and Yang, 2004). Thus, the reported effects of D1-like receptors on individual ionic conductances in PFC neurons are diverse and a coherent view of the modulatory changes that underlie the excitatory effects of these receptors has yet to emerge.

The ionic conductances that underlie the modulatory effects of D2 receptors in PFC pyramidal neurons have not been investigated as extensively. In instances in which D2-like receptor stimulation promotes the intrinsic excitability of subpopulations of L5 pyramidal cells, the effects have been attributed to suppression of K_{ir} channels (Dong et al., 2004) or potentiation of Ca_V1 and voltage-gated Na^+ channels (Gee et al., 2012; Moore et al., 2011; Wang and Goldman-Rakic, 2004).

Prefrontal Cortex Interneurons

One of the most consistent and striking effects of DA on PFC pyramidal cells is a selective increase in the frequency of spontaneous (TTX-sensitive), but not miniature (TTX-resistant), IPSCs and IPSPs, reflecting a net enhancement of local GABAergic interneuron spiking activity (Gulledge and Jaffe, 2001; Kröner et al., 2007; Penit-Soria et al., 1987; Seamans et al., 2001b; Zhou and Hablitz, 1999). This effect is largely attributed to PV-expressing FS basket and chandelier cells. Indeed, in vitro studies in PFC slices have repeatedly demonstrated that DA acting on D1-like receptors induces a direct membrane depolarization and increases the input resistance and excitability of the majority of FS interneurons (Gao and Goldman-Rakic, 2003; Gao et al., 2003; Gorelova et al., 2002; Kröner et al., 2007; Towers and Hestrin, 2008; Trantham-Davidson et al., 2008; Zhou and Hablitz, 1999) but exerts a variable facilitatory effect on the excitability of other non-FS interneurons (Gao et al., 2003; Gorelova et al., 2002; Kröner et al., 2007). D2 receptor agonists have occasionally been reported to further promote interneuron excitability (Tseng and O'Donnell, 2004; Wu and Hablitz, 2005). In FS interneurons, DA's actions are mediated by PKA-dependent suppression of leak, inward rectifying, and depolarization-activated K^+ channels (Gorelova et al., 2002) and amplification of depolarizing currents carried by HCN channels (Gorelova et al., 2002; Trantham-Davidson et al., 2008; Wu and Hablitz, 2005).

Early studies in which GABAergic signaling is left unperturbed had reported that DA predominantly depresses evoked and spontaneous firing of PFC pyramidal cells in vivo (reviewed in Seamans and Yang, 2004) and in vitro (Geijo-Barrientos and Pastore, 1995; Gulledge and Jaffe, 1998; Zhou and Hablitz, 1999). It is now believed that the reported inhibitory effect of DA on pyramidal neuron excitability was indirectly mediated through GABAergic FS cells, which primarily innervate the cell bodies, initial axon segments, and proximal dendritic shafts of pyramidal cells and exert a powerful influence over action potential initiation and timing. Indeed, bath application of $GABA_A$ receptor antagonists reverses the polarity of DA's influence on pyramidal neuron excitability, from inhibition to facilitation (Gulledge and Jaffe, 2001; Zhou and Hablitz, 1999), stressing the importance of excluding synaptic contributions to investigate modulation of intrinsic excitability. In addition to these changes, DA alters the release of glutamate and GABA onto pyramidal and nonpyramidal neurons differentially based on pre- and postsynaptic cell identity through D1- and D2-like receptors (Chiu et al., 2010; Gao et al., 2001, 2003; Gao and Goldman-Rakic, 2003; Gonzalez-Islas and Hablitz, 2001; Penit-Soria et al., 1987; Seamans et al., 2001b; Towers and Hestrin, 2008; Trantham-Davidson et al., 2004), revealing a rich and complex array of modulatory influences that collectively contribute to DA's important role in PFC function.

Future Directions

As described above, dozens of mechanisms have been identified through which DA receptors alter the properties of neurons and synapses. However, several important challenges remain and it is likely that many of these results will have to be revisited with newer approaches. Conclusions from studies using strong pharmacological activation of DA receptors will need to be confirmed with those employing optogenetics, in which light can be used to trigger synaptic DA release directly from dopaminergic axons. Early studies using this approach have demonstrated that midbrain DA neurons additionally release glutamate and GABA that act on ionotropic receptors in SPNs to rapidly regulate postsynaptic excitability (Stuber et al., 2010; Tecuapetla et al., 2010; N.X.T. and B.L.S., unpublished data), adding another dimension to the consequences of DA neuron firing on downstream targets. Similarly, the effects of DA in cortex will need to be reexamined in transgenic mice that allow for the study of specific subsets of DA-sensitive neurons to mitigate the experimental variability that has historically confused this field (e.g., Gee et al., 2012; Seong and Carter, 2012). These technical approaches continue to transform our understanding of DA action in the striatum, where decades of previous studies were plagued by mixing data from two classes of SPNs that express different DA receptors. Lastly, the challenge remains of trying to understand how the results of these largely reductionist studies explain the consequences of DA and DA receptor

perturbation on behavior. The hope is that knowledge from these studies, combined with data gained from more physiological methodologies, will permit the elucidation of the cellular and molecular means by which DA influences neural circuits.

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