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Dopamine release in the basal ganglia

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Abstract

Dopamine (DA) is a key transmitter in the basal ganglia, yet DA transmission does not conform to several aspects of the classic synaptic doctrine. Axonal DA release occurs through vesicular exocytosis and is action-potential and Ca^{2+} dependent. However, in addition to axonal release, DA neurons in midbrain exhibit somatodendritic release, by an incompletely understood, but apparently exocytotic mechanism. Even in striatum, axonal release sites are controversial, with evidence for DA varicosities that lack postsynaptic specialization, and largely extrasynaptic DA receptors and transporters. Moreover, DA release is often assumed to reflect a global response to a population of activities in midbrain DA neurons, whether tonic or phasic, with precise timing and specificity of action governed by other basal ganglia circuits. This view has been reinforced by anatomical evidence showing dense axonal DA arbors throughout striatum, and a lattice network formed by DA axons and glutamatergic input from cortex and thalamus. Nonetheless, localized DA transients are seen *in vivo* using voltammetric methods with high spatial and temporal resolution. Mechanistic studies using similar methods *in vitro* have revealed local regulation of DA release by other transmitters and modulators, as well as by proteins known to be disrupted in Parkinson's disease and other movement disorders. Notably, the actions of most other striatal transmitters on DA release also do not conform to the synaptic doctrine, with the absence of direct synaptic contacts for glutamate, GABA and aceylcholie (ACh) on striatal DA axons. Overall, the findings reviewed here indicate that DA signaling in the basal ganglia is sculpted by cooperation between the timing and pattern of DA input and those of local regulatory factors.

Keywords

dorsal striatum; fast-scan cyclic voltammetry; nucleus accumbens; somatodendritic; substantia nigra; ventral tegmental area

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Introduction

The transmitter dopamine (DA) is critical for movement, motivation, and cognition, as reviewed elsewhere in this issue (Carta and Bezard, 2011; Palmiter, 2011; Redgrave et al., 2011). Forebrain DA originates from midbrain DA neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) (Dahlström and Fuxe, 1964). Axons from these neurons travel through the medial forebrain bundle (MFB) to provide rich DA innervation to the striatal complex, comprising dorsal striatum (caudate-putamen, CPu) and nucleus accumbens (NAc) core and shell (Haber et al., 2000; Voorn et al., 2004), and more limited innervation of other basal ganglia regions, including subthalamic nucleus (STN) (Cragg et al., 2004) and globus pallidus (Fuchs and Hauber, 2004). A role for DA in motor behavior is well-established: DA regulates neuronal output (e.g., Gerfen and Surmeier, 2011) and DA deinnervation contributes to basal ganglia circuit dysfunction and consequent motor deficits of Parkinson's disease (PD) (Carlsson, 2002; Mallet et al., 2008; Wichman and Dostrovsky, 2011, this issue). In addition to axonal DA release, DA neurons release DA from their somata and dendrites in SN and VTA, which helps regulate motor behavior (Robertson and Robertson, 1989; Timmerman and Abercrombie, 1996; Crocker, 1997; Trevitt et al., 2001; Bergquist et al., 2003).

Both axonal and somatodendritic DA signaling depend on DA neuron firing rate and pattern (Patel et al., 1992; Kawagoe et al., 1992; Rice et al., 1997; Cragg, 2003; Beckstead et al., 2007) that vary between low-frequency 'tonic' firing and brief (~200 msec) higher frequency 'phasic' bursts of action potentials (Grace and Bunney, 1984). Phasic activity encodes prediction-related information about rewards or other salient stimuli (Schultz 1998; Matsumoto and Hikosaka 2009), and is thus important for the acquisition of reinforcement seeking behaviors and selection of habitual motor programs independent of reward (Jin and Costa, 2010). Discrete phasic DA-release signals in rat NAc can be detected using fast-scan cyclic voltammetry (FCV) *in vivo* during reward expectation or unexpected presentation, and may be important for reward seeking movement (Phillips et al., 2003; Roitman et al., 2004; Stuber et al., 2005; Gan et al., 2010). Although phasic transients are correlated with DA neuron activity (Sombers et al., 2009), the correspondence between firing and DA release events is complex, with local regulatory mechanisms that gate DA release probability. Axonal DA release shows short-term plasticity, a variation in DA release probability that depends on prior activity (Cragg, 2003; Montague et al., 2004; Cragg, 2006). Neuromodulatory inputs that can also regulate DA release have activity patterns that co-vary with changes in firing of DA neurons, e.g., acetylcholine (ACh) from striatal cholinergic interneurons (ChIs) (Morris et al., 2004). Thus presynaptic processes and local network effects play key roles in governing whether changes in DA neuron activity are reflected faithfully in DA release.

Moreover, elegant anatomical studies by Matsuda and colleagues (2009) demonstrate that the axonal arbor of a single DA neuron can occupy almost 6% of striatal volume. How then is spatially discrete DA signaling achieved? Here we present evidence that DA release in both forebrain and midbrain is regulated dynamically and locally by the microcircuitry surrounding release sites. These data indicate that DA signals can be inhibited or enhanced, often in a frequency dependent manner, by a variety of identified factors that regulate axonal and somatodendritic DA release. Many of these insights were gained from studies using voltammetric or amperometric methods with carbon-fiber microelectrodes, because of the ability of these methods to provide local, dynamic, subsecond detection of changes in extracellular DA concentration ($[DA]_o$) (Wightman, 2006). Specific factors include DA uptake by the DA transporter (DAT), DA autoreceptors, Ca^{2+}, glutamate, GABA, ACh, opioids, cannabinoids, and the diffusible messengers hydrogen peroxide (H_2O_2) and nitric oxide (NO).

DA release sites – designed for volume transmission

A continuing misconception about DA signaling is that it is analogous to the conventional view of glutamate synapse function, with synaptic release followed by activation of synaptic receptors and re-uptake via intra- or peri-synaptic transporters into pre- and perisynaptic cells. However, the similarity between DA and the classic picture of a glutamate synapse is limited. Although recycling of synaptic vesicles occurs after DA release, as seen at glutamatergic synapses (Mani and Ryan, 2009; Daniel et al., 2009; Onoa et al., 2010), there is evidence for a lack of postsynaptic specialization at 60–70% of purported DA release sites in the striatum (Descarries et al., 1996) and limited evidence for either pre- or postsynaptic specializations to delineate somatodendritic DA release sites in midbrain DA neurons (Wilson et al., 1977). Other dissimilarities include location and rate of transporters, distance between release sites, and slow/long response times of metabotropic receptors (Cragg and Rice, 2004; Rice and Cragg, 2008) (Table 1). Specifically, DATs are expressed only by DA neurons, so that once released, DA diffuses in three dimensions away from release sites, with re-uptake only when diffusing molecules encounter DA cell membranes or processes. The DA perisynaptic landscape contrasts with that for the classic glutamate synapse, where abundant glutamate transporters on glial processes that envelope synapses promote synaptic fidelity. Moreover, rates of transport differ: DAT transport cycle rates are an order-of-magnitude slower than those of glutamate transporters (Table 1). Consequently, perisynaptic DATs neither ‘gate’ DA efflux nor facilitate DA clearance from release sites; instead, clearance after quantal release is dominated by the faster process of diffusion (Cragg and Rice, 2004; Rice and Cragg, 2008). This differs from uptake-limited synaptic signaling (Rusakov and Kullmann, 1998; Barbour, 2001), although spillover to immediately extrasynaptic spaces is emerging as a rule rather than an exception for glutamate, as well (Okubo et al., 2010). Furthermore, these features we describe for DA may also be true of other neurotransmitters, particularly those acting at metabotropic receptors.

DA release sites are designed for transmitter spillover. How is specificity established for such broadcast signals? As for all neuroactive substances, there are signal receivers for DA, i.e., DA receptors. Unsurprisingly, given ready DA diffusion from release sites, striatal DA receptors are primarily extrasynaptic, again differing from the prevalent synaptic and perisynaptic localization of ionotropic glutamate receptors (there are also extrasynaptic glutamate receptors) (Table 1). It is relevant to note that analogous characteristics are also found in SNc, including the prevalence of extrasynaptic DA receptors (Cameron and Williams, 1993; Sesack et al., 1994; Yung et al., 1995), absence of axonal DA release sites, only limited number of dendro-dendritic DA synapses defined by membrane structure (Wilson et al., 1977; Groves and Linder, 1983), and limited DAT-dependent regulation of $[DA]_o$ (Cragg et al., 1997a, 2001; Chen and Rice, 2001). Somatodendritic DA release has several functions mediated by DA receptors, including D_2 autoreceptors on DA neurons (Lacey et al. 1987; Cragg and Greenfield, 1997; Beckstead et al., 2004, 2007; Ford et al., 2010) that suppress somatodendritic DA release in SNc (Cragg and Greenfield 1997) and axonal release in striatum (Santiago and Westerink 1991). Moreover, *dendritically* released DA acting at D_1 receptors in the SN pars reticulata (SNr) enhances GABA release from striatonigral terminals (Miyazaki and Lacey, 1998; Radnikow and Misgeld, 1998), and directly influences firing rate and pattern of SNr GABA output neurons (Zhou et al., 2009).

Thus, throughout the nigrostriatal pathway, DA transmission occurs primarily in the extracellular space, where it can be detected by carbon-fiber microelectrodes and voltammetric methods. Changes in $[DA]_o$ monitored with these methods provide a direct index of DA transmission, given that the extent of activation of extrasynaptic DA receptors will be governed by the amplitude and duration of an increase in $[DA]_o$.

In this light, positron emission tomography (PET) studies of DA release in human brain are based on displacement of radio-labeled DA receptor ligands (e.g., [^{11}C]raclopride) by endogenous DA. Although PET measurements are often considered to reflect DA release "in the synaptic cleft," the predominance of extrasynaptic DA receptors means that PET data indicate changes in extracellular rather than synaptic [DA] (*see* Egerton et al., 2009). PET imaging has been invaluable in showing effects of pharmacological agents on DA signaling in humans, including consequences of DAT inhibitors like Ritalin and releasing agents like amphetamines (e.g., Volkow et al., 2002, 2003), with integrated changes in $[DA]_o$ monitored over timescales comparable to microdialysis measurements (Morris et al., 2008). Notably, current PET sensitivity is sufficient for detection of basal ganglia DA release during natural behaviors, including non-rewarded movement (Badgaiyan et al., 2003; Morris et al., 2010).

Sphere and pattern of DA influence and role of the DAT

As noted, DA neurons form impressive axon arbors within striatum, with total axonal lengths from individual rat nigrostriatal DA neurons extending up to 780,000 μm (78 cm) (Matsuda et al., 2009). The density of striatal DA varicosities is 1.0–1.7 × 10^8 per mm^3 (Pickel et al., 1981; Doucet et al., 1986), giving a mean of 0.14 varicosity per μm^3 (1 varicosity per 7 μm^3). Assuming each varicosity is a release site, the distance between release sites is at most 2.4 μm, using the simplest calculation of inter-site distance. Assuming postsynaptic specializations for only 30–40% of varicosities (Descarries et al., 1996) gives an inter-synaptic distance of 3.5 μm (Cragg and Rice, 2004). More elaborate near-neighbor calculations, however, reduce this to 1.2 μm (Arbuthnott and Wickens, 2007), with ~370,000 DA synapses formed by each DA neuron. EM-level studies of striatal microcircuitry by Moss and Bolam (2008) indicate that mesostriatal DA axons form a 3-dimensional lattice with corticostriatal and thalamostriatal glutamate synapses, in which all striatal microstructures are within 1 μm of a DA-release site. This density implies critical roles for the timing and patterns of DA release (Moss and Bolam, 2008), as well as the necessity of local regulation.

How far away from release sites can DA act? The sphere of influence of released DA depends on local diffusion and uptake characteristics, which influence absolute $[DA]_o$ at a given time after release (Stamford et al., 1988; Garris et al., 1994; Gonon et al., 2000; Cragg et al., 2001; Venton et al., 2003; Cragg and Rice, 2004, Rice and Cragg, 2008). For example, despite more efficient uptake in striatum than in SNc or VTA (Cragg et al., 1997a), the extracellular volume fraction (α) in midbrain is 50% larger than in striatum (α = 0.3 *vs.* 0.2; Rice and Nicholson, 1991; Cragg et al., 2001), so that peak $[DA]_o$ most times after release of the same number of molecules would be similar. A more important determinant of the sphere of influence, is the sensitivity of DA receptors that receive concentration- and time-dependent $[DA]_o$ signals (Fig. 1). The two broad classes of DA receptors, D_1-like and D_2-like, have EC_{50} values for activation *in vitro* of ~10 nM for high-affinity states and ~1 μM for low-affinity states (Richfield et al., 1989; Neve and Neve, 1997). Consequently, the greatest sphere of influence of a single release site is defined by a maximum 'effective radius' within which $[DA]_o$ reaches ≥10 nM above baseline (Cragg and Rice, 2004; Rice and Cragg, 2008). Modeling the sphere of influence of quantal DA release in striatum in the presence of normal DAT-mediated DA uptake indicates an effective radius of 7 μm for activation of high-affinity DA receptors, but < 2 μm for low-affinity receptors (Fig. 1A). In the absence of uptake (e.g., after DAT inhibition by cocaine), this radius expands to 8.2 μm for high-affinity DA receptor activation; however, given the limited effect of perisynaptic DATs, the radius for low-affinity receptors is unaltered by uptake blockade (Rice and Cragg, 2008) (Fig. 1A). With limited DA uptake in SNc, increasing quantal size to compensate for the larger midbrain α, effective radii for activation of high and low-affinity DA receptors in SNc (Fig. 1B) are similar to that for quantal release in striatum without uptake. In SNc, DAT

inhibition has little effect on effective radius for activation of either high- or low-affinity DA receptors (Fig. 1B).

Uptake does influence DA signaling, of course. In striatum, DAT-dependent uptake constrains the sphere of influence of DA defined by $[DA]_o \geq 10$ nM for activation of high-affinity DA receptors (Fig. 1C). Regulation by uptake increases as quantal size, *Q,* increases because of the longer time available for DAT-mediated clearance of larger, longer-lasting $[DA]_o$ transients (Rice and Cragg, 2008). Similarly, the DAT has greater influence on larger transients after multiple-vesicle release from single or multiple sites, demonstrated by the greater effect of DAT inhibition on $[DA]_o$ during increased phasic DA neuron activity compared to a simple increase in the rate of tonic firing (Gonon, 1988; Floresco et al., 2003). Given limited DA uptake in SNc, the sphere of DA influence in SNc, even for high-affinity DA receptors, is similar uptake is intact or inhibited (Fig. 1D). As noted, however, the competing effects of greater uptake in striatum and larger α in SNc lead to surprisingly similar spheres of influence for axonal and somatodendritic DA release sites (Fig. 1E). Assuming that the density of predominantly non-DA synapses in striatum, ~1 synapse per μm^3 (Pickel et al., 1981), holds for SNc, released DA would encounter ~300 to 2,500 synapses within the spheres defined by $[DA]_o \geq 10$ nM for $Q = 2{,}000–14{,}000$ molecules in both regions (Fig. 1E) (Rice and Cragg, 2008). This is physiologically relevant, as numerous factors are known to change quantal size (for review, *see* Edwards, 2007; Sulzer et al., 2010), reaching vesicle content of up to 30,000 molecules (Staal et al., 2004). By contrast, the number of non-DA synapses in the spheres defined by $[DA]_o \geq 1$ μM is nearly 200-fold lower, with ~5–35 synapses encountered (Rice and Cragg, 2008). In addition to regulating the sphere of influence in striatum, DA uptake also limits the active lifetime of DA within a given sphere. For the quantal range examined, the active lifetime over which $[DA]_o \geq 10$ nM is 10–100 ms (Fig. 1F,G). In this model, region-specific uptake in striatum curtails active $[DA]_o$ lifetime by typically 50% (Fig. 1F), whereas lifetime in SNc shows little DAT influence (Fig. 1G). Despite limited DAT influence in SNc in this quantal DA release model, experimentally, DAT inhibition in SNc causes an increase evoked $[DA]_o$ (Cragg et al., 1997a; Chen and Rice 2001; Beckstead et al., 2004), reflecting the greater time for DAT action on larger, longer-lasting $[DA]_o$ increases when a population of DA neurons is activated. Note that the evidence for quantal size in SNc is limited: only one study recorded quantal events in SN (Jaffe et al., 1998). Because amperometry was used in that study, the possibility that synaptically release 5-HT contributed to the results cannot be discounted; nevertheless, those data were used in the model of quantal release just discussed (Cragg and Rice, 2004; Rice and Cragg, 2008).

Dreyer and colleagues (2010) have extended such models of single-site release to simulate how spatiotemporal patterns of DA neuron activity affect striatal $[DA]_o$ and DA-receptor occupancy during tonic, out-of-phase activity and during population bursts. Receptor binding studies suggest that a majority of striatal D_2-like receptors are in a high-affinity state, whereas D_1-like receptors are low-affinity (Richfield et al., 1989). Assuming these relative affinities are valid *in vivo*, these simulations suggest that high-affinity D_2-like receptors will be largely occupied during tonic, asynchronous DA neuron firing, with minimal occupancy of D_1-like receptors. However, relative receptor occupancy changes during phasic bursts, with a prediction of increased D_1 occupancy, but a slight decrease in D_2 occupancy. Given the role of D_1-receptor-expressing striatal medium spiny neurons (MSNs) in facilitating movement via the direct (striatonigral) pathway and corresponding role of D_2-receptor-expressing MSNs in movement suppression via the indirect (striatopallidal) pathway (Kravitz et al., 2010; Gerfen and Surmeier, 2011), these predictions suggest that phasic DA signals might provide a transient motor signal by enhancing direct-pathway MSN responsiveness, with decreased opposition of the inhibitory indirect pathway.

D_2 autoreceptor regulation of DA release

The family of D_2-like receptors includes DA autoreceptors that regulate axonal and somatodendritic DA release, DA neuron firing rate, and DA synthesis. In striatal slices, D_2 agonists like quinpirole cause a concentration-dependent suppression of single-pulse evoked $[DA]_o$ in rodent CPu and NAc (Palij et al., 1990; Bull and Sheehan, 1991; Stamford et al., 1991; Kennedy et al., 1992; Patel et al., 1995, 2003), and in the striatal analogue in avian brain, area X (Gale and Perkel, 2005). This effect is lost in D_2-receptor knockout mice (Schmitz et al., 2002) and in mice with selective D_2-autoreceptor deletion (Bello et al., 2011), implying a direct action on DA axons. However, these findings do not exclude the possibility of striatal DA release regulation by activation of D_2 receptors on other striatal elements. Agonists of D_2 receptors also inhibit somatodendritic DA release in midbrain; however, D_2 receptor regulation is less in SNc than in striatum (Cragg and Greenfield, 1997), and is apparently absent in VTA (Iravani et al., 1996; Cragg and Greenfield, 1997; Kita et al., 2009).

In striatal slices, antagonism of D_2 receptors has no effect on single-pulse or pseudo-one-pulse evoked $[DA]_o$, indicating no basal $[DA]_o$ tone (Limberger et al., 1991; Trout and Kruk, 1992; Patel et al., 1992; Kennedy et al., 1992; Cragg and Greenfield, 1997; Bello et al 2011). However, endogenous DA released during local stimulation activates D_2 receptors that inhibit subsequent DA release: pulse-train evoked $[DA]_o$ is amplified by a D_2-receptor antagonist like sulpiride (Limberger et al., 1991; Trout and Kruk, 1992; Patel et al., 1992; Kennedy et al., 1992; Cragg and Greenfield, 1997; Bello et al., 2011). The use of paired pulses applied at varying interpulse intervals indicates D_2 receptors regulate DA release by 100 ms after an initial stimulus, is maximal 550–700 ms later depending on striatal subregion, and lasts as along as 5 s (Lee et al., 2002; Phillips et al., 2002). *In vivo* estimates of autoreceptor activation differ somewhat from those *in vitro*, with a similar onset time (> 150 ms), but earlier times of maximal activation (150–300 ms) and termination (600–800 ms) (Benoit-Marand et al., 2001). These differences may reflect a higher basal $[DA]_o$ tone *in vivo* than *in vitro*. Nonetheless, genetic or pharmacological manipulations that change $[DA]_o$ *in vivo* lead to a persistent changes in DA autoinhibition detectable in slices, including subsensitivity of D_2 autoinhibition when $[DA]_o$ is chronically elevated in DAT knockout mice (Jones et al., 1999), and supersensitivity resulting from chronically low $[DA]_o$ in VMAT2 mutant mice (Patel et al., 2003). Altered D_2 receptor sensitivity is also seen in rat NAc *in vitro* after *in vivo* administration and/or withdrawal from cocaine or amphetamine (Muscat et al., 1993; Jones et al., 1996a; Davidson et al., 2000).

Ca^{2+}-dependence of DA release

Axonal release—One similarity between axonal DA and glutamate release is that both are action-potential and Ca^{2+}-dependent processes. Locally evoked DA release in CPu *in vitro* is blocked by tetrodotoxin (TTX), a blocker of voltage-gated Na^+ channels, and by removal of extracellular Ca^{2+} (e.g., Chen and Rice, 2001). Determination of the Ca^{2+}-dependence of striatal DA release evoked by single-pulse stimulation, which is unaffected by concurrently released glutamate and GABA (Chen et al., 2006), shows that in both CPu and NAc shell, evoked $[DA]_o$ is detectable at an extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$) of 1.0 mM and increases exponentially with increasing $[Ca^{2+}]_o$ (Chen et al., 2011) (Fig. 2). The $[Ca^{2+}]_o$ at which evoked $[DA]_o$ is half-maximal (EC_{50}) in both regions is ~2 mM, which suggests a similar Ca^{2+}-dependent mechanisms of release throughout the striatal complex. In CPu, Hill analysis of the Ca^{2+} dependence for axonal DA release gives a Hill coefficient of three, indicating the cooperative action of three Ca^{2+} ions, whereas DA release in NAc shell shows a slightly steeper fourth power dependence on $[Ca^{2+}]_o$ in striatal slices (Chen et al., 2011). The Ca^{2+} dependence of DA release is within the range of well-studied glutamate synapses, including a second power dependence on $[Ca^{2+}]_o$ at squid giant synapses (Katz and Miledi,,

1970), cerebellar parallel fiber-Purkinje cell synapses (Mintz et al. 1995), and hippocampal Schaeffer collateral synapses (Qian et al., 1997), and fourth power dependence at the neuromuscular junction (Dodge and Ramahmimoff, 1967).

The primary sources of Ca^{2+} entry for axonal DA release are voltage-gated Ca^{2+} channels. Striatal DA release has been shown with a variety of methods to depend primarily on N- and P/Q-type Ca^{2+} channels (Herdon and Nahorski, 1989; Turner et al., 1993; Dobrev and Andreas, 1997; Bergquist et al., 1998; Phillips and Stamford, 2000; Chen et al., 2006), with little effect of blocking T-type or R-type channels, and no effect of L-type channel blockade (Chen et al., 2006).

Somatodendritic release—Release of DA from cell bodies and dendrites is typically referred to as somatodendritic release. This term is accurate for release in SNc and VTA in which somata and dendrites (and axons in VTA) intermingle, so that somatic and dendritic release cannot readily be distinguished. Moreover, most data about midbrain DA release have been obtained in these regions. Although DA release in the SNr is exclusively from DA dendrites originating from SNc, this 'dendritic' release has rarely been studied in isolation. In general, mechanistic understanding of somatodendritic DA release is less complete than that of axonal release. The notion that somatodendritic DA release is mediated by a novel mechanism is attractive; however, few characteristics contradict the original suggestion by Geffen et al. (1976) that the process is vesicular and exocytotic, like axonal release. Release of DA occurs in both SNc and VTA (Björkland and Lindvall, 1975; Geffen et al., 1976; Nieoullon et al., 1977; Cheremy et al., 1981; Rice et al. 1994, 1997; Cragg et al., 1997a,b; Iravani et al., 1996; Jaffe et al., 1998; Chen and Rice, 2001, 2002; John et al., 2006; Patel et al. 2009). However, in SNc, DA release sites are exclusively somatodendritic (Juraska et al. 1977; Wassef et al. 1981), whereas VTA also receives synaptic DA input from its own axon collaterals and those from SNc (Deutch et al., 1988; Bayer and Pickel, 1990). It should be noted that guinea pigs are the species of choice for voltammetric studies of evoked somatodendritic DA release in SNc, because signature voltammograms obtained with FCV in guinea-pig SNc indicate DA detection only (Rice et al., 1994, 1997; Cragg et al., 1997a,b), whereas 5-HT is predominantly detected in rat and mouse SNc (and SNr) (Iravani and Kruk 1997; Cragg et al., 1997b; Threlfell et al., 2004, 2010a; John et al., 2006; Ford et al., 2010). On the other hand, only DA is detected in the VTA of any rodent examined (Iravani and Kruk 1997; Rice et al., 1997; Cragg et al., 1997a,b; John et al., 2006).

Consistent with Ca^{2+}-dependent exocytosis, somatodendritic DA release in SNc requires Ca^{2+} (Rice et al., 1994, 1997; Patel et al., 2009), is blocked by TTX (Santiago et al., 1992; Chen and Rice, 2001) and prevented by VMAT2 inhibitors (Rice et al., 1994; Heeringa and Abercrombie, 1995; Beckstead et al., 2004) and by botulinum toxins (Bergquist et al., 2002; Fortin et al., 2006). Prevention by VMAT2 inhibitors alone does not confirm vesicular release, as VMAT2 is expressed by subcellular organelles in addition to vesicles in DA neurons (Nirenberg et al., 1996b). Unlike axonal release, however, somatodendritic DA release in SNc persists in submillimolar $[Ca^{2+}]_o$ (Bergquist et al. 1998; Hoffman and Gerhardt, 1999; Chen and Rice, 2001; Fortin et al., 2006; Chen et al., 2011) and is resistant to voltage-gated Ca^{2+} channel blockers at concentrations that abolish striatal DA release (Elverfors et al., 1997; Bergquist et al., 1998; Bergquist and Nissbrandt, 2003; Chen et al., 2006).

These Ca^{2+}-dependence data imply that somatodendritic DA release requires minimal Ca^{2+} entry, which was confirmed in FCV studies of the Ca^{2+} dependence of single-pulse evoked $[DA]_o$ in SNc and VTA (Chen et al., 2011). The $[Ca^{2+}]_o$ EC_{50} is only 0.3 mM for both regions, which is ~7-fold lower than in CPu or NAc (Fig. 2). The overall Ca^{2+} dependence

of somatodendritic DA release in SNc is also less steep than that of axonal DA release, with a Hill coefficient of 1.6 (Fig. 2A). Notably, two distinct Hill fits are required for VTA Ca^{2+}-dependence data: the slope for single-pulse evoked $[DA]_o$ in $[Ca^{2+}]_o \leq 1.5$ mM is 1.0, whereas that for $[Ca^{2+}]_o \geq 1.0$ mM is 3.5 (Fig. 2B). Thus, VTA exhibits both somatodendritic and axonal DA release (Chen et al., 2011), implying a functional role for axonal synapses in VTA (Deutch et al. 1988; Bayer and Pickel, 1990).

Minimal Ca^{2+} entry required for somatodendritic DA release suggests involvement of an amplification process, including Ca^{2+}-induced Ca^{2+} release from intracellular stores. SNc DA neurons express the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), as well as intracellular Ca^{2+}-release channels, inositol 1,4,5-triphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs) (Patel et al., 2009). Morever, FCV studies of pulse-train evoked $[DA]_o$ in SNc demonstrate that Ca^{2+} release from SERCA-dependent IP_3R- and RyR-gated stores facilitates somatodendritic DA release (Patel et al., 2009).

The higher Ca^{2+} sensitivity and lower Ca^{2+} cooperativity of somatodendritic *versus* axonal DA release also suggests involvement of differing exocytotic machinery (Bergquist et al., 2002; Fortin et al., 2006; Witkovsky et al., 2009). Consistent with this hypothesis, the somatodendritic compartment of DA neurons expresses different complements of SNARE proteins than typically found at axon terminals (Bergquist et al. 2002; Witkovsky et al. 2009; Mendez et al., 2011). SNc DA neurons lack low-Ca^{2+}-affinity vesicle proteins synaptotagmin 1 and 2 (Witkovsky et al., 2009), but express high-affinity synaptotagmin 7 (Mendez et al., 2011), which would increase the Ca^{2+} sensitivity of somatodendritic release. Although some conventional exocytotic proteins are expressed in SNc DA neurons, including syntaxin-3, synaptopbrevin-2/VAMP-2, SNAP-25 and synapsin-III (Witkovsky et al., 2009; Kile et al., 2010), others are absent, including syntaxin1, synaptic vesicle proteins-1a and 1b, synaptophysin, and synaptobrevin-1/VAMP-1 (Witkovsky et al., 2009).

Interestingly, VMAT2 and proton ATPase, required for DA storage, are found in SNc DA somata, but absent in distal DA dendrites (Witkovsky et al., 2009). Such data coupled with the limited number of vesicles in DA neurons (Wilson et al., 1977; Groves and Linder, 1983; Nirenberg et al., 1996b), have suggested alternative or additional mechanisms of somatodendritic or dendritic release, including reversal of the DAT (Groves and Linder, 1983; Nirenberg et al., 1996b; Elverfors et al., 1997; Falkenburger et al., 2001; Opazo et al., 2010). Arguing against DAT reversal as the *only* release mechanism in SNc is the enhancement in basal or evoked $[DA]_o$ usually seen with DAT inhibition (Engberg et al., 1997; Cragg et al., 1997a; Chen and Rice 2001; Beckstead et al., 2004).

Axonal DA release characteristics differ among basal ganglia regions

How DA neuron activation translates into axonal DA release can vary through a variety of subregion-dependent factors that regulate activity-dependent DA release probability. Regional differences are seen in patterns of evoked $[DA]_o$ during pulse-train stimulation (10 Hz): in CPu, evoked $[DA]_o$ is maximal < 500 mses after stimulus initiation then decays during continued stimulation, in part from D_2 receptor activation (Trout and Kruk, 1992; Patel et al., 1992; Cragg and Greenfield 1997), whereas in NAc shell, evoked $[DA]_o$ increases progressively through a stimulus train. Such regional differences are also seen in the ratio of $[DA]_o$ evoked by pulse-train stimulation (20–25 pulses at 50 Hz) to $[DA]_o$ evoked by a single pulse in rat striatal slices (Trout and Kruk, 1992; Patel et al., 1992; Davidson and Stamford, 1993), with a pulse-train to single-pulse evoked $[DA]_o$ ratio < 2 in anterior dorsolateral CPu, but ≤6 in discrete areas of medial CPu and NAc. In general, high $[DA]_o$ ratio sites receive input primarily from VTA and are found in limbic-associated striatal subregions, whereas low-ratio sites receive input from SNc and are in sensorimotor areas. In striatal slices, CPu DA release shows little frequency dependence, whereas release

in NAc core and shell is more strongly dependent on frequency (with maximal release at 20–50 Hz) and pulse number (Trout and Kruk, 1992; Patel et al., 1992; Davidson and Stamford, 1993; Cragg et al., 2000; Cragg, 2003; Rice and Cragg, 2004; Exley et al., 2008).

Several factors contribute to these differences, including more efficient DA uptake in CPu *versus* NAc, with DAT expression in CPu > NAc core > NAc shell (Stamford et al., 1988; Marshall et al., 1990; Jones et al., 1995, 1996b; Cragg et al., 2000). Conversely, autoreceptor regulation of DA release is NAc > CPu (Trout and Kruk, 1992; Patel et al., 1992; Davidson and Stamford, 1993; Wieczorek and Kruk, 1995). Notably, heterogeneity in DA release regulation within CPu of non-human primates (marmoset) is more pronounced than in rodents (Cragg et al., 2000; Cragg et al., 2002; Cragg, 2003), although regional differences in short-term DA-release plasticity reflect variation in initial DA release probability, for which CPu > NAc, in primate and in rodents (Trout and Kruk, 1992; Patel et al., 1992; Davidson and Stamford, 1993; Cragg. 2003). Underlying mechanisms responsible are unresolved, although contributing factors include Ca^{2+} (Cragg, 2003) and regulation by other transmitter systems, particularly ACh.

Spatial and temporal variation in DA release is also seen within striatal subregions. For example, when a carbon-fiber microelectrode is advanced at 100-μm steps through the dorsal-to-ventral extent of the striatal complex *in vivo*, $[DA]_o$ evoked by MFB stimulation shows significant site-to-site variation (May and Wightman, 1989). Although this variation is similar to the dimensions of striatal patch-matrix compartments (Gerfen, 1992), other contributing factors could include interference from the myelinated fibers that characterize striatum, as well as local DA release regulation. Spontaneous $[DA]_o$ transients of ~50 nM are also seen in NAc *in vivo* (Phillips et al., 2003; Roitman et al., 2004; Stuber et al., 2005; Wightman et al., 2007; Sombers et al., 2009). Transients can be detected in many, but not all recording sites, even though sites with no transients show MFB-evoked increases in $[DA]_o$ (Wightman et al., 2007). Moreover, at sites where $[DA]_o$ transients occur, cocaine enhances their frequency and magnitude, whereas there is no effect at sites lacking spontaneous events. Modeling studies suggest that spatial and temporal fluctuations in $[DA]_o$ during synchronous phasic firing could reflect heterogeneity in release *versus* uptake (Venton et al., 2003). However, it is also increasingly recognized that there are subpopulations of DA neurons, especially in the VTA (Margolis et al., 2008; Lammel et al., 2008, 2011; Dobi et al., 2010; Mileykovskiy and Morales, 2011), that have distinct projections, inputs, and electrophysiological characteristics that could also contribute to site-to-site variation in $[DA]_o$ in target regions.

Dynamic regulation of axonal DA release in other basal ganglia regions is less well-characterized than in striatum. In STN, DA is released from *en passant* tyrosine hydroxylase (TH) positive axons that form some synapses, but the low densitiy of DA fibers and release sites is matched by low evoked $[DA]_o$, which hinders studies of release kinetics or regulatory mechanisms. Indeed, pulse-train evoked $[DA]_o$ (50 pulses, 50 Hz) in STN is ten-fold lower than that evoked by single-pulse stimulation in any striatal territory, but, like striatal release, is Ca^{2+}- and Na_V-dependent, and regulated by DA uptake (Cragg et al., 2004).

Regulation of axonal DA release by glutamate, GABA, and cannabinoids via H_2O_2

Glutamate and GABA—How glutamate and GABA regulate axonal DA release in striatum was a long-standing conundrum. Much existing literature is based on *in vivo* microdialysis, which provides evaluation of net neurochemical changes over minutes. This is useful for exploring local, drug-induced neurochemical changes, but not necessarily the origin or underlying mechanisms, given the possibility of multiple sites of action. Even local drug application through reverse dialysis can produce local changes involving interactions

among basal ganglia structures, which cannot be determined easily. The use of glutamate agonists, in particular, can induce wide-spread depolarization, including pathophysiological spreading depression (Moghaddam et al., 1990; Westerink et al., 1992). Thus, local regulation of DA release can be more effectively examined in brain slices using local stimulation to elicit DA release (Bull et al., 1990; Schmitz et al., 2003; Patel and Rice, 2006; Rice et al., 2007; Threfell and Cragg, 2007), with the caveats that accompany any *in vitro* preparations.

DA release regulation by glutamate and GABA in CPu was resolved using pulse-train stimulation with FCV *in vitro* (Wu et al., 2000; Avshalumov et al., 2003, 2008). With brief (submillisecond) single-pulse stimulation, evoked $[DA]_o$ is unaffected by concurrently released glutamate or GABA because DA release happens before modulation by other transmitters occurs. For example, single-pulse evoked $[DA]_o$ monitored in CPu with FCV is unaltered by antagonists of AMPA, NMDA, metabotropic glutamate, $GABA_A$, or $GABA_B$ receptors (AMPARs, NMDARs, mGluRs, $GABA_A$Rs, or $GABA_B$Rs), whether applied individually or as a cocktail (Avshalumov et al., 2003; Zhang and Sulzer, 2003; Chen et al., 2006). However, pulse-train stimulation permits evaluation of concurrently released transmitters. Suprisingly, AMPAR antagonism in CPu causes a ~2-fold increase in pulse-train evoked $[DA]_o$ (Fig. 3A), indicating that glutamate *inhibits* axonal DA release. By contrast, $GABA_A$Rs blockade causes a ~50% decrease in pulse-train evoked $[DA]_o$ in CPu (Fig. 3C), showing that GABA *enhances* DA release. In contrast, pulse-train evoked $[DA]_o$ in CPu is unaffected by NMDAR or $GABA_B$R antagonists (Avshalumov et al., 2003).

The apparent absence of AMPA and $GABA_A$ receptors on CPu DA axons (Bernard and Bolam, 1998; Chen et al., 1998: Fujiyama et al., 2000) suggests that regulation by these receptors involves an intermediary. This is the case: both glutamate and GABA modulate DA release in CPu through diffusible H_2O_2 (Avshalumov et al., 2003, 2008). The effects of AMPAR and $GABA_A$R antagonists on pulse-train evoked $[DA]_o$ are blocked by H_2O_2 scavenging enzymes, catalase (Fig. 3B,D) or glutathione (GSH) peroxidase. Moreover, amplification of endogenous H_2O_2 levels by GSH-peroxidase inhibition with mercaptosuccinate (MCS) suppresses pulse-train evoked $[DA]_o$ (Fig. 3E). This suppression reverses with MCS washout or addition of exogenous catalase in the continued presence of MCS (Fig. 3F). Generation of modulatory H_2O_2 is entirely AMPAR dependent: $GABA_A$R antagonists and MCS have no effect on pulse-train evoked $[DA]_o$ when AMPARs are blocked (Avshalumov et al., 2003).

The subcellular source of dynamically generated H_2O_2 is mitochondrial respiration (Bao et al., 2009). Other, slower sources of H_2O_2, including NADPH oxidases and DA metabolism by monoamine oxidases, do not contribute. What is the cellular source of modulatory H_2O_2? The pharmacological profile of DA release regulation by glutamate and GABA in CPu points to striatal MSNs, which express AMPARs and $GABA_A$Rs (Bernard and Bolam, 1998; Chen et al., 1998: Fujiyama et al., 2000) that are activated during local stimulation (Jiang and North, 1991; Kita, 1996). Morever, simultaneous whole-cell recording and fluorescence imaging of an H_2O_2-sensitive dye (dihydro-dichlorofluoresein) demonstrate activity-dependent H_2O_2 generation in CPu MSNs during local pulse-train stimulation (Fig. 4A,D), with prevention of action-potential and H_2O_2 generation by an AMPAR antagonist (Fig. 4B,D). Inhibition of GSH peroxidase increases MSN H_2O_2 levels (Fig. 4C,D), whereas catalase eliminates stimulated fluorescence changes, confirming H_2O_2 detection (Avshalumov et al., 2008). Thus, AMPAR-dependent H_2O_2 levels in CPu MSNs are inversely related to peak evoked $[DA]_o$.

Activity-dependent H_2O_2 inhibits DA release by opening ATP-sensitive K^+ (K_{ATP}) channels, indicated by prevention of the usual changes in evoked $[DA]_o$ in CPu with

AMPAR and $GABA_AR$ antagonists and MCS by K_{ATP} channel blockers, tolbutamide and glibenclamide (Avshalumov et al., 2003; Avshalumov and Rice, 2003). In contrast to glutamate and GABA receptors, H_2O_2-sensitive K_{ATP} channels are located directly on DA axons (Patel et al., 2011) (Fig. 3G). Regulation of DA release by these presynaptic channels is rapid, yet transient. Using a paired pulse-paradigm similar to that used to examine DA-release regulation by D_2 autoreceptors, Patel et al. (2011) found H_2O_2/K_{ATP}-channel-dependent suppression of subsequently evoked $[DA]_o$ in a time-window of 500–1000 ms after an initiating stimulus.

These data suggest a model in which glutamate input to MSNs generates modulatory H_2O_2 that diffuses to adjacent DA axons, opens K_{ATP} channels, and inhibits DA release (Rice, 2011) (Fig. 3G). Regulation of striatal glutamate release by DA occurs through inhibition of glutamate release via D_2 DA receptors and CB1 cannabinoid receptors on corticostriatal afferents (Cepeda et al., 2001; Bamford et al., 2004a,b; Lovinger, 2010). Regulation of striatal DA release by glutamate input is now also explained through the action of diffusible H_2O_2 at K_{ATP} channels which inhibits DA release. In this model, GABA input to MSNs opposes glutamate-dependent excitation and consequent H_2O_2 generation (Fig. 3C,G)

Glutamate can also modulate DA release via metabotropic glutamate receptors (mGluRs), presumably located on DA axons (Paquet and Smith, 2003) (Fig. 3G). Inhibition of the glial glutamate transporter, GLT1, suppresses single-pulse evoked $[DA]_o$ in CPu, as does repetitive, high-frequency stimulation of corticostriatal afferents, suggesting that prolonged glutamate spillover can also inhibit DA release via mGluRs (Zhang and Sulzer, 2003). This suppression is mimicked by a group I mGluR agonist, DHPG, and blocked by a group I antagonists, apparently through mobilization of Ca^{2+} stores and consequent opening of apamin-sensitive Ca^{2+}-activated K^+ (SK) channels (Zhang and Sulzer, 2003).

Cannabinoids—The main psychoactive component of marijuana, ^{9}-tetrahydrocannabinol (THC), acts in the CNS through type-1 cannabinoid receptors (CB1Rs). Consistent with dense CB1R expression in the basal ganglia (Herkenham et al., 1990, 1991; Mailleux and Vanderhaeghen, 1992), CB1R agonists alter motor performance, with dose-dependent effects ranging from increased activity to catalepsy (*see* Sidló et al., 2008). A well-established action of presynaptic CB1Rs is transmitter-release inhibition (Szabo and Schlicker, 2005; Lovinger, 2008). *In vivo* FCV recordings in NAc show that systemic WIN55,212-2, a CB1R agonist, suppresses $[DA]_o$ evoked by MFB stimulation, yet increases the number and amplitude of spontaneous $[DA]_o$ transients in NAc core and shell (Cheer et al., 2004, 2007). CB1R antagonists have no effect on MFB-evoked $[DA]_o$ in NAc, implying the absence of endocannabinoid release with this stimulation; however, CB1R antagonists suppress spontaneous $[DA]_o$ transients induced by CB1R agonists, or by nicotine, ethanol, and cocaine (Cheer et al., 2004, 2007).

Supporting circuitry-dependent effects of CB1R activation, rather than direct effects on DA axons, single-pulse evoked $[DA]_o$ in striatal slices is unaffected by CB1R agonists or antagonists in either CPu or NAc (Szabo et al., 1999; Sidló et al., 2008). However, CB1R agonists, including WIN55,212-2, cause a decrease in pulse-train evoked $[DA]_o$ in CPu, implicating the involvement of local striatal circuitry (Sidló et al., 2008). As seen *in vivo*, pulse-train evoked $[DA]_o$ is not altered by CB1R antagonists, indicating the absence of DA release regulation by endocannabinoids with brief, mild stimulation. The effect of WIN55,212-2 on pulse-train evoked $[DA]_o$ is also prevented by $GABA_AR$ blockade, by catalase, and by blockade of K_{ATP} channels (Sidló et al., 2008). These data implicate presynaptic inhibition of GABA release via presynaptic CB1Rs (Fig. 3G), with consequently increased MSN activation and H_2O_2 generation. Consistent with this explanation, the effect of WIN55,212-2 in CPu is also lost with AMPAR antagonism (Sidló and Rice,

unpublished). Local inhibition of DA release consequent to GABA release inhibition might explain CB1R-agonist induced catalepsy, despite evidence for increased phasic DA-neuron activity (Cheer et al., 2004).

Regulation of somatodendritic DA release by glutamate, GABA, and H_2O_2

Glutamate and GABA—Glutamate and GABA provide the primary synaptic input to midbrain DA neurons (*see* Chen and Rice, 2002; Morikawa and Paladini, 2011, this issue) (Fig. 5A). However, the balance between excitatory and inhibitory input differs between SNc and VTA, with predominant GABA input to SNc (Bolam and Smith, 1990) and glutamate input to VTA (Smith et al., 1996; Sesack and Grace 2010). In midbrain slices, single-pulse evoked somatodendritic DA release in SNc is unaffected by a cocktail of ionotropic glutamate and GABA receptor antagonists (Chen et al., 2006), indicating the absence of tonic regulation by these transmitters *in vitro*. When pulse-train stimulation is used, however, regulation by concurrently released glutamate and GABA is seen in both SNc and VTA (Chen and Rice, 2002). In the SNc, antagonism of AMPARs or NMDARs increases pulse-train evoked $[DA]_o$ (Fig. 5B), as does antagonism of $GABA_A$Rs or $GABA_B$Rs (Chen et al., 2002). When $GABA_A$Rs and $GABA_B$Rs are blocked, the effect of AMPAR antagonism is lost (Fig. 5C), suggesting that glutamate inhibits somatodendritic DA release via AMPARs on inhibitory cells and terminals (Paquet et al., 1997; Yung, 1998) (Fig. 5A). Even in the presence of GABA antagonists, however, an increase in evoked $[DA]_o$ persists when NMDARs are antagonized (Fig. 5C), suggesting the involvement of an inhibitory mediator besides GABA. In VTA, antagonists of $GABA_A$Rs, $GABA_B$Rs or AMPARs alone have no net effect on pulse-train evoked $[DA]_o$, whereas NMDAR antagonism causes a decrease, consistent with normal glutamate-dependent enhancement of DA release (Chen and Rice, 2002). In the presence of a cocktail of GABA-receptor antagonists, AMPAR or NMDAR antagonism in VTA decreases evoked $[DA]_o$, demonstrating conventional excitatory effects of direct glutamate input to VTA DA neurons.

Somatodendritic DA release in SNc is also regulated by glutamate acting at mGluR1s, with abundant expression of mGluR1α in SNc DA neurons (e.g., Patel et al., 2009) (Fig. 5A). Activation of mGluR1 initiates IP_3R-mediated Ca^{2+} release from ER stores (Fiorillo and Williams, 1998; Morikawa et al., 2003), which can hyperpolarize DA neurons via Ca^{2+}-activated K^+ channels. However, FCV studies of pulse-train evoked $[DA]_o$ show that endogenous glutamate acting at mGluR1 normally *facilitates* somatodendritic DA release, as evoked $[DA]_o$ is suppressed by mGluR1 antagonism, in a process that requires Ca^{2+} release from IP_3R-sensitive stores (Patel et al., 2009) (Fig. 5D). Activation of mGluR1 also facilitates dendritic DA release in SNr, possibly via DAT reversal (Opazo et al., 2010).

H_2O_2—Somatodendritic DA release is also regulated by H_2O_2, at least in SNc (Chen et al., 2002). In contrast to AMPAR-dependent H_2O_2 generation in CPu, however, H_2O_2 is continually produced in SNc DA neurons during spontaneous activity. Tonic H_2O_2-dependent activation of K_{ATP} channels in these cells (Fig. 5A) inhibits DA neuron firing rate (Avshalumov et al., 2005); further amplification of endogenous H_2O_2 levels by GSH peroxidase inhibition causes K_{ATP} channel dependent hyperpolarization and cessation of spontaneous activity (Avshalumov et al., 2005). GSH peroxidase inhibition also suppresses pulse-train evoked $[DA]_o$ in SNc, albeit not in VTA (Fig. 5E), suggesting that differential H_2O_2 generation or regulation between SNc and VTA might contribute to greater vulnerability of SNc *versus* VTA DA neurons in PD.

Regulation of axonal DA release by ACh, opioids, and NO

ACh—ACh plays a major role in shaping DA release probability and dynamic short-term plasticity that underlies the frequency and activity dependence of axonal DA release. Large,

aspiny striatal cholinergic interneurons (ChIs) are only ~2–5% of striatal neurons (Oorschot, 1996; Descarries and Mechawar, 2000), but produce an extensive axonal arbor within the striatal complex, analogous to that of DA axons (*see* Zhou et al., 2002; Exley and Cragg, 2008). Striatal ChIs are tonically active *in vivo* and *in vitro* in slices, and also known as 'tonically active neurons' (TANs) (Wilson et al., 1990; Aosaki et al., 1995; Bennett and Wilson, 1999; Zhou et al., 2002). Like mesostriatal DA neurons, ChIs/TANs signal unexpected primary reinforcers, and participate in the learning and signaling of environmental cues that predict high-salience events (Calabresi et al., 2000; Morris et al., 2004; Pisani et al., 2005; Pisani et al., 2007). An antagonistic balance between striatal ACh and DA regulates postsynaptic integration within striatum. However these transmitters do not necessarily act in opposition simultaneously: significant presynaptic interactions between ACh and DA reciprocally influence the dynamic availability of the other transmitter (Cragg, 2006).

ACh modulates DA release directly via nicotinic receptors (nAChRs) on DA axons, albeit without direct synaptic contacts, and apparently indirectly via muscarinic receptors (mAChRs) (Fig. 6). Rodent SNc and VTA DA neurons express mRNAs for nAChR subunits α3–7 and β2–4 (Azam et al., 2002); in turn, DA axons express diverse subtypes of heteropentameric nAChRs (*see* Exley and Cragg, 2008). Presynaptic nAChRs are all β2-subunit-containing (*) (e.g., Jones et al., 2001), and fall in to three broad groups according to their inclusion of subunit α4 (α4β2*) or α6 (α6β2*), or both (α4α6β2*). FCV in striatal slices indicates that single pulse-evoked $[DA]_o$ is suppressed when β2* nAChRs are antagonized (Fig. 7), indicating normal enhancement of DA release by ACh (Zhou et al., 2001; Zhang and Sulzer, 2004; Rice and Cragg, 2004). Besides decreasing initial DA release probability, nAChR antagonists also relieve the short-term depression that normally follows initial release (Cragg, 2003; Rice and Cragg, 2004) (Fig. 7A,B). This reorganization of DA release probabilities by nAChR inhibition depends on the frequency of DA-neuron activity: the shorter the interpulse interval (e.g., higher frequency), the greater the relief from short-term depression (Fig. 7C). As a result, pulse-train evoked $[DA]_o$ becomes highly sensitive to frequency and pulse number, with enhancement of evoked $[DA]_o$ *versus* control with trains of sufficiently high frequency and/or pulse number (Rice and Cragg, 2004; Exley et al., 2008) (Fig. 7D,E). Thus, nAChR activation normally keeps initial DA release probability high, but limits subsequent release that constrains $[DA]_o$ during pulse trains, whereas switching off nAChRs facilitates release by high frequencies (Figs. 6,7). The same effect is seen in mice lacking striatal ACh (Patel et al., submitted) and with nicotine at concentrations approximating plasma levels in cigarette smokers that cause nAChR desensitization (Zhou et al., 2001; Rice and Cragg, 2004) (Fig. 7). The findings with nicotine may be significant for signaling reinforcement-related information and nicotine actions. During burst activity in DA neurons that signals reward presentation or conditioned reward-predicting stimuli, ChIs simultaneously and transiently pause in activity (Morris et al., 2004). The effects of synchronous ChI pauses on DA release may be mimicked by nAChR desensitization by nicotine, which increases the contrast in DA signals when DA neurons switch firing mode (Cragg, 2006) (Figs. 6,7).

The identity of β2*-nAChRs that regulate striatal DA transmission is a research focus for the nicotine and PD research communities, with the goal of therapy development for smoking cessation or PD (Quik and McIntosh, 2006). Particular targets include α6*-nAChRs because of their primary expression in catecholamine neurons (Le Novere et al., 1996; Quik et al., 2001; Quick and Lester, 2002). Despite expression of α6-mRNA in both VTA and SNc neurons and other evidence for α6β2*-nAChRs throughout striatum (Zoli et al., 2002; Grady et al., 2002; Champtiaux et al., 2003; Salminen et al., 2004; Gotti et al., 2010), FCV DA release studies indicate that functional regulation by α6*-nAChRs depends on striatal territory, with dominant control of DA release in NAc by α6α4β2*-nAChRs

(Exley et al., 2011), and by a complementary population of α4(nonα6)β2*-nAChRs in CPu (Exley et al., 2008). These data suggest region specific roles of different nAChRs in DA release regulation (*see* Fig. 6).

Non-β2*-nAChRs, i.e., homomeric α7-nAChRs, are apparently not expressed on DA axon terminals, but α7-nAChRs can regulate striatal [^{3}H]DA release indirectly through mechanisms that involve nAChRs on glutamate terminals (Kaiser and Wonnacott, 2000). Although there is evidence that α7-nAChRs participate in the frequency sensitivity of endogenous DA release (Seipel and Yakel 2010), this finding has not been supported by other studies (Exley et al., 2008).

Striatal mAChRs also regulate DA release. Considerable controversy has existed about whether mAChRs enhance or inhibit DA transmission and which subtype(s) are involved. This was resolved in part by FCV studies of frequency-dependent regulation of axonal DA in striatal slices from subtype-specific knockout mice (Threlfell et al., 2010b; Threlfell and Cragg, 2011). These studies show that a broad-spectrum mAChR agonist, oxotremorine, has bidirectional effects on DA release. Oxotremorine decreases single-pulse evoked $[DA]_o$, but relieves short-term DA release depression by subsequent pulses, thereby enhancing the sensitivity of DA release to frequency and pulse number. This effect is identical to, substitutes for, and is prevented by prior application of nAChR antagonists, indicating activation of mAChRs on ChIs, which inhibit ChI firing (e.g., Ding et al., 2006), and thus reduced ACh release and reduced activation of nAChRs on DA axons (Fig. 6). Specific mAChRs responsible for this indirect frequency-dependent regulation of striatal DA release were revealed using subtype-specific knockouts, with a requirement for M_4-mAChRs in NAc, but both M_2- and M_4-mAChRs in CPu (Threlfell et al., 2010b). This regional distinction was surprising, but consistent generally with the reported expression of M_2-family (M2/M4) mAChRs by ChIs (Yan and Surmeier, 1996; Alcantara et al., 2001).

The role of M_5-mAChRs, however, remains incompletely resolved. M_5-mAChRs are expressed by DA neurons, but contrary to popular cartoons used in the literature (e.g. Pisani et al., 2007), they have not been anatomically identified on DA axons (Weiner et al., 1990). In M_5 knockouts (M_5-KO), unlike $M_{2/4}$-KOs, the effects of mAChR agonists on frequency sensitivity of evoked $[DA]_o$ are intact (Threlfell et al., 2010b). However, M_5-KO mice have decreased evoked $[DA]_o$ (Bendor et al., 2010), and the effects of mAChR agonists on single-pulse-evoked $[DA]_o$ are enhanced (Threlfell et al 2010b; Bendor et al., 2010), in keeping with suggestions that M_5-mAChRs play a role in facilitating striatal DA release (Zhang et al., 2002) in a frequency-independent manner. These mAChRs are not expressed by ChIs and have been suggested to be presynaptic on DA axons (Bendor et al., 2010). Arguing against this, however, the effects of mAChRs agonists are lost after prior application of nAChR antagonists (Threlfell et al., 2010b), suggesting that direct regulation of DA release by mAChRs does not occur, or at least requires intact ACh input. This issue has yet to be resolved.

Opioids—ChIs also mediate DA release regulation by other striatal modulators, including opioid receptor agonists that have activity-specific effects on DA transmission in NAc via nAChRs on DA axons (Fig. 6). Using FCV and amperometry, Britt and McGehee (2008) showed that in NAc shell (but not other regions), μ- and δ-opioid-receptor agonists depress single-pulse evoked $[DA]_o$, but enhance release by short 25 Hz pulse trains, as does nicotine. This effect is prevented by nicotine, and appears to involve decreased ChI activity, consistent with localization of these receptors on ChIs, but not DA axons (e.g., Svingos et al., 2001a) (Fig. 6). By contrast, agonists for κ-opioid receptors, which are expressed on DA axons (Svingos et al., 2001b), suppress DA release with all stimuli in a ChI-independent manner (Britt and McGehee, 2008). Given that different populations of MSNs differently

produce dynorphins (D1-expressing, striatonigral pathway) and enkephalins (D2-expressing, striatopallidal pathway) that have different efficacy at opioid receptor subtypes, these findings suggest that DA release may be differentially modulated by opioid-peptide release from different MSN populations. More generally, they reveal remarkable similarity between effects of nicotine and opiates on mesolimbic DA release.

NO—NO is thought to be a striatal neuromodulator produced by NOS-containing GABA interneurons (Hidaka and Totterdell, 2001; Kraus and Prast, 2001). NO donors (SIN-1, PAPA/NONOate) have variable, activity-specific effects on DA release involving multiple sites of action, including enhancement of the frequency dependence of DA release through an indirect mechanism requiring intact ACh input to nAChRs, which mimics decreased nAChR activation (Hartung et al., 2011) (Fig. 6). However, NO also enhances evoked $[DA]_o$ across frequencies through a presumably direct action on DA axons that does not involve ACh, GABA, glutamate, guanylyl cyclase, the DAT, or large conductance Ca^{2+}-activated K^+ (BK) channels.

Regulation of DA release by proteins associated with neurological disease: transgenic and knockout mouse models

Several studies have identified changes in DA release in striatum from mice that are mutant or knockout for PD-associated proteins, including those associated with autosomal-dominant PD, e.g., α-synuclein (Abeliovich et al., 2000; Yavich et al., 2005; Senior et al., 2008; Anwar et al., 2011) and leucine-rich repeat kinase 2 (LRRK2) (Li et al., 2010), as well as those associated with early-onset recessive forms, e.g., parkin (Goldberg et al., 2003; Kitada et al., 2009), DJ-1 (Goldberg et al., 2005) and PTEN-induced kinase 1 (PINK1) (Kitada et al., 2007). In most of these, changes in DA release occur in the absence of changes in other *indirect* markers of DA neuron function (e.g., neuron number, DA content). Thus, DA release impairment may represent a common pathophysiological change in genetically modified animal models of PD, and may be a marker that not only accompanies, but also precedes**,** nigrostriatal degeneration in PD. Altered DA transmission has also been identified in transgenic mouse models of hyperkinetic moment disorders, including dystonia and Huntington's disease.

α-Synuclein—Alpha-synuclein is a major component of the protein aggregates, Lewy bodies, that are cytological hallmarks of SNc degeneration in PD (Spillantini and Goedert, 2000; Mizuno et al., 2001). Although missense mutations and locus multiplications in *SNCA*, the gene encoding α-synuclein, cause rare familial disease, emerging genome-wide association (GWAS) data also demonstrate that genetic variation at the *SNCA* locus is commonly associated with sporadic PD (Venda et al., 2010). These findings place both gene and protein at the center of molecular mechanisms of PD. Studies of presynaptic functions of α-synuclein in release regulation suggest that this protein may directly limit transmitter release, particularly glutamate (Chandra et al., 2004; Cabin et al., 2002; Nemani et al., 2010). Surprisingly, given its association with PD, few studies have examined DA release specifically. Although there is consensus that deletion of α-synuclein alone has little effect on single-pulse or brief pulse-train evoked $[DA]_o$, there is evidence for modified regulation of DA re-release with repetitive stimulation in some studies but not others (Abeliovich et al., 2000; Yavich et al., 2004; Yavich et al., 2005; Senior et al., 2008; Anwar et al., 2011). Resolution of α-synuclein function has been obscured by functional substitution by different members of the synuclein family (α, β, γ). Two recent studies of DA release after double synuclein deletion (α,γ-double knockout, DKO) or triple synuclein deletion (α,β,γ-triple knockout, TKO) have shown effects of DKO or TKO on DA release not seen after deletion of each synuclein alone (Senior et al., 2008; Anwar et al., 2011). Specifically, axonal DA release in CPu in slices from DKO or TKO mice is greater than in wildtype (WT) for all

stimulus trains tested (single pulses and 1–100 Hz, 5 pulses), consistent with hyperdopaminergic-like behaviors in these mice, despite lower DA content and no detectable change in DA synthesis, DA neuron number, vesicle availability, regulation by Ca^{2+} or ACh, or SNARE complex formation (in TKOs) (Anwar et al., 2011). These data suggest that synucleins limit vesicular DA release through mechanisms that differ from those indicated for other transmitters in separate studies also using TKOs (e.g., Burre et al., 2010; Greten-Harrison et al., 2010). Notably, DA release in TKO NAc does not differ from WT, indicating that synucleins differently govern nigrostriatal versus mesolimbic DA transmission, and pointing to another factor that could influence the susceptibility of SNc DA neurons to degeneration (Anwar et al., 2011).

LRRK2—At least 20 different missense mutations in the *LRRK2* gene have been linked to late-onset PD, and collectively form one of the most common causes of familial PD (Mata et al., 2006; Moore, 2008). These mutations typically replace one amino acid in the LRRK2 protein. The G2019S mutation is most common, accounting for ~7% of familial and 1–2% of sporadic cases, but up to 40% in some Arab and Jewish populations (Mata et al., 2006). Enhanced LRRK2 kinase activity after G2019S mutation correlates with neurotoxicity *in vitro* (Smith et al., 2006), whereas LRRK2 inhibition is protective *in vivo* (Lee et al., 2010). The association of LRRK2 protein with synaptic vesicles (Shin et al., 2008) implies a role in neurotransmission. Release facilitation was demonstrated by a ~25% increase in single-pulse evoked $[DA]_o$ in CPu from 12-month-old mice overexpressing LRRK2 *versus* WT, with unaltered DA uptake or DA content (Li et al., 2010). Consistent with enhanced DA release, LRRK2 overexpressers are hyperactive and show enhanced motor performance. By contrast, overexpression of LRRK2 G2019S causes an age-dependent decrease in single-pulse evoked $[DA]_o$ and DA uptake in CPu, as well as decreased DA content, with no change in SNc DA neuron number, striatal DA axon density, or evidence of neurotoxicity. Sustainability of evoked $[DA]_o$ with subsequent stimulations is decreased in G2019S overexpressers (Li et al., 2010), possibly reflecting impaired vesicular filling/recycling with LRRK2 mutation (Piccoli et al., 2011). Thus, LRRK2 enhances vesicular release, but G2019S mutation impairs this function. Two other LRRK2 mouse lines expressing rarer R1441G/C mutations also exhibit impaired DA transmission without overt DA neuron loss (Li et al., 2009; Tong et al., 2009). Notably, higher expression of mutant G2019S LRRK2 can also lead to SNc degeneration (Lee et al., 2010; Dusonchet et al., 2011).

Parkin—Loss-of-function mutations in *parkin* are the most common causative gene of juvenile and early-onset familial PD; parkin protein is an E3 ubiquitin ligase in the ubiquitin-proteasome system. *Parkin−/−* mice have grossly normal brain morphology, but show deficits in behavioral tasks that reflect nigrostriatal dysfunction (Goldberg et al., 2003), as well as decreased evoked $[DA]_o$ in striatal slices and impaired corticostriatal plasticity (Kitada et al., 2009). Interestingly, striatal $[DA]_o$ monitored *in vivo* using microdialysis are slightly elevated in *parkin−/−* mice (Goldberg et al., 2003), indicating that other processes, e.g., DA neuron activity, contribute to basal levels.

DJ-1 and PINK1—Loss-of-function mutations in the *DJ-1* gene cause early-onset familial PD. *DJ-1−/−* mice have normal SNc DA neuron number; however, single-pulse evoked $[DA]_o$ in striatal slices is decreased *versus* WT, primarily from increased DA uptake (Goldberg et al., 2005). Loss-of function mutations in the *PINK1* gene have also been linked to early-onset PD. Although DA neuron number, striatal DA content, and DA receptor characteristics appear normal in *PINK1−/−* mice, evoked $[DA]_o$ in striatal slices is decreased and corticostriatal plasticity impaired (Kitada et al., 2007).

Dystonia—The pathophysiology of dystonia is not well understood. Unlike PD, there is no obvious neuronal degeneration (Breakefield et al., 2008); however, emerging evidence implicates DA dysfunction in mouse models of early-onset (DYT1) dystonia (Shashidharan et al., 2005; Pisani et al., 2006; Balcioglu et al., 2007; Bao et al., 2010; Hewett et al., 2010; Page et al., 2010). DYT1 dystonia is an autosomal-dominant condition caused by a three base-pair (GAG) deletion in the *DYT1* gene, resulting in loss of a glutamate residue in the protein product, torsinA, which is widely expressed in brain. Overexpression of mutant torsinA (ΔE-torsinA) in heterologous cells suggests interaction with VMAT2 and thus may impair DA storage or release (Misbahuddin et al., 2005), while other studies show interference with vesicle recycling (Granata et al., 2008). Supporting these mechanisms, single-pulse evoked $[DA]_o$ in CPu is ~40% lower in slices from mice that selectively express ΔE-torsinA in DA neurons *versus* non-transgenic mice or mice overexpressing WT torsinA, with unaltered DA uptake or tissue content and only subtle changes in motor coordination (Page et al., 2010). *In vivo* microdialysis in these mice and in mice with pan-cellular expression of ΔE-torsinA also show attenuated psychostimulant-evoked $[DA]_o$ in CPu (Balcioglu et al., 2007; Page et al., 2010). Another mouse line originally developed to express human ΔE-torsinA in all neurons exhibited motor hyperactivity and dystonic-like limb movements in 30–40% of transgenics (Shashidharan et al., 2005; Chiken et al., 2008), although whether these motor abnormalities can be attributed to ΔE-torsinA *per se* is not clear (*see* Bao et al., 2010). Nevertheless, $[DA]_o$ evoked by single pulses or brief trains in CPu is lower in slices from transgenic mice with the behavioral phenotype *versus* those without or non-transgenic controls (Bao et al., 2010). Moreover, phenotype-positive mice exhibit enhanced frequency-dependent DA release in CPu that is insensitive to nAChR blockade (Bao et al., 2010) implying dysfunctional cholinergic transmission, as seen in other DYT1 dystonia models (Pisani et al., 2006; Martella et al., 2009). By contrast, frequency dependence is normal in mice expressing ΔE-torsinA only in DA neurons (Bao et al., unpublished). These observations indicate that ΔE-torsinA can interfere with release of DA and ACh, disrupting their dynamic reciprocal relationship in striatum and thereby disrupting coordinated motor behavior.

Huntington's disease—Huntington's disease (HD) is an autosomal dominant hyperkinetic movement disorder caused by an expanded CAG repeat in the gene encoding huntingtin protein. This mutation leads to degeneration of striatal cells that ultimately results in choreic movements, mood disturbances, and cognitive impairment. Unlike most transgenic PD and dystonia models, transgenic HD mice exhibit pronounced behavioral phenotypes. Although DA neurons do not degenerate in HD, data from HD mice suggest impaired striatal DA release regulation, including lower striatal $[DA]_o$ monitored using microdialysis in R6/1 mice with ~116 CAG repeats (Petersén et al., 2002). Moreover, FCV data show an age-dependent decrease in evoked $[DA]_o$ in the CPu of slices from R6/1, as well as R6/2 mice (~144 CAG repeats) that exhibit more rapid and severe phenotypic motor changes, with decreased uptake in R6/1 but not R6/2 mice (Johnson et al., 2006, 2007; Ortiz et al., 2010, 2011). Whether these changes are direct or indirect consequences of the neurodegenerative process has not been established, but contributing factors include an age-dependent impairment in DA loading into vesicles in the readily releasable pool and loss of DA vesicles in the reserve pool.

Optogenetics and DA release

Most studies of DA release regulation have used electrical or chemical stimulation. However, advances in optogenetics permit optical stimulation (or suppression) of specific cell types (Deisseroth, 2010; 2011; Zhang et al., 2010; Fenno et al., 2011; Kravitz and Kreitzer, 2011; Toettcher et al., 2011), allowing new questions about DA release to be addressed. For example, channelrhodopsin-2 (ChR2), which is permeable to Na^+ and Ca^{2+},

can be introduced into DA neurons through viral-vector-mediated transfer of a loxP-controlled transgene in mice expressing Cre in either TH- or DAT-containing neurons (TH-Cre and DAT-Cre mice, respectively) to permit selective activation of DA axons by blue light in slices (Hnasko et al., 2010; Stuber et al., 2010; Tecuapetla et al., 2010) and *in vivo* (Tsai et al., 2009). The use of DAT-Cre mice allows expression of ChR2 in DA, but not NE neurons, with a caveat that heterozygous DAT-Cre mice exhibit some DAT downregulation (Bäckman et al., 2006) and decreased DA uptake rates (unpublished observation, Threlfell and Cragg). Nevertheless, light-evoked $[DA]_o$ profiles are broadly similar to those evoked by electrical stimulation (Fig. 8A–C), and are TTX-sensitive and abolished by inhibition of TH or VMAT2 (Tecuapetla et al., 2010). The value of this technique for exploring DA transmission was illustrated by the demonstration that DA axons arising from adult VTA, but not SNc, co-release glutamate and DA (Tecuapetla et al., 2010; Stuber et al., 2010). Co-release had been suggested by data from cultured cells and slices (*see* El Mestikawy et al., 2011); however, these use of optogenetics to activate DA neurons selectively provided conclusive evidence that DA axons were the source of glutamate and consequent excitatory post-synaptic currents in NAc MSNs (Fig. 8D,E,F).

The use of optical technology should continue to improve understanding of DA release regulation, particularly in regions in which voltammetric measurements are contaminated by NE or 5-HT, e.g., STN (Cragg et al., 2004), SNc, and SNr (Cragg et al., 1997b; John et al., 2006). A limitation of current optogenetics is the relative restriction at present to transgenic mice, although transgenic rats are begining to appear. Overcoming this limitation, optically evoked DA release was recently examined in CPu in non-transgenic rats after ChR2 transfection of SNc (Bass et al., 2010). This study demonstrated similar kinetics of striatal DA release and uptake following optical *versus* electrical stimulation, uncontaminated by pH shifts that can interfere with detection of electrically evoked $[DA]_o$ *in vivo* (Bass et al., 2010). This approach, while useful, also has limitations, inasmuch as potentially unintended targets will also be transfected. For example, transfection of VTA would include glutamate neurons that project to the NAc as well as DA neurons (Yamaguchi et al., 2011). Of course neuronal specificity is not necessary for all questions; with known pathways, careful positioning of light stimulus and DA detection probe can provide novel insights into how input from one brain region might regulate another. Thus, optogenetic technologies may generate cleaner data than other methods of stimulation, provided that the specificity of channel incorporation is confirmed and appropriate controls for photoelectric currents are considered.

Conclusions

Release of DA in the basal ganglia is best understood for striatum, which has the richest DA innervation in the CNS. The striatal DA-axon network contains overlapping projection fields from thousands of DA neurons that each contribute almost half a million synapses (plus other potential nonsynaptic release sites) from which released DA interacts by volume transmission with local neuronal elements. Nonetheless, locally discrete, subsecond $[DA]_o$ signals that vary within striatal subregions are detected *in vivo*, indicating greater temporal and spatial regulation than predicted from DA neuron firing patterns alone. Differences in release regulation in limbic- *versus* motor-related domains as well as micro-heterogeneity of DA release activity reveal the ability of DA systems to generate a diverse array of DA signals in response to a given firing pattern. As discussed here, studies in slices have shown that local $[DA]_o$ is regulated through differential expression of proteins (e.g., DATs, D_2 receptors, synucleins) in different DA neuron populations, by modulatory signals generated within projection fields by interacting neurons (e.g., MSNs, ChIs), and by discrete regional localization of modulatory ion channels (e.g., K_{ATP} channels) and receptor subtypes (e.g., AMPA, nicotinic, muscarinic, cannabinoid, opioid). The roles of these many powerful

mechanisms have yet to be fully resolved *in vivo* when the timing or activity of each mechanism may be different. However, given that DA powerfully regulates MSN excitability, any factors that modulate local $[DA]_o$ have the potential to modulate basal ganglia output. This is exemplified by DA-ACh interactions through the patterned interleaving of DA neuron bursts and striatal ChI pauses (Morris et al., 2004; Cragg, 2006), but could also include DA-glutamate interactions, in which elevated striatal $[DA]_o$ would be expected to increase D1-expressing MSN excitability, leading to increased glutamate-dependent H_2O_2 generation in MSNs, and consequent suppression of DA release via presynaptic K_{ATP} channels on DA axons (e.g., Avshalumov et al, 2008; Patel et al., 2011). Thus, a model in which DA release in the basal ganglia is simply a read-out of activity in DA neurons that provides a diffuse DA tone to enable signal processing, with spatial and temporal specificity provided by other circuits, is no longer tenable. Rather, DA can be released with dynamic probabilities gated by local mechanisms that generate temporally and regionally diverse signals, which in turn contribute to regional selection and plasticity in basal ganglia function.

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Highlights

- Dopamine is a key transmitter in the basal ganglia.
- Dense axonal arbors and evidence for overlapping dopamine neuron activity argue against signaling specificity for dopamine.
- However, discrete local regulation by transmitters and modulators alter release probability and phasic responsiveness to sculpt local signaling.

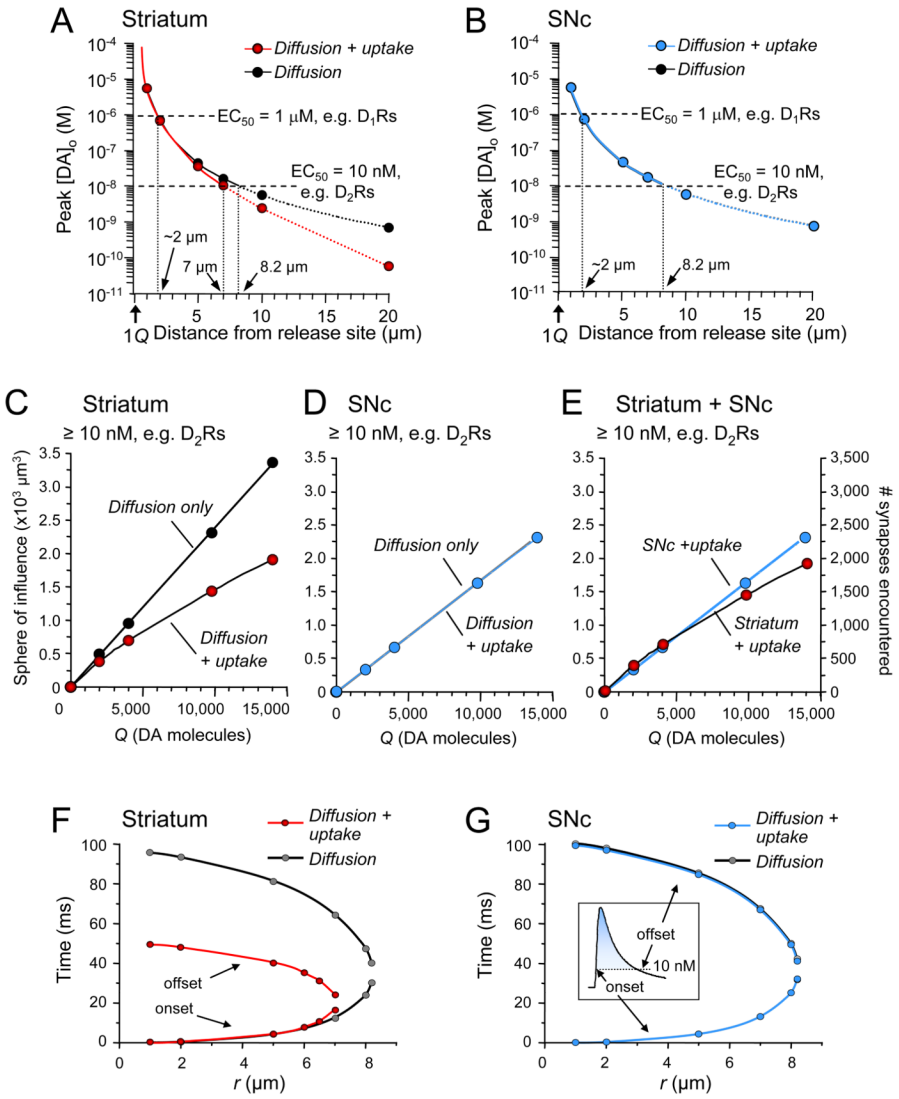

Figure 1. Effective radius and sphere of influence for DA after quantal release in SNc and striatum and effect of DAT-dependent uptake on active DA lifetime

A,B) Peak extracellular DA concentration ($[DA]_o$) *vs.* diffusion distance, *r*, derived from simulations using experimentally determined parameters (*see* Rice and Cragg, 2008). Maximum radius at which peak $[DA]_o$ reaches 10 nM (e.g., the concentration required for activation of high-affinity D_2-DA receptors, D_2Rs) was 8.2 μm in **(A)** striatumor **(B)** SNc or for diffusion only (non-specific k') and in SNc with region-specific uptake and normalized Q to compensate for the larger extracellular volume fraction, α, of SNc. In striatum, region-specific uptake decreases effective radius to 7.0 μm, resulting in a 40% smaller sphere of influence than for diffusion only. Maximum radius at which peak $[DA]_o$ reaches 1 μM (e.g., for activation of low affinity D_1 DA receptors, D_1Rs) is ~2 μm in both striatum and SNc. **C–E)** Sphere of influence of DA ($[DA]_o \geq 10$ nM) *vs.* quantal size, Q, in **(C)** striatum and **(D)** SNc, with and without specific region-dependent DA uptake. Uptake increasingly diminishes the sphere of influence in striatum as Q increases, whereas that for DA in SNc is not affected by region-specific uptake, regardless of Q. **(E)** Comparison of the spheres of influence of DA defined by the $[DA]_o$ required to activate high-affinity DA receptors (EC_{50} ≥10 nM) for a range of Q released in striatum and SNc, with region-specific uptake and

diffusion parameters. Although the influence of uptake differs markedly between striatum and SNc **(C, D)**, the competing effects of a and DA uptake in each region yield similar spheres of influence for equal Q released **(E)**. For $Q > 5{,}000$ DA molecules, the sphere of influence in striatum is smaller than that in SNc because of greater striatal uptake. The spheres defined by $[DA]_o \geq 10$ nM would contain 300–2,500 primarily non-DA synapses. **(F, G)** Uptake of DA also influences active lifetime after quantal release. Onset and offset times at varying r after quantal release in **(F)** striatum and **(G)** SNc, defined as the times at which a change in $[DA]_o$ reaches (onset) and then falls below (offset) 10 nM. The inset in **(G)** indicates these time points for a theoretical DA diffusion curve at $r = 5$ μm in SNc. The effect of uptake on onset and offset times in **(F)** striatum and **(G)** SNc was also assessed; compare diffusion only (gray lines) with diffusion + region-specific DA uptake (red lines). In SNc, DAT-mediated uptake does not alter active lifetime. In striatum, uptake curtails offset time, leading to a ~50% decrease in active lifetime at all distances within the effective radius. Although the maximum effective radius in SNc is unaltered by the DAT, striatal uptake limits the effective radius for activation of high-affinity DA receptors. Panels A–D, F and G were adapted from Cragg and Rice, 2004 and Rice and Cragg, 2008; values used for simulations can also be found in those references.

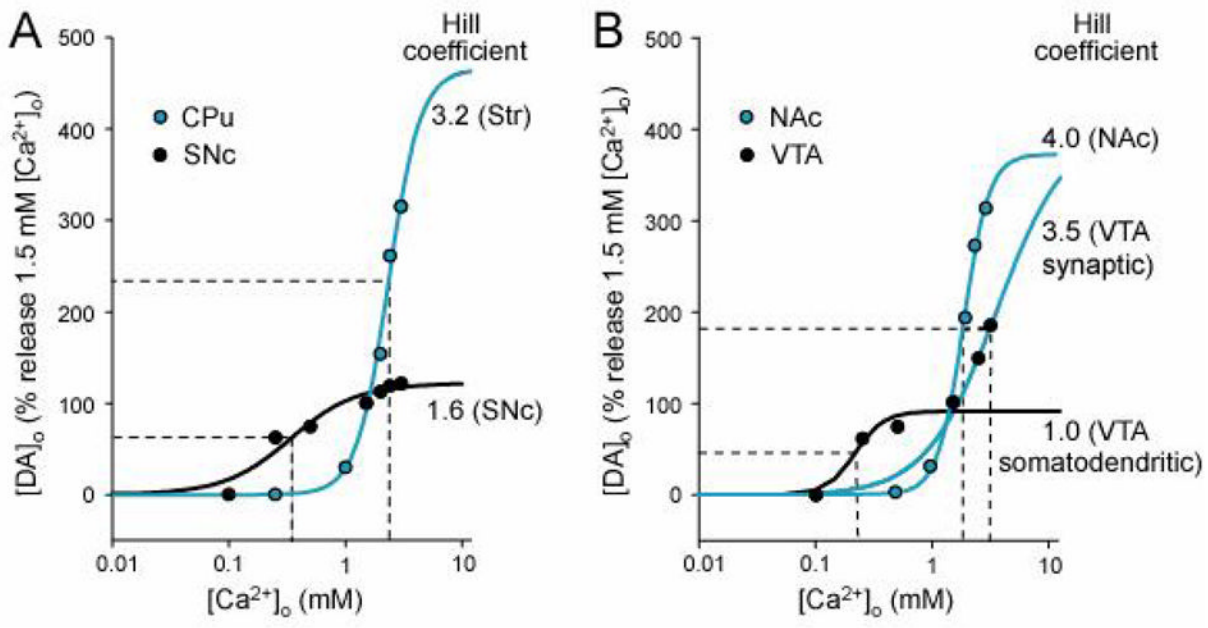

Figure 2. Hill analysis of the Ca^{2+}-dependence of nigrostriatal and mesolimbic DA release

Single-pulse evoked $[DA]_o$ data normalized to peak evoked $[DA]_o$ in 1.5 mM $[Ca^{2+}]_o$ as 100% for each region for **(A)** CPu and SNc and **(B)** NAc and VTA. Blue lines indicate Hill fit for axonal release, black lines for somatodendritic release. The Hill coefficient for each fit indicates the exponential dependence of DA release on $[Ca^{2+}]_o$. Both axonal and somatodendritic were needed to fit data from the VTA ($[Ca^{2+}]_o$ < 1.5 mM *vs.* $[Ca^{2+}]_o$ > 1.0 mM) **(B)**. The *x*-axis for each Hill plot was extended to 10 mM $[Ca^{2+}]_o$ to permit extrapolation of the Ca^{2+} dependence to a roughly maximal level for each region. These expanded plot then permitted calculation of an EC_{50} (the $[Ca^{2+}]_o$ at which DA release is half maximal) for each region (dashed lines). The EC_{50} for dorsal striatum was 2.3 mM $[Ca^{2+}]_o$ and that for SNc was 0.3 mM. In NAc, EC_{50} was 1.9 mM, with 0.3 mM for somatodendritic release in VTA. Data points are given as means without error bars for clarity. Modified from Chen et al., 2011.

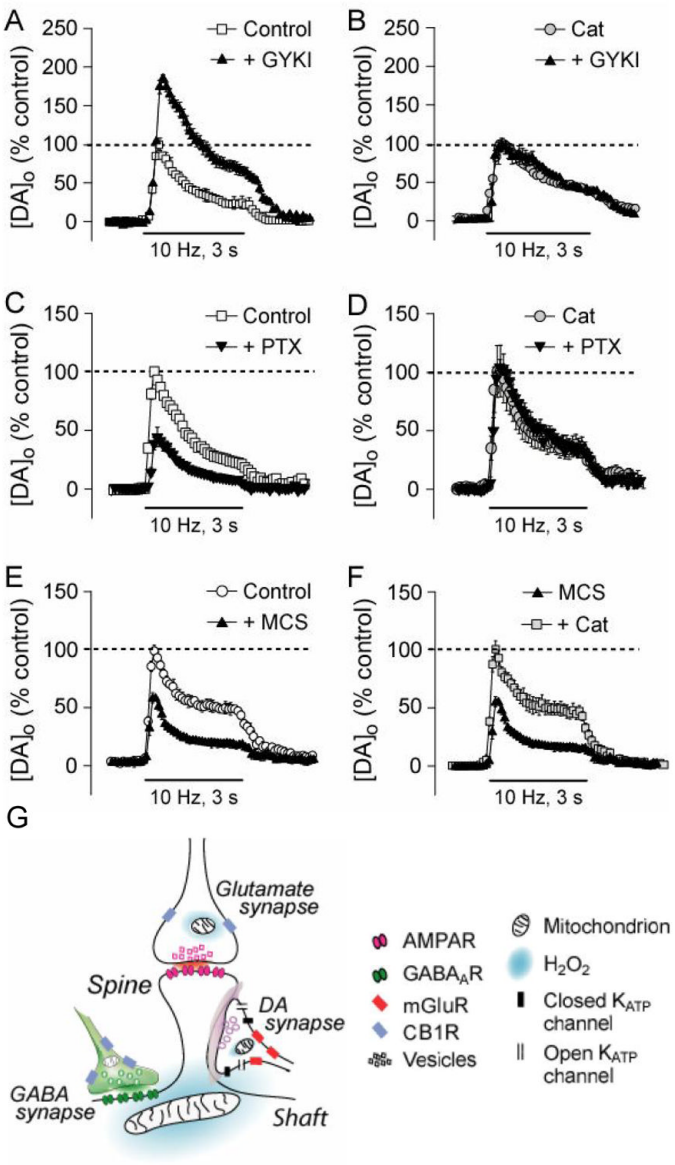

Figure 3. Indirect regulation of DA release in CPu by activation of AMPARs, $GABA_A$Rs, and CB1Rs requires H_2O_2, whereas consequences of mGluR activation do not

A–F) Evoked $[DA]_o$ in CPu in guinea-pig brain slices; DA release was evoked using 10 Hz, 30-pulse trains and monitored with carbon-fiber microelectrodes and fast-scan cyclic voltammetry. Data are means ± SEM, shown as percentage of same-site control (modified from Avshalumov et al., 2003; copyright Journal of Neuroscience, used with permission). **A)** AMPAR blockade by GYKI-52466 (GYKI; 50 μM) causes a ~100% increase in pulse-train evoked $[DA]_o$ in CPu ($p < 0.001$, $n = 6$). **B)** The effect of AMPAR blockade is prevented by catalase (Cat; 500 IU/mL), an H_2O_2-metabolizing enzyme. **C)** $GABA_A$R blockade by picrotoxin (PTX; 100 μM) causes a ~50% decrease in evoked $[DA]_o$ ($p < 0.001$, $n = 6$). **D)** Catalase abolishes the effect of picrotoxin. **E)** Inhibition of GSH peroxidase by mercaptosuccinate (MCS; 1 mM) leads to suppression of evoked $[DA]_o$ (inset shows DA voltammograms under control conditions and in MCS). **F)** Application of catalase in the continued presence of MCS reverses H_2O_2-dependent DA release suppression. Responses in the presence of heat-inactivated catalase were the same as

control. **G)** Triad of striatal DA, glutamate, and GABA synapses on a CPu medium spiny neuron (MSN) dendrite, linked by diffusible H_2O_2. Modulatory H_2O_2 is generated in CPu MSNs when AMPARs are activated; diffusible H_2O_2 leaves MSNs and opens K_{ATP} channels on DA axons to inhibit DA release (Patel et al., 2011). Glutamatergic excitation and consequent of H_2O_2 generation are opposed by $GABA_AR$ activation; this regulation is lost with $GABA_AR$ blockade by picrotoxin **(C)** and attenuated with CB1R activation (Sidló et al., 2008) leading to inhibtion of DA release. In contrast to this indirect modulation, mGluRs located on DA axons can attenuate evoked $[DA]_o$ directly (Zhang and Sulzer, 2003). Modified from Avshalumov et al., 2008; Sidlo et al., 2008.

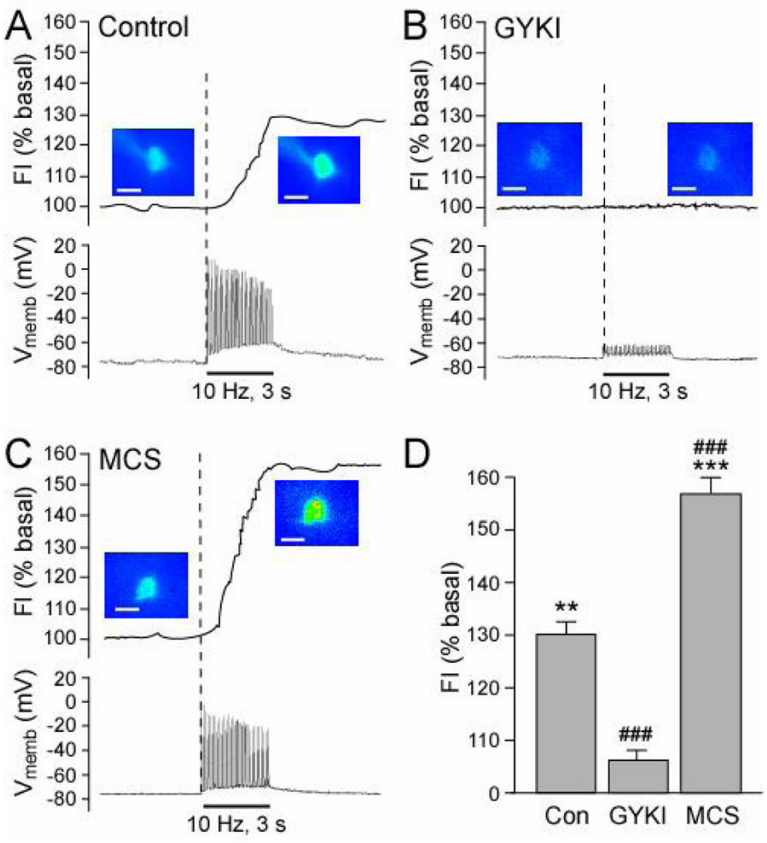

Figure 4. Activity-dependent H_2O_2 generation in MSNs during local stimulation in CPu

A–C) Representative examples of simultaneous current-clamp recordings of membrane voltage (V_{memb}) and intracellular H_2O_2 in CPu MSNs indicated by changes in dichlorofluorescein (DCF) fluorescence intensity (FI) in guinea-pig striatal slices. Time course of stimulus-induced changes in DCF FI is accompanied by pseudocolor DCF images recorded under basal conditions and at the end of stimulation (scale bar = 20 μm in DCF images). **A)** In all recorded CPu MSNs (n = 11), each stimulus pulse during local pulse-train stimulation (30 pulses, 10 Hz) generated a single action potential (*lower panel*). In 7 of 11 MSNs, this was accompanied by an increase in DCF FI ($p < 0.01$ *vs.* basal) (*upper panel*). **B)** Stimulus-evoked action potentials in MSNs during local pulse-train stimulation were prevented by an AMPAR antagonist, GYKI-52466 (50–100 μM) (*lower panel*), as was the usual increase in DCF FI (*upper panel*) (n = 7; $p > 0.05$ *vs.* basal). **C)** Inhibition of GSH peroxidase by MCS (1 mM) amplifies stimulus-evoked increases in DCF FI (30 pulses, 10 Hz) (*upper panel*), with no effect on action potential generation in recorded MSNs (*lower panel*). In MCS, 7 of 7 MSNs showed a significant increase in DCF FI ($p < 0.001$). **D)** Average stimulus-induced changes in DCF FI in H_2O_2 source MSNs under control conditions (Con; n = 7), in GYKI (n = 7), or in MCS (n = 7) (**$p < 0.01$ *vs.* basal; ***$p < 0.001$ *vs.* basal). The increase in DCF FI in MCS was nearly 2-fold greater than under control conditions, whereas AMPAR blockade with GYKI markedly attenuated the usual control response (###$p < 0.001$ *vs.* control) (modified from Avshalumov et at., 2008; copyright American Physiological Society, used with permission).

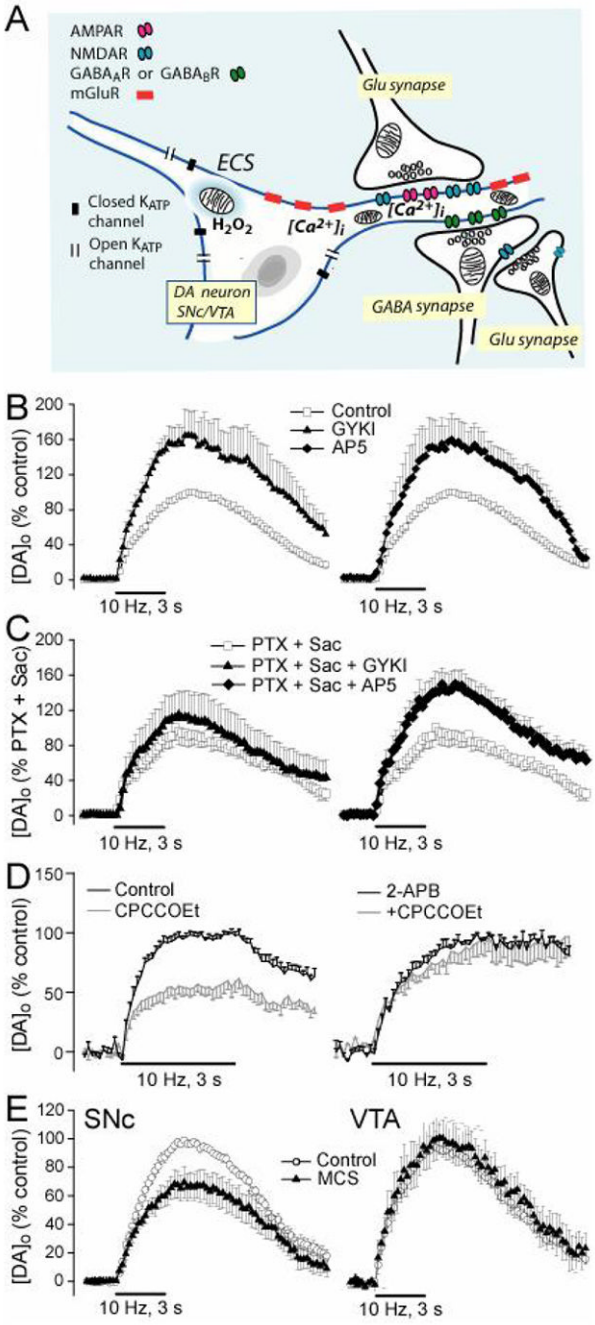

Figure 5. Regulation of somatodendritic DA release in SNc by glutamate, GABA, and H_2O_2

A) Schematic representation of glutamate and GABA input to midbrain DA neurons. In SNc, GABA input predominates, such that excitatory glutamate input *enhances inhibition* via presynaptic AMPARs and NMDARs on GABA terminals; in VTA, excitatory input predominates (*see* text). Somatodendritic DA release in SNc is also facilitated by glutamate acting at mGluRs on DA neurons with consequent activation of IP_3Rs (*ECS* is extracellular space; elements not to scale), but inhibited by elevated endogenous H_2O_2 acting via K_{ATP} channels. **B)** Average $[DA]_o$ *versus* time profiles in SNc evoked by local stimulation (30 pulses, 10 Hz) when AMPARs are antagonized by GYKI-52466 (GYKI, 50 μM, n = 7;

control, n = 28; $p < 0.001$ *vs.* control) or NMDARs are antagonized by AP5 (100 μM, n = 6; $p < 0.01$ *vs.* control). **C)** The presence of the GABA-receptor antagonists PTX (100 μM) and saclofen (Sac, 50 μM) prevents the increase in evoked $[DA]_o$ seen with GYKI (50 μM); compare with **(A)** (PTX + Sac, n = 10; PTX + Sac + GYKI, n = 5; $p > 0.05$). The GABA antagonist cocktail alone causes an increase in evoked $[DA]_o$, which is taken as 100%. The increase in evoked $[DA]_o$ in the presence of AP5 (100 μM) persists when GABARs are antagonized (PTX + Sac + AP5, n = 5; $p < 0.01$). **D)** Average $[DA]_o$ *versus* time profiles in SNc in the absence and presence of an mGluR1 antagonist, CPCCOEt (100 μM, n = 9; $p < 0.001$) (*left*) and in CPCCOEt after pretreatment with an IP_3 receptor (IP_3R) antagonist 2-APB (100 μM, n = 6; $p > 0.05$) (*right*). Inhibition of IP_3Rs alone decreased evoked $[DA]_o$ (n = 8; $p < 0.001$ *vs.* control); peak evoked $[DA]_o$ in 2-APB is taken as 100% in the right panel. **E)** Evoked $[DA]_o$ with pulse-train stimulation in SNc and VTA. Inhibition of GSH peroxidase with MCS (1 mM) leads to suppression of DA release in SNc, but not VTA. Panels **B,C** are modified with permission from Chen and Rice, 2002; panel **D** is modified from Patel et al., 2009; panel **E** is modified from Chen et al., 2002, copyright Journal of Neuroscience, used with permission.

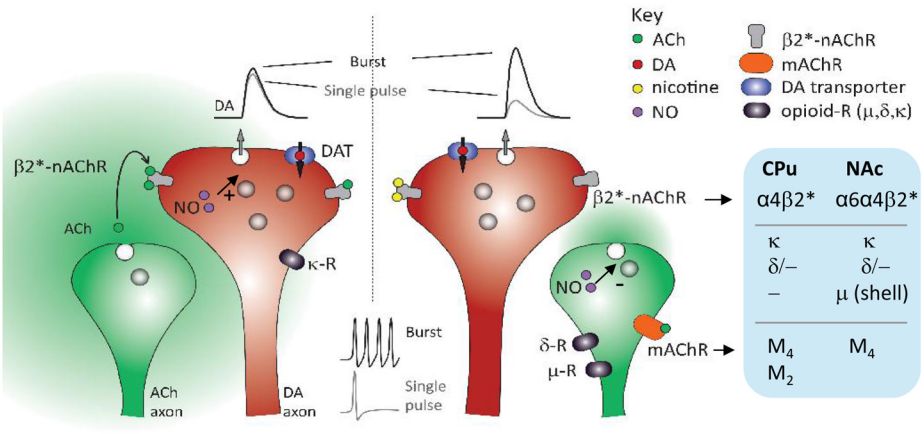

Figure 6. Role of ACh, nAChRs and cholinergic interneurons in the regulation of DA release by striatal muscarinic receptors, opioid receptors, and NO

Cartoon illustrating the change in sensitivity of DA release to axonal activity (*left*, low sensitivity, *right*, high sensitivity) as a result of deactivation or desensitization of presynaptic nAChRs on DA terminals by the action of muscarinic receptors on ChIs, μ-opioid receptors on ChIs in NAc shell, δ-opioid receptors in some sites (*δ/–*) in NAc or CPu, or NO. Note the different receptor subtypes involved in NAc and CPu. Data taken from Exley et al., 2008, 2011; Britt and McGehee, 2008; Threlfell et al., 2010b; Hartung et al., 2011.

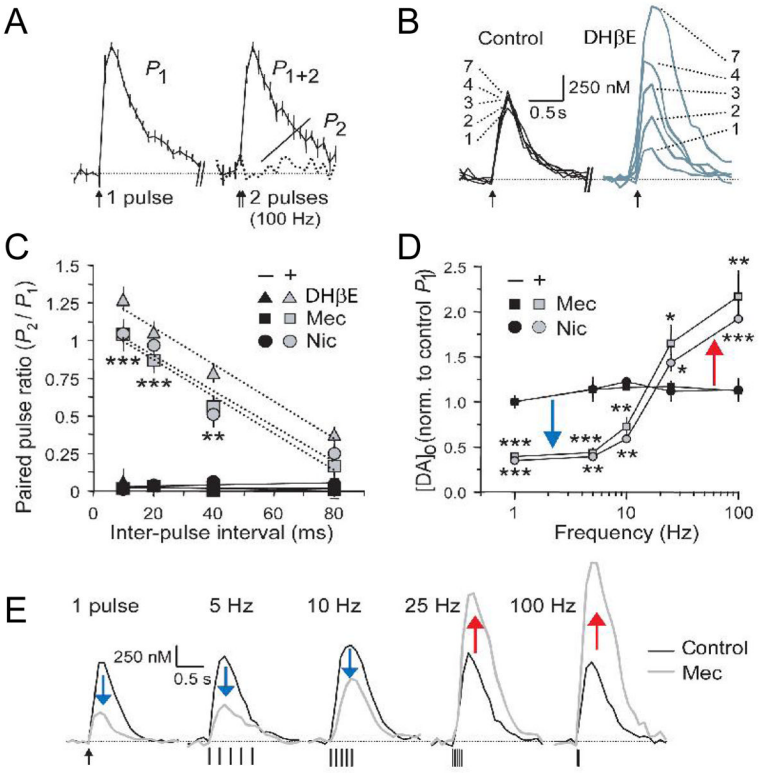

Figure 7. ACh or nicotine action at striatal nAChRs governs DA release probability and sensitivity of DA release to activity (pulse number, inter-pulse interval, frequency)

A) Average profiles of extracellular DA concentration ($[DA]_o$) ± SEM versus time ('DA transients') in guinea-pig striatal slice evoked by 1 (P_1) or 2 pulses (P_{1+2}) paired at a 10 ms inter-pulse interval (100 Hz) show depression of release at P_2 at this frequency (P_2 is obtained from P_{1+2} minus P_1). **B)** Effect a selective β*-nAChR antagonist, DHβE (dihydro-β-erythroidine), on dynamic release probability of DA following 1–7 pulses (*arrows*) at 100 Hz. DHβE (*right*) suppresses $[DA]_o$ released by a single pulse ($p < 0.001$) but in turn relieves short-term depression during a burst: $[DA]_o$ becomes strongly dependent on number of pulses within the burst and can exceed concentrations seen in control (*left*, $p < 0.001$). **C)** ACh gates dynamic release probability of DA according to activation frequency. In control, mean paired-pulse release ratios (P_2/P_1) vary little with inter-pulse interval ($p > 0.05$, R^2 =0.05–0.31). Reduction of nAChR activity by competitive nAChR antagonists (DHβE or mecamylamine, Mec, or desensitization by nicotine, Nic), enhances paired-pulse ratios compared to controls (**$p < 0.01$; ***$p < 0.001$) consistent with high frequency-pass filtering (linear inverse dependence on pulse interval, *dotted lines*, $p < 0.01$–0.05; $R^2 >$ 0.92). Control (−) or with (+) drug. **D)** Mean peak $[DA]_o$ ± SEM versus frequency in 5-pulse trains (normalized to control P_1) reveal that nAChR inhibition (Mec) enhances DA transients released by high, reward-related frequencies (red arrows) but diminishes release by low frequencies (blue arrows, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ *vs.* controls), thus enhancing DA signal contrast. (**e**) Representative $[DA]_o$ transients following 5-pulse stimulus trains at 5–100 Hz illustrate how a reduction in nAChR activity (Mec, *gray lines*), e.g., due to a pause in striatal ChI firing, polarizes how DA neuron firing patterns are transduced into DA release (*arrows*), with increased contrast in DA transients evoked by different frequencies. Adapted from Rice and Cragg, 2004 and Cragg, 2006, with permission.

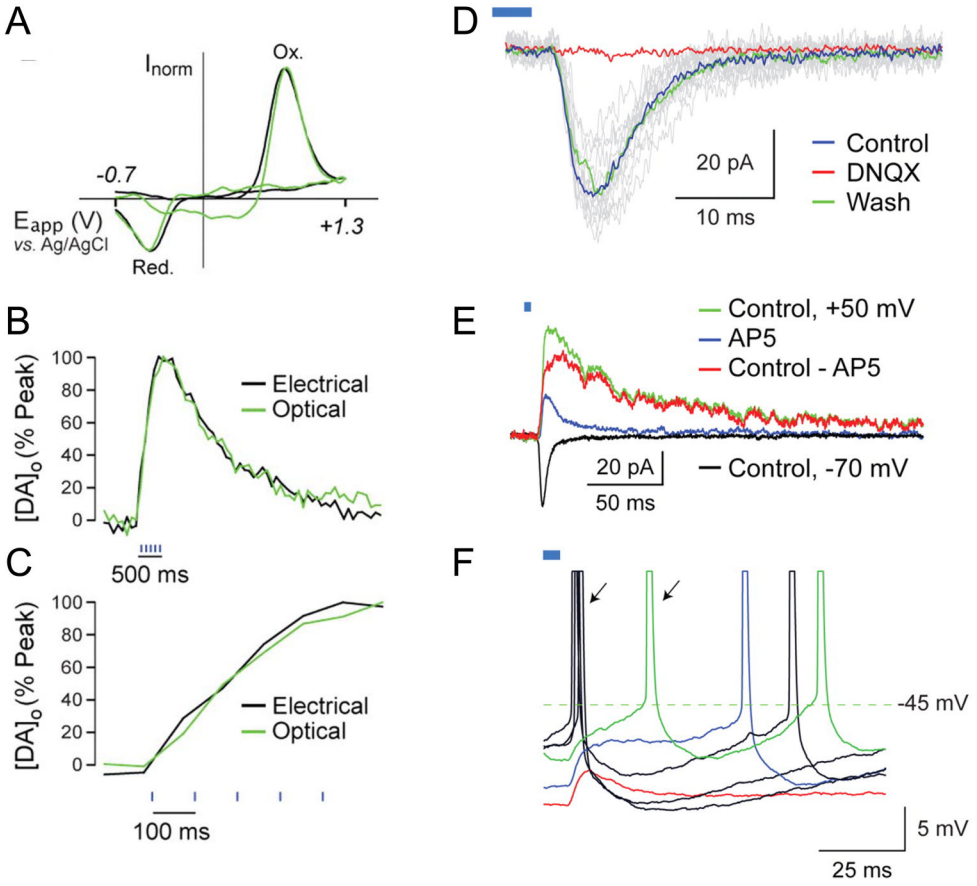

Figure 8. Glutamatergic signaling by optical stimulation of mesolimbic DA axons

A) Representative cyclic voltammograms obtained with FCV during optical stimulation of DA axons in the NAc shell (*green*) and in a 1 μM DA standard solution (*black*), with oxidation (Ox) and reduction (Red) peak potentials that identify DA as the detected moelcule. **B–C)** Representative $[DA]_o$ traces evoked by optical (*green*) and electrical (*black*) stimulation (5 pulses, 10 Hz) in the NAc shows similar time course for both stimulation methods, including the onset of release **(C). D–E)** Voltage-clamp records of optically evoked (5 ms pulses, *blue bars*) EPSCs in NAc MSNs mediated by AMPARs **(D)** and NMDARs **(E)**. Colored traces show the average of 10 EPSCs; gray traces show individual control responses. An AMPAR antagonist, DNQX (10 μM), reversibly abolished evoked EPSCs in MSNs **(D).** In contrast, an NMDAR antagonist, AP5 (50 μM) only partially suppressed EPSCs, indicating a predominant excitatory effect at AMPARs. **F)** Current-clamp records show that optical stimulation of DA axons produces EPSPs that trigger spikes (*arrows*) in MSNs at holding potentials above −52 mV. Modified from Tecuapetla et al., 2010, copyright Journal of Neuroscience.

Table 1

Differences between DA transmission and glutamate transmission at ionotropic receptors

Parameter	Dopamine	Glutamate	refs.
Transporter localization	DA axons, somata and dendrites	Pre- and postsynaptic, surrounding glia	Nirenberg et al., 1996a Seal and Amara, 1999 Danbolt, 2001
Transporter cycle rate (molecules/s/transporter)	2–5	35	Wadiche et al., 1995 Povlock and Schenk, 1997 Prasad and Amara, 2001
Intersynaptic distance (forebrain)	1.2–3.5 μm	0.5 μm	Doucet et al., 1986 Pickel et al., 1981 Descarries et al., 1996 Cragg and Rice, 2004 Arbuthnott and Wickens, 2007
Receptor localization	extrasynaptic	intra- and extrasynaptic	Sesack et al., 1994 Yung et al., 1995 Hersch et al., 1995 Khan et al., 1998 Ottersen and Landsend, 1997 Galvan et al., 2006
Receptor sensitivity	nM-μM	μM-mM	Richfield et al., 1989 Neve and Neve, 1997
Receptor response time	1–5 ms	50 ms - >1 s	Rusakov and Kullman, 1998 Barbour, 2001