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Cite this article: Rice ME, Patel JC. 2015
Somatodendritic dopamine release: recent
mechanistic insights. *Phil. Trans. R. Soc. B* **370**:
20140185.
<http://dx.doi.org/10.1098/rstb.2014.0185>

Accepted: 8 April 2015

One contribution of 16 to a discussion meeting
issue 'Release of chemical transmitters from
cell bodies and dendrites of nerve cells'.

Subject Areas:

neuroscience, physiology

Keywords:

exocytosis, volume transmission, voltammetry,
midbrain slices

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Somatodendritic dopamine release: recent mechanistic insights

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Dopamine (DA) is a key transmitter in motor, reward and cognitive pathways, with DA dysfunction implicated in disorders including Parkinson's disease and addiction. Located in midbrain, DA neurons of the substantia nigra pars compacta project via the medial forebrain bundle to the dorsal striatum (caudate putamen), and DA neurons in the adjacent ventral tegmental area project to the ventral striatum (nucleus accumbens) and prefrontal cortex. In addition to classical vesicular release from axons, midbrain DA neurons exhibit DA release from their cell bodies and dendrites. Somatodendritic DA release leads to activation of D2 DA autoreceptors on DA neurons that inhibit their firing via G-protein-coupled inwardly rectifying K⁺ channels. This helps determine patterns of DA signalling at distant axonal release sites. Somatodendritically released DA also acts via volume transmission to extrasynaptic receptors that modulate local transmitter release and neuronal activity in the midbrain. Thus, somatodendritic release is a pivotal intrinsic feature of DA neurons that must be well defined in order to fully understand the physiology and pathophysiology of DA pathways. Here, we review recent mechanistic aspects of somatodendritic DA release, with particular emphasis on the Ca²⁺ dependence of release and the potential role of exocytotic proteins.

1. Introduction

The transmitter dopamine (DA) plays critical roles in movement and motor learning, emotion and reward, and memory and cognition [1–3]. The importance of DA in motor behaviour is particularly well established: DA regulates neuronal output from the basal ganglia [4], and loss of DA leads to basal ganglia dysfunction and the consequent motor deficits of Parkinson's disease (PD) [5–8]. Forebrain DA innervation originates in midbrain DA neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) [9]. Axons from these DA neurons provide rich innervation of the distant striatal complex [10]: the nigrostriatal DA pathway projects from SNc preferentially to dorsal striatum (caudate-putamen, CPu), and the mesolimbic DA pathway projects from VTA preferentially to ventral striatum (nucleus accumbens, NAc) and to prefrontal cortex [11,12].

Midbrain DA neurons in the SNc and VTA also release DA from their somata and dendrites [13–26]. The term 'somatodendritic' accurately describes evoked DA release in the SNc and VTA, in which somata and dendrites intermingle (figure 1), so that somatic and dendritic release cannot readily be distinguished. However, mechanisms and regulation of somatodendritic DA release have been studied primarily in SNc, in which DA release is exclusively somatodendritic: the SNc is devoid of synaptic DA input from axon collaterals [28,29], whereas the VTA has collaterals arising from its own axons, as well as axons from SNc [30,31]. As discussed further below, this anatomy has functional consequences, with a uniquely somatodendritic Ca²⁺-dependence of DA release in the SNc, but mixed axonal and somatodendritic characteristics in the VTA [32].

What are the physiological roles of somatodendritic DA release? In SNc and VTA, locally released DA binds to D2 autoreceptors to regulate the rate and pattern of firing of the DA neurons [23,33–36], thereby regulating distal release of DA in dorsal and ventral striatum [37]. Local autoinhibition via DA and D2 receptors provides feedback to limit somatodendritic DA release as well [38].

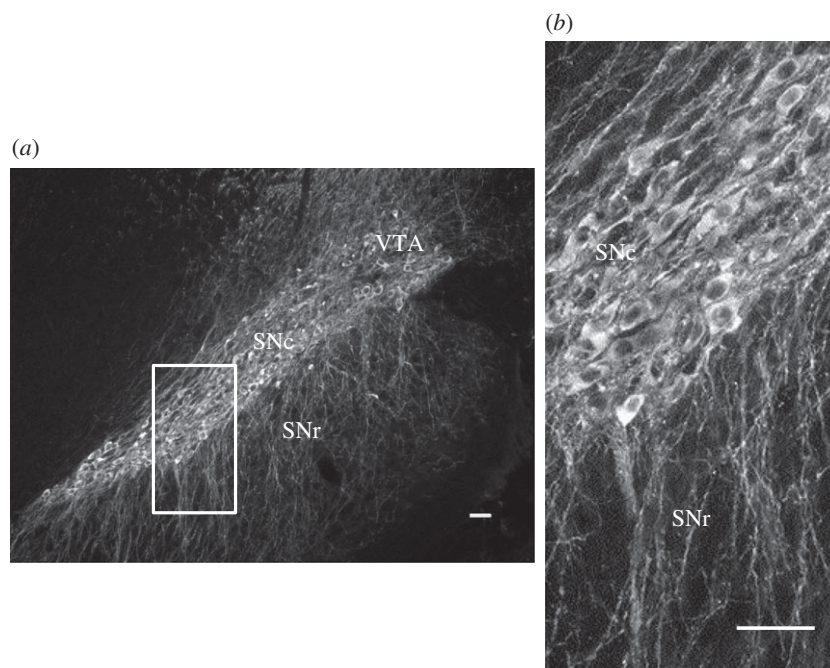


Figure 1. Tyrosine hydroxylase immunoreactive (TH-ir) cell bodies and processes in midbrain. (a) Low magnification view of SNc, SNr and VTA revealed by TH immunostaining. The SNc and more medially located VTA contain a mix of TH-ir somata and dendrites, whereas SNr is nearly free of TH-ir cell bodies, but contains abundant TH-ir dendrites. (b) Higher magnification view of the portion of SNc and SNr outlined in (a) to show the mixture of somata and dendrites in the SNc and primarily ventrally projecting dendrites in the SNr. Scale bars, 50 μm (adapted from [27]).

Additionally, DA is released from dendrites of SNc DA neurons that project ventrally into the adjacent substantia nigra pars reticulata (SNr) (figure 1b). Dendritically released DA acts at D1 DA receptors on the terminals of striatonigral (direct pathway) axons in the SNr to enhance gamma-aminobutyric acid (GABA) release from these axons to amplify inhibition of the principle cells of the SNr, which are GABAergic projection neurons [39–41]. Through these pathways, somatodendritic as well as axonal release regulate motor behaviour [31,42–48].

Several previous reviews of somatodendritic DA release have summarized the history and fundamental issues [49–55]. To complement and extend those earlier articles, this review will emphasize recent findings that shed light on unresolved questions, including the role of volume transmission in somatodendritic DA transmission, mechanisms of somatodendritic DA release, the Ca^{2+} dependence of release, and regulation by autoreceptor and heteroreceptor activation. Although many of the mechanistic studies discussed have been conducted in the SNc rather than VTA, insight into DA release in VTA will also be noted when available.

2. Methods to study somatodendritic dopamine release

The earliest studies of somatodendritic DA release examined ^3H -DA overflow from *ex vivo* midbrain slices [14] or *in vivo* using push–pull perfusion [15,16]. Later, *in vivo* studies of DA release regulation used microdialysis [37,56–61], which includes a separation step that permits selective detection of DA, as well as DA metabolites or other transmitters. A caveat for microdialysis, or any *in vivo* method, however, is the potential confounding influence of either systemic or locally applied drugs on regulatory processes that could be either local or mediated by long pathways.

In light of the potential ambiguity of *in vivo* data, most recent mechanistic studies of somatodendritic DA release have returned to midbrain slice or *in vitro* cell culture preparations. The primary methods for DA detection in slices are electrochemical or electrophysiological, which permit real-time monitoring of endogenous DA release, as discussed further below. Detection of overflow in culture requires sensitive, albeit off-line, DA detection using high performance liquid chromatography or radioassay [62,63].

(a) Voltammetry and amperometry

The primary electrochemical method used to study somatodendritic DA release has been fast-scan cyclic voltammetry (FCV) with carbon-fibre microelectrodes, which permits quantification of subsecond changes in extracellular DA concentration ($[\text{DA}]_o$) with micrometre spatial resolution [64–66]. This voltammetric method allows detection of evoked release of DA in discrete brain regions, including the SNc and VTA [17–19,21,25,26,32,38,67–69]. Identification of DA can be confirmed by its characteristic voltammogram (figure 2) [18,22], as well as by amplification of the release response by inhibition of the DA transporter (DAT) [20,21], or suppression of release following inhibition of the vesicular monoamine transporter, VMAT2 [17]. Another method is amperometry, in which a carbon-fibre microelectrode is held at a constant potential, sufficient for the oxidation of DA, with the resulting current reflecting the number of oxidized molecules. This method has been used to demonstrate quantal release of DA from DA somata [70,71]. As with microdialysis, there are also caveats for voltammetric and amperometric recording. For example, voltammetric studies of somatodendritic DA release in the substantia nigra of some species, including mice and rats, has been hindered by the predominant detection of 5-HT (5-hydroxytryptamine; serotonin), which is also electroactive (reviewed in [52,65]). This is not a concern in

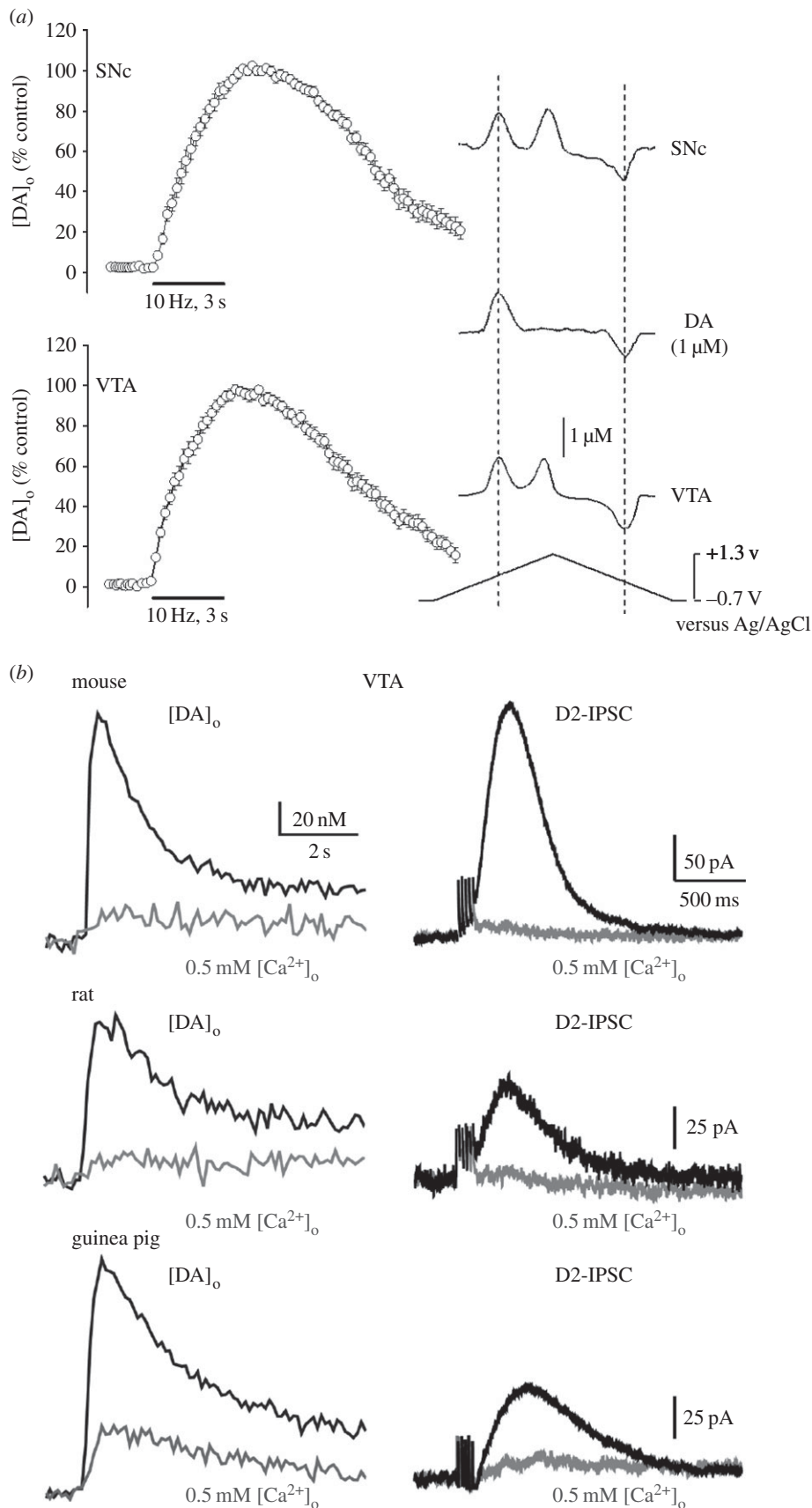


Figure 2. Somatodendritic DA release in the SNc and VTA monitored using voltammetry and electrophysiology. (a) Left panel: average evoked increases in extracellular DA concentration ($[DA]_0$) during pulse-train stimulation (30 pulses, 10 Hz) recorded using FCV with carbon-fibre microelectrodes in the SNc and VTA in midbrain slices. Maximal evoked $[DA]_0$ was $0.81 \pm 0.08 \mu\text{M}$ ($n = 13$) in the SNc, and $0.61 \pm 0.06 \mu\text{M}$ ($n = 16$) in the VTA. Right panel: evoked responses detected using FCV were identified as DA by the characteristic peak potentials, which were the same as for a solution of DA (1 μM); typical oxidation and reduction peak potentials are 0.60 V and -0.25 V versus Ag/AgCl, respectively (adapted from Chen *et al.* [22]). (b) Left panel: averaged increases in $[DA]_0$ evoked by five pulses at 40 Hz monitored using FCV ($n = 7-10$ traces) in the VTA in midbrain slices from mouse, rat and guinea pig; responses were recorded in 2.5 mM $[Ca^{2+}]_0$ (black) or in 0.5 mM $[Ca^{2+}]_0$ (grey). Right panel: representative D2-IPSCs (DA-dependent inhibitory postsynaptic currents) obtained using voltage-clamp recording of VTA DA neurons from mouse, rat and guinea pig recorded in 2.5 mM (black) or 0.5 mM $[Ca^{2+}]_0$ (grey) (adapted from Courtney *et al.* [69]).

microdialysis studies that include a chemical separation step. It is also not a concern when guinea pigs are used for FCV studies of somatodendritic DA release in the SNc, because 5-HT innervates distal DA dendrites in the SNr, which is further away from the SNc in guinea pig than in smaller rodents, allowing detection of clean DA release (figure 2a). Notably, the VTA of mice, rats and guinea pigs lacks 5-HT innervation so that a pure DA signal can be detected using FCV [20,22,68,69] (figures 1a and 2b, left panel). A caveat for the use of amperometry, however, is that detection of current only does not provide electrochemical evidence of the current source, so that additional pharmacological manipulations would be required to confirm a pure DA release response in a given region and species.

(b) Electrophysiology

The most recent addition to the repertoire of methods to study somatodendritic DA release is electrophysiological and involves whole-cell voltage-clamp recording from DA neurons. Williams and co-workers pioneered the use of D2 DA autoreceptor-dependent currents as a 'biosensor' for evoked DA release in the SNc and VTA [23,24,26,55,69,72]. The detected currents arise from the DA-dependent activation of D2 autoreceptors, which are linked to G-protein-coupled inwardly rectifying K^+ (GIRK) channels in DA neurons [73–76]. These are referred to as D2-dependent inhibitory post-synaptic currents (D2-IPSCs; figure 2b, right panel). Evoked D2-IPSCs are abolished by the D2 receptor antagonist sulpiride and by VMAT2 inhibitors, and are amplified by the DA precursor L-DOPA or inhibition of the DAT by cocaine [23,24,26,69,72]. Notably, consistent D2-IPSCs can be evoked repetitively by brief pulse-train stimulation (five pulses, 40 Hz). This contrasts with pulse-train evoked $[DA]_o$ detected using FCV, which tends to run down with repetitive stimulation [65].

The interpretation of D2-IPSCs is that they are a post-synaptic response to DA release from adjacent DA neurons at dendro-dendritic synapses. Despite strong evidence to support this interpretation [23,24,26,55,69,72], this is not fully consistent with anatomical data given that dendro-dendritic synapses [77–79] are absent in DA dendrite-rich SNr [78] and are relatively rare in SNc and VTA [78]. Moreover, Pickel *et al.* [80] have shown that D2Rs on midbrain DA neurons cluster extrasynaptically near presumed *glutamatergic* synapses on DA dendrites. An alternative, or at least complementary, explanation for D2-IPSCs is that they reflect an autocrine DA signal from the recorded neuron, with dendritic release following very rapid, localized, dendritic action potentials [81], which would be difficult to clamp.

3. Dopamine neuron anatomy, biochemistry and physiology

The number of DA neurons per hemisphere ranges from 3500 to 7200 for rat SNc [82,83]. These DA neurons were initially broadly subdivided according to anatomical location within the SNc. Neurons in the ventral tier of the SNc have large ovoid somata (20–30 μm long) with multiple dendrites that extend laterally along the band of cell bodies in SNc, as well as ventrally into the SNr, which has few DA cell bodies [9,28,29,84] (figure 1a,b). Cells in the dorsal tier of the SNc tend to be slightly smaller, and also populate the

VTA, which is medially adjacent to the SNc (figure 1a). The axons of DA neurons emerge from a proximal dendrite and project to the striatal complex in a roughly topographical manner [85–88]. All DA neurons innervate both the striosome (also called patch) and matrix compartments of the striatum, although the axonal arborization of dorsal tier neurons favour the matrix, whereas ventral tier neurons tend to favour striosomes [10,86,89,90].

Within these populations, additional biochemical and physiological differences confer differential excitability, as well as differential vulnerability to pathophysiological insults [88,91–94], with greater susceptibility of ventral tier neurons of the SNc to degeneration in PD (and animal models of the disease) than those in the dorsal tier of SNc or the VTA [95,96]. Among other biochemical differences, dorsal tier SNc DA neurons and VTA DA neurons are enriched in the Ca^{2+} -buffering proteins, calbindin-D28 K and calretinin, whereas the majority of ventral tier SNc DA neurons appear to lack these proteins [97]. This difference has been implicated in the Ca^{2+} dependence of somatodendritic DA release, with high calbindin levels in VTA DA neurons contributing to the regulation of DA release probability [98]. Higher levels of Ca^{2+} buffering proteins also confer a neuroprotective advantage to VTA DA neurons compared to ventral tier DA neurons in SNc [99]. Expression of the DAT also differs, with higher protein and mRNA levels in ventral tier SNc neurons than in dorsal tier cells in SNc or VTA [97,100,101]. This difference is reflected in the greater DAT-dependent regulation of $[DA]_o$ in SNc versus VTA [19,102]. Similarly, SNc DA neurons have greater D2 autoreceptor expression versus VTA [100], which is reflected in greater autoreceptor regulation of somatodendritic DA release in SNc than in VTA [38].

It is increasingly recognized that levels of Ca^{2+} -binding proteins alone are not predictive of cell properties or projection target. For example, two types of mesocorticolimbic DA neurons with similar levels of calbindin d28k expression not only differ in firing properties and in the ratio of DAT to tyrosine hydroxylase (TH) or VMAT2 expression in each cell, but also in forebrain target regions [87,103]. Another subpopulation of VTA DA cells projecting to the medial prefrontal cortex lack functional somatodendritic GIRK2-coupled DA D2 autoreceptors [87]; this would preclude physiological recording of D2-IPSCs as an index of DA release in the D2 receptor-lacking cells. Further distinctions are seen in expression of ATP-sensitive potassium (K_{ATP}) channels, which contribute to the greater effect of DA-selective neurotoxins on SNc versus VTA DA neurons [104]. Moreover, differences in K_{ATP} channel subtypes between two populations of DA neurons within SNc contribute to the relative responsiveness of these cells to metabolic stress and to H_2O_2 [105,106]. Differences in Ca^{2+} channel expression among DA neuron populations is also well recognized, with a greater role for Cav1.3 L-type Ca^{2+} channels in the regulation of pacemaker activity in SNc versus VTA DA neurons that contributes to the greater vulnerability of SNc cells to degeneration [107]. Liss and co-workers have further shown a functional link between Cav1.3 L-type Ca^{2+} channels and the desensitizing/non-desensitizing state of D2 DA autoreceptors, which is governed by intracellular levels of a neuronal Ca^{2+} sensor (NCS-1) [108].

The differential chemical and electrophysiological properties of DA neurons also contribute differentially to animal behaviour. For example, transmission of aversive or reward related behaviour by DA neuron populations is correlated

with neuronal properties [103]. Similarly, the activity of K_{ATP} channels in DA neurons in medial SNc regulates burst firing in these cells, which in turn contributes to exploratory behaviour in animals placed in a novel environment [92,94].

(a) Subcellular dopamine neuron anatomy

Subcellular anatomical characteristics of DA neurons also have several implications for somatodendritic DA release and its regulation. First, in contrast to DA axons in the striatum that show abundant clusters of vesicles near the plasma membrane at presumed release sites [109,110], DA somata in the SNc generally lack such clusters [78], as do DA dendrites within the SNr ([29,77], but see [79]). Indeed, somatodendritic vesicles are sparse and appear to be insufficient in number to provide an adequate source of DA for vesicular exocytotic release. Nevertheless, there is evidence for quantal DA release from DA somata in the SNc, with an estimated quantal size of 14 000 molecules per vesicle [70], which is of similar magnitude to that determined for release from chromaffin granules [111], as well as from axonal varicosities of DA neurons in culture [112,113]. Second, primary storage of somatic DA in both SNc and VTA appears to be in 'tubulovesicles' (sacculi of smooth endoplasmic reticulum (ER)) that express VMAT2, although VMAT2 is also associated with occasional small clear vesicles or large dense core vesicles [78]. VMAT2 is also present on the limiting membranes of multivesicular bodies that may be involved in recycling vesicular membrane proteins [78]. Whether or how DA is released from tubulovesicles is not known, as loss of release with VMAT2 inhibition confirms a role for DA storage, but not for exocytosis *per se*. Third, in addition to the absence of axonal synapses, noted above, dendro-dendritic synapses are rare [29,77–79]. Indeed, although dendro-dendritic DA synapses are found in the SNc and VTA, albeit infrequently [79], they are virtually absent in DA-dendrite-rich SNr [77] (figure 1b).

4. What is the role of volume transmission in the substantia nigra pars compacta and ventral tegmental area?

Given the anatomical characteristics of SNc and VTA neurons described in the previous section, somatodendritic DA release in midbrain must be at least in part non-synaptic. Moreover, DA receptors and the DAT on DA cell bodies and dendrites are largely extrasynaptic [110,114–116], as are D1 receptors on non-dopaminergic terminals in these regions [115,117]. Thus, somatodendritically released DA relies on volume transmission [53,118,119], with an efficacy regulated by the diffusion and uptake characteristics of the local extracellular microenvironment, and negligible contributions from enzymatic degradation [53,102]. Consistent with the higher density of DA somata and dendrites in the SNc and VTA than in the SNr (figure 1), experimentally determined uptake rates for DA in guinea pig midbrain slices are higher in SNc and VTA than in SNr [102]. However, further distinctions occur, with greater efficacy of DAT inhibition in SNc than in VTA [19,102]. Data from these experimental studies were then used to model the influence of a 20-vesicle point source, which produced sufficiently high $[DA]_o$ for DA receptor activation (assuming 10 nM sensitivity) up to 20 μ m away, with a DA half-life at this distance of several hundred milliseconds

[102]. This model also showed that diffusion rather than uptake was the most important determinant of DA time course in midbrain [53,102].

In contrast to these findings based on DA diffusion and uptake assessed using voltammetric detection, a different picture emerges from evaluation of D2-IPSCs, which appear to be largely diffusion independent [23,24,69]. The concentration of exogenous DA required to activate comparable D2-IPSCs to those seen with endogenously evoked somatodendritic DA release is at the micromolar level, rather than the nanomolar levels expected for low-affinity-state receptors. Given that $[DA]_o$ falls rapidly with distance from a release site [53,69,120], the site of receptor activation would need to be synaptic or at least peri-synaptic. The relatively constant time course of D2-IPSPs would also be consistent with diffusion across a constant distance [23], e.g. a synaptic cleft, with the caveat that this time course is primarily determined by the kinetics of the D2-receptor-activated GIRK channel. Peak $[DA]_o$ after quantal release at a distance even 5 μ m from a release site, occurs only 10 ms after release, whereas the D2-IPSC peak is seen several hundred milliseconds after a stimulus (figure 2b). These results do not exclude a role for volume transmission in DA transmission in the SNc and VTA, but do suggest that this would not be readily assessed using D2-IPSC data [53,55].

5. Ca^{2+} dependence of somatodendritic dopamine release

Although DA release sites in the somatodendritic compartment may lack a conventional synaptic structure, they nevertheless use a Ca^{2+} -dependent exocytotic mechanism for DA release. In the first report of somatodendritic DA release [14], Geffen and colleagues proposed that release was vesicular and exocytotic, like axonal DA release. However, the precise mechanism remains a matter of debate. Somatodendritic DA release requires Na^+ -dependent action potentials (e.g. [21,121]) and is prevented by VMAT2 inhibitors [17,23,59]. As noted above, prevention by VMAT2 inhibitors alone does not confirm vesicular release, as VMAT2 is expressed by subcellular organelles in addition to vesicles in DA neurons [78].

(a) Ca^{2+} entry

Evidence for the role of Ca^{2+} in facilitating somatodendritic DA release is still inconclusive and often contradictory. Although release is abolished in the absence of extracellular Ca^{2+} (Ca^{2+} -free media with EGTA) or when Ca^{2+} entry is blocked by Cd^{2+} [17,18,25,32], somatodendritic release persists in submillimolar extracellular Ca^{2+} concentrations ($[Ca^{2+}]_o$) that do not support axonal DA release, at least when examined in guinea pig SNc. Indeed, using FCV to quantify single-pulse evoked increases in $[DA]_o$ in guinea pig midbrain and striatum [32], the $[Ca^{2+}]_o$ required for half maximal release (EC_{50}) is only 0.3 mM in SNc, but is 2.3 mM in CPu, with similar results for VTA and NAc shell (figure 3). Moreover, somatodendritic DA release in SNc is resistant to a cocktail of voltage-gated Ca^{2+} channel (VGCC) blockers that abolishes axonal release in striatum [21,60,62,122–125]. The persistence of release in these conditions presumably reflects the incomplete blockade of VGCCs, coupled with the minimal Ca^{2+} entry required for

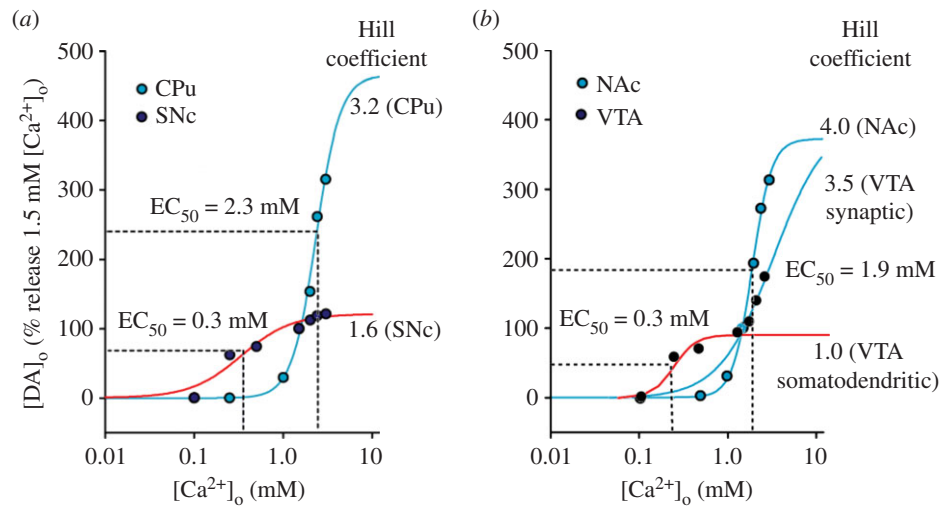


Figure 3. Ca^{2+} dependence of DA release in nigrostriatal (a) and mesolimbic (b) pathways. Normalized single-pulse evoked increases in $[\text{DA}]_o$, where release in $1.5 \text{ mM } [\text{Ca}^{2+}]_o$ is 100%. Hill curves are fit for axonal (blue lines) and somatodendritic release (red lines). Ca^{2+} sensitivity is indicated by the $[\text{Ca}^{2+}]_o$ required for half maximal release (EC_{50} , dotted lines). Notably, two distinct Hill analyses are needed to fit data from the VTA ($[\text{Ca}^{2+}]_o < 1.5 \text{ mM}$ versus $[\text{Ca}^{2+}]_o > 1.0 \text{ mM}$) revealing both axonal and somatodendritic release components. Hill coefficients indicate cooperativity of Ca^{2+} in DA release. Data are means without error bars for clarity ($n = 5\text{--}7$ per point) (adapted from Chen *et al.* [32]).

initiation of somatodendritic DA release. Thus, somatodendritic DA release shows a weak dependence on $[\text{Ca}^{2+}]_o$. It should be noted, however, that differences in the reliance on Ca^{2+} entry among rodent species have been reported, with evidence for a stronger dependence on $[\text{Ca}^{2+}]_o$ for somatodendritic DA release in rat and mouse midbrain than in guinea pig [26,69].

The question of which VGCCs are involved in initiating somatodendritic DA release is also unresolved. N- and P/Q-type, but not L-type, channels are critical in mediating basal somatodendritic DA release measured by radioimmunoassay in mesencephalic cultures [63]. However, L- and T-type channels, but not N- or P/Q-type channels are involved in K^+ -evoked DA release in the same preparation [122], and also a play role in K^+ -induced exocytotic events detected by amperometry in dissociated DA cells [71]. Therefore, current evidence suggests that the precise VGCCs that appear to be involved in somatodendritic DA release depend on the conditions employed, including species, stimulation procedure and experimental preparation.

(b) Intracellular Ca^{2+} stores

The persistence of evoked somatodendritic DA release in low $[\text{Ca}^{2+}]_o$ suggests involvement of an amplification process. A strong candidate for such amplification is Ca^{2+} -induced Ca^{2+} release from intracellular ER stores [25,126,127]. Neuronal ER forms a continuous network extending from the soma to axons and presynaptic release sites, as well as to dendrites and dendritic spines [128]. In SNc DA neurons, Ca^{2+} from somatic ER stores is propagated through this system to dendrites [129].

Proteins typically involved in Ca^{2+} mobilizing from ER stores have been identified in SNc DA somata and proximal dendrites using immunohistochemistry [25]. These include sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA 2), which sequesters cytosolic Ca^{2+} into the ER, and the intracellular Ca^{2+} -release channels inositol 1,4,5-triphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs) (figure 4). Moreover,

each of these has been shown to facilitate somatodendritic DA release evoked in SNc by pulse-train stimulation and detected using FCV (figure 4), although RyR - and IP_3R -gated stores subserve different roles [25]. Specifically, RyRs are clustered near the plasma membrane of DA neurons, as though poised for activation by Ca^{2+} entry, and amplify somatodendritic DA release when at physiological $[\text{Ca}^{2+}]_o$, although this boost is lost when transmembrane Ca^{2+} flux is increased in higher $[\text{Ca}^{2+}]_o$ (figure 4b) [25]. By contrast, amplification of SNc DA release by IP_3Rs (figure 4c) may occur primarily downstream from metabotropic receptors, including metabotropic glutamate receptors (mGluRs) [25].

It should be noted that the role of intracellular Ca^{2+} stores in facilitating somatodendritic DA release is complex and appears to vary with experimental condition or species tested [26,63,69]; moreover, it has yet to be demonstrated in VTA. Another factor to consider is that somatodendritic DA release may require a very rapid elevation in $[\text{Ca}^{2+}]_i$ close to the releasing organelle to trigger release, whereas slower global increases in $[\text{Ca}^{2+}]_i$ could act to enhance priming, for example, as seen for the release of oxytocin from the dendrites of hypothalamic neurons [126]. Whether, the differential expression of RyRs near the plasma membrane versus cytoplasmic IP_3Rs reflect these different functions remains an open question.

6. Is somatodendritic dopamine release exocytotic?

Neurotransmitter release by vesicle exocytosis depends on a multistage process [130], involving an interlocking network of proteins distributed among different sites including the releasing vesicle and active zones of the plasma membrane where vesicle fusion and exocytosis occur. Current evidence using botulinum toxins suggests that somatodendritic DA release is primarily exocytotic via SNARE (soluble N-ethylmaleimide-sensitive factor activating receptor) proteins [61,62,131]. Vesicles involved in exocytosis at fast glutamate synapses express a large number of intrinsic proteins [130,132]. However,

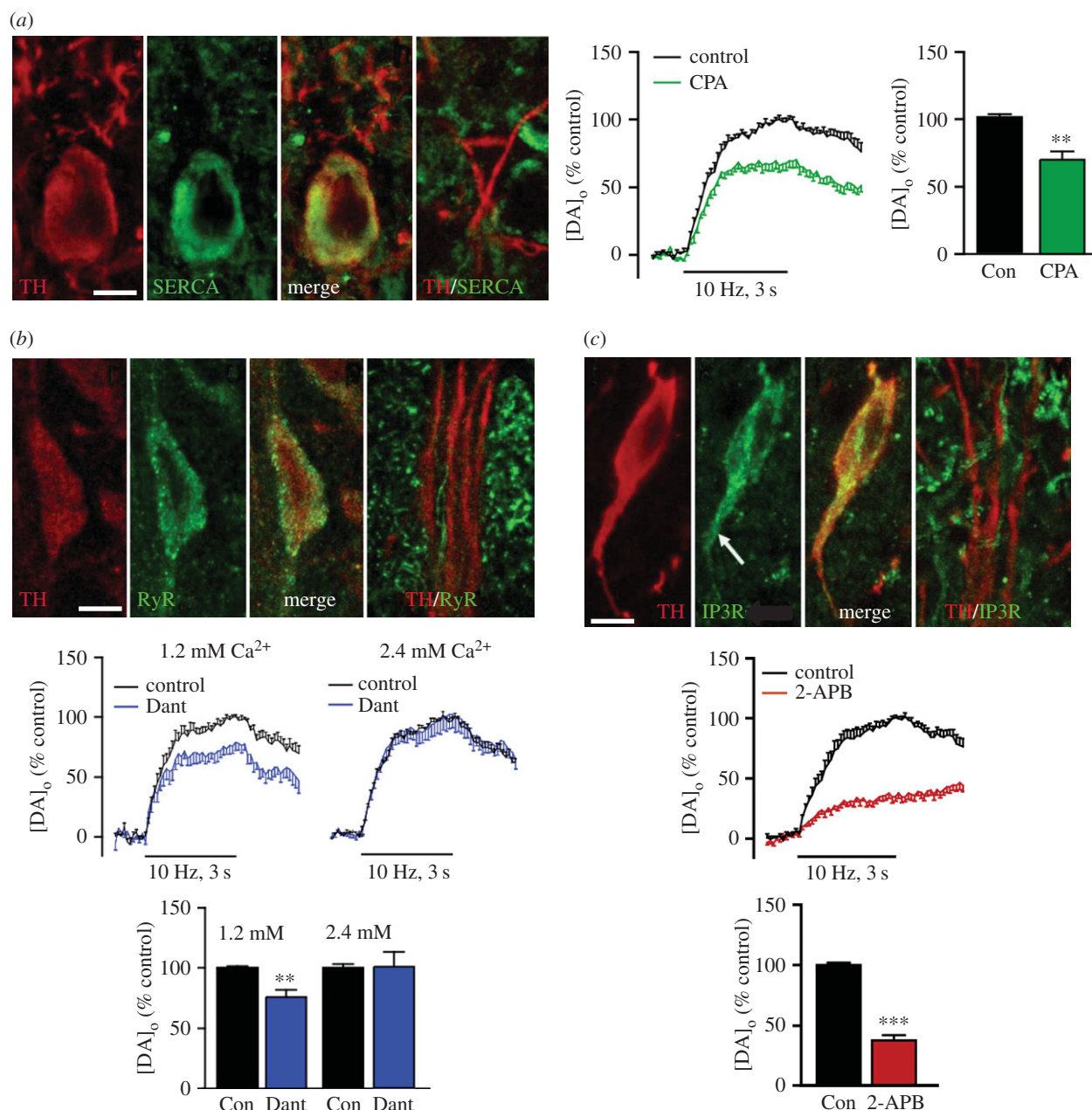


Figure 4. Role of intracellular Ca^{2+} stores in somatodendritic DA release in SNc. (a) Left panel: Colocalization of TH and SERCA2 (overlap in merge images is yellow) in SNc DA neurons is seen in the soma and proximal dendrites (first three images), but not in distal dendrites (far right image). Right panel: a decrease in evoked $[\text{DA}]_o$ (30 pulses, 10 Hz) detected by FCV when SERCA is inhibited with cyclopiazonic acid (CPA, 30 μM) demonstrates amplification of release by ER Ca^{2+} stores. (b) Upper panel: colocalization of TH and RyRs shows a mixture of large puncta located near the soma surface and smaller puncta within the cytoplasm (first three images). No staining is seen in SNr (far right image), implying low levels in distal dendrites. Lower panel: blockade of RyRs with dantrolene (Dant, 10 μM) decreases evoked $[\text{DA}]_o$ in physiological $[\text{Ca}^{2+}]_o$. (c) Upper panel: colocalization of TH and IP3Rs in the cell soma which extends down a proximal dendrite (first three images) but with minimal IP3R expression in distal dendrites (far right image). Lower panel: blockade of IP3Rs with 2-aminoethoxydiphenyl borate (2-APB, 100 μM) decreases evoked $[\text{DA}]_o$ confirming involvement of IP3R-gated ER Ca^{2+} stores in facilitating somatodendritic DA release. Scale bar in all panels is 10 μm . (** $p < 0.01$, *** $p < 0.001$) (adapted from Patel *et al.* [25]).

consistent with the relative absence of conventional synaptic vesicles in DA neurons, immunohistochemical studies show that TH-positive somata and dendrites in the substantia nigra lack proteins typically associated with vesicles, including sv2a and sv2b (isoforms of synaptic vesicle protein 2), synaptophysin and the Ca^{2+} sensors synaptotagmin 1 and 2 [27]. Moreover, several common SNARE proteins involved in vesicle docking, including the plasma membrane protein syntaxin 1a and the vesicle protein synaptobrevin 1 (Vamp 1), are also absent (figure 5). However, other plasma membrane SNARE protein isoforms are present throughout DA perikarya, including

SNAP-25 and syntaxin 3b [27,63], which is also used at 'slow' photoreceptor ribbon synapses [133]. DA somata express synaptobrevin 2 (Vamp 2), an intrinsic vesicle protein (figure 5). Overall, the molecular organization of DA release in the SNc appears to differ substantially from conventional vesicular release, with an unconventional triad of Vamp 2/SNAP-25/syntaxin 3 (figure 5). Importantly, although SNc DA somata and dendrites lack synaptotagmin 1 and 2 [27,63], which are low-affinity isoforms of the vesicular Ca^{2+} sensors found at fast synapses [134], they have the higher affinity isoforms, synaptotagmin 4 and 7 [63]. This could contribute to the high

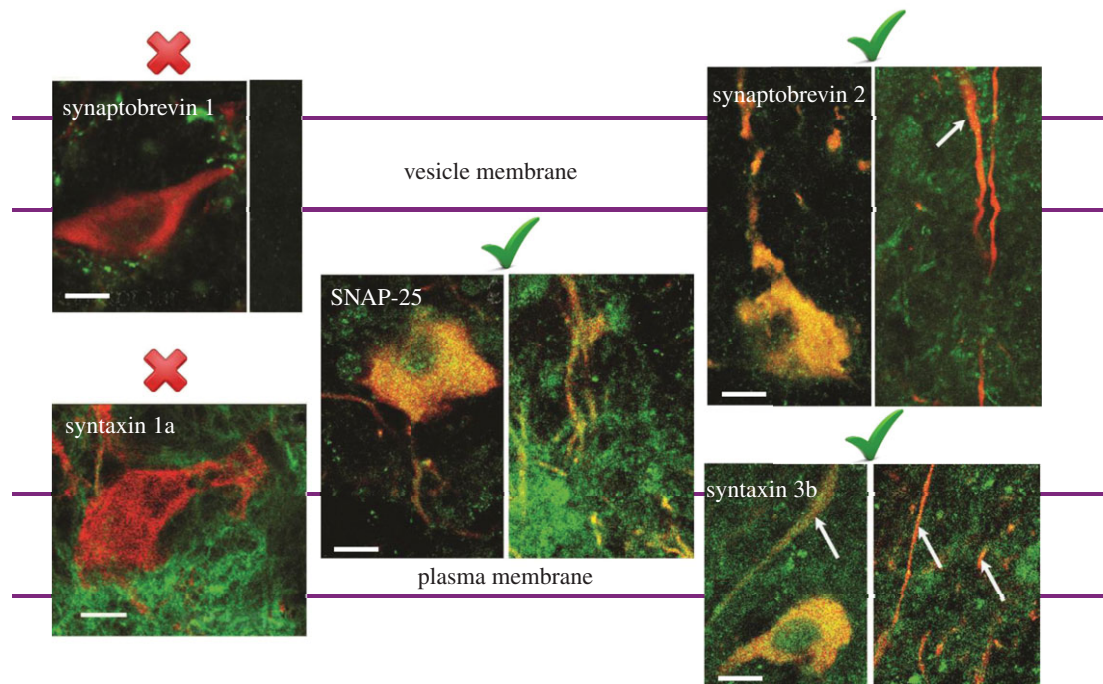


Figure 5. Identification of unusual SNARE proteins for exocytosis in SNc DA neurons. Immunostaining with TH (red) and SNARE proteins (green) shows that SNc DA somata lack the vesicular protein, synaptobrevin 1 and the plasma membrane protein, syntaxin 1a, that are conventionally used at glutamate synapses. However, DA somata and proximal dendrites do express conventional SNAP-25 as well as unconventional isoforms of exocytotic proteins, e.g. the vesicular protein, synaptobrevin 2 and the plasma membrane protein, syntaxin 3b (left-side image for each protein). SNAP-25, synaptobrevin 2 and syntaxin 3b are also present in distal dendrites within the SNr (right side images for each protein). Colocalization with TH is seen in yellow. Scale bar in all panels is 10 μm (adapted from Witkovsky *et al.* [27]).

Ca^{2+} sensitivity of somatodendritic release (figure 3) [32]. Notably, however, synaptotagmin 1 mRNA is present in DA neurons and is presumably used for axonal DA release in the striatum. Consistent with roles for synaptotagmin 4 and 7, but not synaptotagmin 1, in somatodendritic DA release, siRNA down-regulation of synaptotagmin 4 and 7, but not 1, decreases somatodendritic DA release in cultured neurons [63]. Other protein classes required for exocytosis have not been examined in DA neurons.

(a) Alternative mechanisms for somatodendritic dopamine release

Intriguingly, levels of VMAT2 and v-ATPase (the vacuolar proton pump that establishes the vesicular proton gradient driving VMAT2-dependent transport) decrease from somata to distal dendrites of DA neurons [27], despite the presence of the SNARE proteins syntaxin 3b, SNAP-25 and synaptobrevin 2 (figure 5). This suggests a possible difference between the mechanism(s) of DA release—from cell bodies and proximal dendrites in SNc versus distal dendrites in SNr. Involvement of intracellular Ca^{2+} stores in DA release regulation may also differ between somata and proximal dendrites in SNc versus distal dendrites, given the apparently low levels of SERCA, IP₃R and RyRs in distal DA dendrites in SNr [25] (figure 4).

Such data, along with the limited number of classical small clear vesicles and dendro-dendritic synapses [29,77–79,135], have suggested alternative release mechanisms, including DA release by reverse transport of the DAT [77,78,122,136,137]. Under normal conditions, cytoplasmic DA concentrations are not considered to be sufficient to reverse the DAT unless enhanced by pharmacological agents like amphetamine [138,139]. However, DA storage in tubulovesicles allows the

possibility that DA might escape from these organelles causing an increase in intracellular DA concentration that could be released into the extracellular compartment by DAT reversal. This does not appear to be a *primary* mechanism in SNc, however, given that evoked increases in $[\text{DA}]_o$ are usually enhanced, rather than abolished, with DAT inhibition [19,21,23]. Transporter reversal also would not account for the quantal release events recorded using amperometry in SNc [70]. By contrast, release from distal dendrites in SNr appears to be abolished by DAT inhibition when stimulated by glutamate afferents from the subthalamic nucleus [136]. The proposed release mechanism involves mGluR activation and subsequent protein kinase C-induced DAT reversal [136,137].

7. Modulation of somatodendritic dopamine release by synaptic input

Glutamate and GABA provide the primary synaptic input to midbrain DA neurons, with a differing balance between excitatory and inhibitory input between SNc and VTA. As reviewed previously, GABA input predominates in SNc and glutamate input predominates in the VTA [54,140]. In the SNc, somatodendritic DA release evoked by a single stimulus pulse in midbrain slices is unaffected by a cocktail of ionotropic glutamate and GABA receptor antagonists [125], suggesting the absence of tonic regulation by these transmitters *in vitro*. The use of pulse-train stimulation, however, reveals regulation by concurrently released glutamate and GABA in both SNc and VTA [141]. In SNc, local stimulation leads to DA release that is inhibited by concurrently released glutamate acting at AMPA and NMDA receptors. Consistent with anatomical data showing AMPA receptors

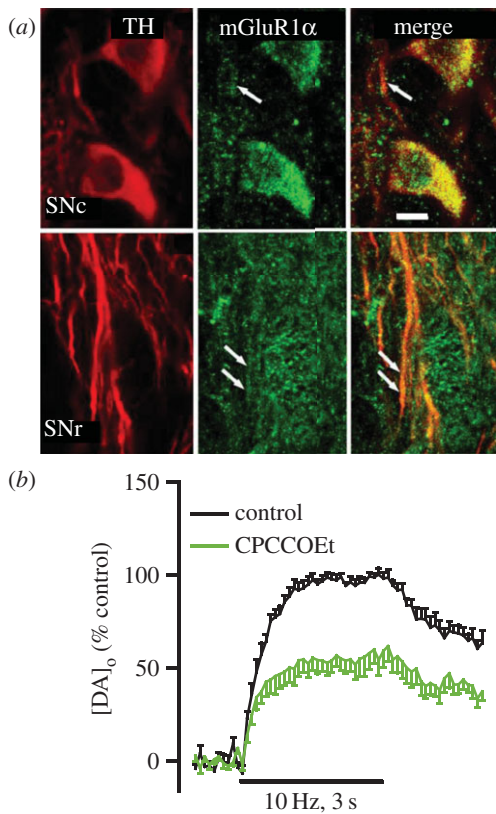


Figure 6. Activation of mGluR1 in SNc by endogenous glutamate enhances somatodendritic DA release. (a) Colocalization of TH and mGluR1α (overlap in merge images is yellow); mGluR1α puncta colocalize with TH in somata and proximal dendrites in SNc and distal dendrites in SNr. Arrows show dendritic colocalization. Scale bar, 10 μm. (b) Antagonizing mGluR1s with CPCCOEt (100 μM) decreases [DA]_o in SNc evoked by pulse-train stimulation (30 pulses, 10 Hz). Release was monitored using FCV ($n = 9$, $***p < 0.001$) (adapted from Patel *et al.* [25]).

on inhibitory cells and terminals in the SNc [142,143], this regulation is prevented by GABA receptor antagonists [141]. By contrast, the increase in [DA]_o evoked by pulse-train stimulation when NMDARs are antagonized versus control persists in a cocktail of GABA receptor antagonists, suggesting the involvement of an inhibitory mediator besides GABA. One possibility might be endogenously generated H₂O₂, which inhibits somatodendritic DA release in SNc [22] and which could be generated downstream from NMDA receptor activation.

In VTA, blocking GABA_A, GABA_B or AMPA receptors has no net effect on pulse-train evoked [DA]_o, although NMDA receptor antagonism causes a decrease, consistent with a glutamate-dependent enhancement of DA release [141]. When GABA receptors are blocked, however, blocking either AMPA or NMDA receptors leads to a decrease in evoked [DA]_o, revealing the expected direct excitatory effect of glutamate input to VTA DA neurons on DA release. It should be noted that the requirement for a cocktail of glutamate and GABA receptor antagonists to isolate D2-IPSCs as biosensors of DA release [23] precludes the use of that method to study DA release regulation by synaptic input to those receptors.

Somatodendritic DA release in SNc is also regulated by glutamate acting at mGluR1s [25], with abundant expression of mGluR1α in SNc DA neurons (figure 6) [25]. Activation of mGluR1 can lead to IP₃R-mediated Ca²⁺ release from ER stores, as discussed above. However, a complicating factor in

studying this process is the potential for competing inhibitory effects from the activation of Ca²⁺-activated K⁺ channels [144,145], which depends on agonist concentration for exogenous mGluR1 application or stimulus intensity for endogenous glutamate release [25,146]. Notably, the use of local pulse-train stimulation (10 Hz) to evoke somatodendritic DA release in SNc (detected using FCV), also causes the concurrent release of glutamate. This concurrently released glutamate activates mGluR1s to *facilitate* somatodendritic DA release, as indicated by the suppression of evoked [DA]_o in the presence of an mGluR1 antagonist [25] (figure 6). This process also involves Ca²⁺ release from IP₃R-sensitive stores [25,54]. As noted above, mGluR1 activation also facilitates dendritic DA release in SNr, possibly via DAT reversal [137].

(a) Influence of co-released glutamate and GABA?

A new question about somatodendritic DA release is whether co-released transmitters may introduce a novel twist in the concept of 'autoreceptor' regulation, in addition to inhibition of somatodendritic DA release by D2 autoreceptors [38], as noted in the Introduction. Long-standing evidence, primarily from cultured DA neurons, had indicated that glutamate could be synthesized and released by DA neurons [147,148]. Using optogenetic methods with selective expression of channelrhodopsin (ChR2) in DA neurons, several groups have now shown that glutamate released from DA axons produces glutamate receptor-dependent excitatory postsynaptic currents in striatal neurons in *ex vivo* slices [149–154] and mediates behavioural consequences *in vivo* [155]. Similar methods have shown that co-release of GABA from DA axons produces GABA_A receptor-dependent IPSCs in striatal neurons, although DA neurons do not synthesize GABA but rather obtain it via plasma membrane uptake [152,156]. Thus, if also co-released from DA somata or dendrites, glutamate or GABA could provide autoregulation of somatodendritic DA release. In support of this possibility, vesicular glutamate transporters (vGluT2) are found in VTA DA neurons [148,157], and co-released GABA appears to be stored via VMAT2 [152], which is found in all midbrain DA cells [78].

8. Conclusion and open questions

Somatodendritic DA release in SNc, SNr and VTA is involved in critical functions from motivation to motion. Although the mechanism of release remains incompletely answered, a role for exocytosis seems certain, albeit with a different Ca²⁺ dependence than seen in axonal DA release. The extent to which synaptic (dendro-dendritic) versus non-synaptic release contribute to functional levels of [DA]_o remains to be determined. Also unknown are how disorders of the nervous system affect somatodendritic DA release, or how somatodendritic DA release might contribute to disorders. Drugs of abuse can also alter somatodendritic DA release, suggesting a role in addiction, as in recent studies showing that a single dose of cocaine can induce long-term potentiation of spontaneous D2-IPSCs in SNc DA neurons [36]. DA neurons are also the primary targets of as yet unknown processes that cause neurodegeneration in PD, with greater susceptibility of ventral tier SNc DA neurons versus dorsal tier or VTA DA neurons. Among factors that have been implicated in PD are genetic mutations that lead to deficits in synaptic transmission, including altered

exocytosis, endocytosis and vesicle recycling, each of which has also been implicated causally in degeneration in PD and PD mouse models [158–160]. Strikingly, however, most evidence for release dysfunction in PD models has come from studies of glutamate release, plus a few studies of axonal DA release—but no studies of somatodendritic DA release—amplifying the value of mechanistic studies of this release process.

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Funding statement. The authors are grateful for support from NIH/NINDS R01 NS036362, NIH/NIDA R01 DA033811 and NIH/NIDA R01 DA038616.

Authors' contributions. The authors contributed equally to the planning, writing and illustrating of this article. The authors are grateful to Kayla Siletti for expert assistance in editing.

Conflict of interests. The authors declare no competing interests.

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