Chapter 10

Axonal regulation of dopamine transmission by striatal neuromodulators

Stephanie J. Cragg[a,b,], David Sulzer[b,c] and Kathryn L. Todd[a,b]*

[a]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK [b]Aligning Science Across Parkinson's Collaborative Research Network, Chevy Chase, MD, USA [c]Departments of Psychiatry,Neurology, Pharmacology, School of the Arts, Columbia University, New York, NY, USA
**Corresponding author: e-mail address: stephanie.cragg@dpag.ox.ac.uk*

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Introduction

Striatal dopamine (DA) release can be modulated by multiple neuromodulators that influence somatodendritic integration and generation of action potentials by dopamine neurons in midbrain, but also by modulators acting on dopamine axons in striatum. Axons have historically been difficult structures to interrogate anatomically and functionally within intact circuits, but a wealth of accumulating evidence indicates that striatal axons of dopamine neurons are key sites for regulating dopamine transmission. Dopamine axons are the most branched axonal arbours (Matsuda et al., 2009) documented for any CNS neuron type to date. They form thousands of branches and ~10^5 varicosities per axonal tree, comprising more than 99% of the surface of each neuron and offering a network of strategic sites for neuromodulation. Neuromodulators within the striatum offer diverse means to govern dopamine axon function: their receptors form or regulate ion channels that regulate axonal excitability and action potential propagation, as well as dopamine release probability and its short-term plasticity. Striatal neuromodulators can therefore potentially also offer therapeutic opportunities for treating the many psychomotor disorders in which dopamine dysfunction or dysregulation is a hallmark, including Parkinson's disease, dystonias, addiction disorders and psychoses (see chapters this volume).

The striatum receives diverse brain-wide afferent inputs and contains important intrinsic circuits, that together generate a rich neuromodulator landscape, comprising amino acid transmitters, amines, purines, lipids, gaseous, neuropeptides and hormones, and their respective receptors. Recent studies, aided by new technologies including genetically encoded actuators (e.g., opsins for optogenetics) and reporters (e.g., fluorescent neurotransmitter sensors), are increasingly informing our understanding of how diverse striatal circuits, their modulators and receptors, shape dopamine output in health. Here, we provide a concise overview of current knowledge of the endogenous striatal modulators and their receptors that influence dopamine release, building on earlier reviews on this topic

(Rice et al., 2011; Sulzer et al., 2016; Zhang & Sulzer, 2012)(**Figure 1**). For inputs to dopamine neurons in midbrain, see Watabe-Uchida 2025, and for the actions of non-endogenous psychostimulants on dopamine transmission, see Luscher and Reva 2025.

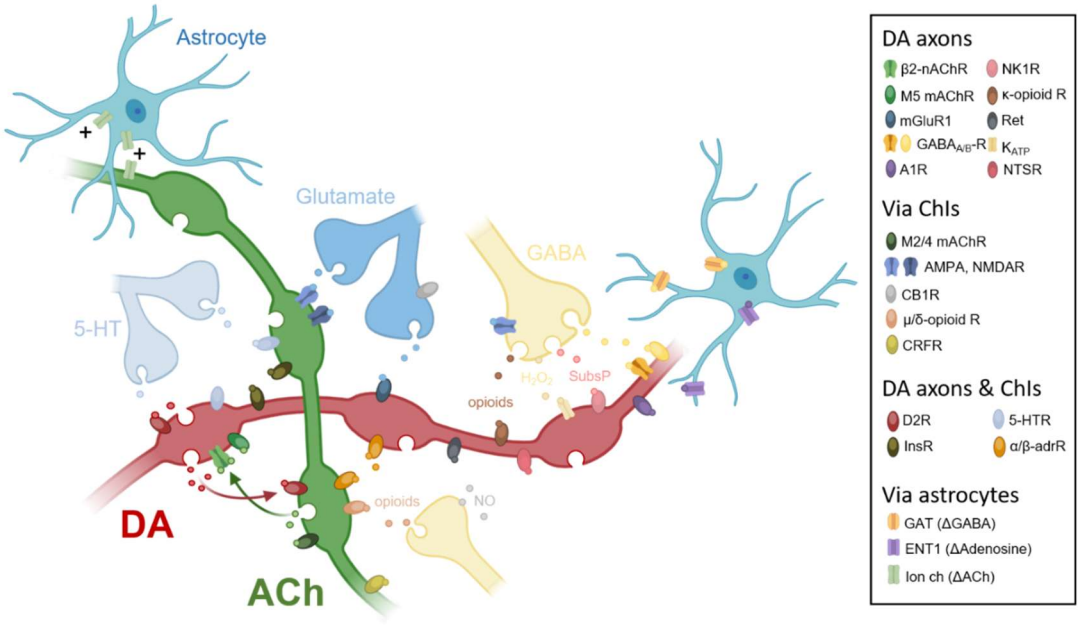

***Figure 1**: Schematic summary of striatal receptors that modulate dopamine release, either directly at dopamine axons or via ChIs, as defined functionally. Neuromodulator sources are not represented where actions are undefined. For simplicity, all actions on ChIs and ACh (whether somatodendritic or axonal) are represented here by the ACh axon. Created in BioRender. Cragg, S. (2024). BioRender.com/t42w940.*

Acetylcholine

The large, aspiny intrinsic cholinergic interneurons (ChIs) of the striatum constitute only ~2% of striatal neurons, but form an extensive axonal arborization leading to an acetylcholine (ACh) varicosity density rivalling that of dopamine (Descarries & Mechawar, 2000; Kawaguchi et al., 1995; Zhou et al., 2001). Like midbrain dopamine neurons, ChIs are tonically active (Bennett & Wilson, 1999) and have an intriguing relationship to dopamine neurons in their firing: in rodents and primates, when dopamine neurons show brief burst activity in response to unexpected reward and conditioned reward-predicting stimuli (see Schultz 2025; Uchida 2025), ChIs can exhibit a coincident pause in firing (Morris et al., 2004), indicating co-ordinated functionality of dopamine and striatal ACh. A lesser extrinsic ACh input also arises from the pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDT; Dautan et al., 2020; Dautan et al., 2014). ACh sourced from ChIs but not PPN/LDT (Brimblecombe et al., 2018) has a profound influence in shaping axonal dopamine release, through actions at ionotropic nicotinic

receptors (nAChRs), modulated by metabotropic muscarinic receptors (mAChRs), described below. The regulation of striatal dopamine release by nAChRs also offers a potentially powerful means through which other striatal neuromodulators can shape dopamine release, through actions on ChIs and changes to ACh action at nAChRs **(Figure 1)**.

Nicotinic acetylcholine receptors (nAChRs)

Dopamine neurons express mRNA for nAChR subunits α2-7 and β2-3 (Azam et al., 2002). On dopamine axons, diverse subtypes of heteropentameric β2-subunit-containing nAChRs are enriched throughout the dorsal and ventral striatum (Champtiaux et al., 2003; Jones et al., 2001; Zoli et al., 2002). Studies of dopamine release in *ex vivo* brain slices, detected using fast-scan cyclic voltammetry (FCV) in subtype-specific knockout mice, and exploiting an α6-subunit-specific antagonist (α-conotoxin), indicate that the axonal nAChR subtypes that regulate dopamine release in mouse striatum are predominantly α4α5β2-containing in dorsal striatum and α4α6β2β3-containing in NAc (Exley et al., 2008; Exley et al., 2012), although a role for α6-containing nAChRs is also reported in dorsal striatum (Exley & Cragg, 2008; Exley et al., 2012; Liu et al., 2022). These nAChRs are predominantly Na^+-permeable, with channel properties (conductances, activation and desensitisation kinetics) that vary with receptor stoichiometry, supporting the possibility that ACh could differently regulate dopamine release between regions. Non-β2-containing α7-nAChRs are more Ca^{2+}-permeable and rapidly activated/desensitizing, but have not been identified on striatal dopamine axons; however, α7-subunit-specific antagonists modulate evoked [3H]-dopamine release, which has been suggested to be due to effects of the antagonists on α7-nAChRs on glutamate axons (Kaiser & Wonnacott, 2000) (see *Glutamate* section below).

The impact of nAChRs on striatal dopamine transmission continues to be debated. Initial studies led to the suggestion that β2-containing nAChRs might filter how striatal dopamine release reports the frequency of action potential firing in dopamine axons (Exley & Cragg, 2008): β2-selective nAChR antagonists, or nicotine acting through nAChR desensitization, suppress dopamine release evoked by a single local electrical stimulus pulse or low-frequency trains of pulses (Zhou et al., 2001), but enhance the relative release evoked by high-frequency trains of pulses (Rice & Cragg, 2004; Zhang & Sulzer, 2004). These observations seemed consistent with lower initial dopamine release probability when nAChRs are inactive, and an accompanying relief from short-term depression. This state seemed to resemble a high-frequency pass filter, such that dopamine release becomes more sensitive to higher frequencies of dopamine neuronal firing in the absence of nAChR activity. Reward-related pauses in ChI activity were therefore suggested to improve how dopamine release could report high versus low frequency ascending firing activity in dopamine neurons (Cragg 2006).

However, the introduction of optogenetics to control neuronal activity, and its use with FCV and patch-clamp recordings in *ex vivo* brain slices and *in vivo*, established that action potentials

synchronized in a small network of striatal ChIs can drive dopamine release, via nAChR-dependent ectopic generation of action potentials in dopamine axons, bypassing action potential generation in the midbrain (Cachope et al., 2012; Liu et al., 2022; Threlfell et al., 2012). These findings revealed why ACh release can promote dopamine release by 'single' local electrical stimulus pulses (Zhou et al., 2001): these stimuli drive direct dopamine axon activation followed ~10 ms later by an nAChR-mediated depolarisation, driving two dopamine release events that summate (Wang et al., 2014). Striatal dopamine release can be driven by optogenetic activation of striatal ChIs, or by activation of ChIs via optogenetic activation of their glutamatergic corticostriatal or thalamostriatal afferents (Kosillo et al., 2016). However, it is not evident when or whether the conditions are met *in vivo* to reach a sufficient level of synchronised activation of ChIs and nAChRs to support this mechanism. Some recent studies *in vivo* have found little evidence for activation of dopamine release by nAChR activation (Chantranupong et al., 2023; Krok et al., 2023).

Alternatively, the impact of ChIs and nAChRs on dopamine axon activity and dopamine release might operate through different principles impacting axonal signal integration. A recent study spanning *ex vivo*, *in vivo* and *ex silico* approaches found that the dominant physiological outcome of ChI activity and nAChR activation on dopamine signalling in the intact brain is a dynamically scaling suppression of the amplitude of dopamine release (Zhang et al., 2024). Activation of nAChRs might not reach the level required to depolarise dopamine axons to a threshold to drive action potentials, but rather, nAChR-mediated depolarisation can impair subsequent depolarisation and dopamine release in response to ensuing action potentials in dopamine neurons, even for low physiological levels of ChI activation that are not sufficient to drive dopamine release (Zhang et al., 2024). This depression of subsequent dopamine release could be caused by either depolarisation-dependent ion channel inactivation or a form of shunting inhibition. It persists for up to ~100 ms, meaning that stimuli or action potentials arriving within 100 ms of nAChR activation have limited impact on subsequent dopamine release. This effect provides a mechanism to understand several observations, including: why nAChR activation limits re-release during short trains of electrical stimuli with interpulse intervals of up to 100 ms (Rice & Cragg, 2004; Zhang & Sulzer, 2004); why antagonists of nAChRs *in vivo* drive an increase in dopamine release in response to reward (Collins et al., 2016); and why some studies *in vivo* cannot find evidence for nAChRs boosting dopamine release (Chantranupong et al., 2023; Krok et al., 2023). Rather, *in vivo*, where ChIs are tonically and dynamically active providing a continuously varying ACh tone at nAChRs, we expect the relationship between nAChR and dopamine signalling to be predominately an inverse amplitude scaling. This relationship will vary dynamically over time, strongest after recent ChI activity, and will potentially show localised heterogeneity.

Brainstem sources of striatal ACh (Dautan et al., 2014) do not seem to be required for nAChR modulation of striatal dopamine release. In mice lacking forebrain ACh, nAChR-regulation of striatal dopamine release is abolished, while in mice lacking brainstem ACh, nAChR control is intact (Patel et

al., 2012). Furthermore, in a study in rats, targeted optogenetic stimulation of striatal ChIs alone was sufficient to modulate nAChR-mediated dopamine release, while stimulation of cholinergic brainstem afferents was not (Brimblecombe et al., 2018).

Muscarinic acetylcholine receptors (mAChRs)

The striatum exhibits a dense expression of mAChRs. Dopamine neurons are thought to express only M5-mAChRs (Vilaró et al., 1990; Weiner et al., 1990), while M2- and M4-mAChRs are expressed on striatal ChIs in rodent (Bernard et al., 1992) and primate (Alcantara et al., 2001). Early pharmacological studies of the effect of striatal mAChRs on dopamine release in rodents and cats were contradictory, in part due to poor ligand selectivity (De Klippel et al., 1993; Lehmann & Langer, 1982; Raiteri et al., 1984; Schoffelmeer et al., 1986).

An FCV study in mouse striatal slices showed that mAChRs modulate dopamine release strongly via indirect actions involving changes to the level of activation of nAChRs (Threlfell et al., 2010). A broad-spectrum mAChR agonist suppressed dopamine release evoked by a single-pulse or low frequencies, but enhanced release evoked by high frequencies, mirroring the effects of, and preventable by, nAChR antagonists. These effects are thought to be mediated via activation of mAChRs on ChIs, which inhibits ChI firing (Ding et al., 2006; Yan & Surmeier, 1996), reduces ACh release (Raiteri et al., 1984; Schoffelmeer et al., 1986) and consequently, reduces activation of nAChRs on dopamine axons. Subtype-specific mAChR knockout mice revealed regional variation: in the dorsal striatum, M2- and M4-mAChRs are required for these effects on dopamine, while in the NAc, only M4-mAChRs are required (Threlfell et al., 2010).

Striatal M5-mAChRs have also been shown to potentiate striatal dopamine release via presumed direct effects on dopamine axons (Bendor et al., 2010; Shin et al., 2015). M5-mAChRs are expressed by dopamine neurons although have not been definitively identified on striatal dopamine axons (Vilaró et al., 1990; Weiner et al., 1990). The knockout of M5-mAChRs leads to a modest diminution in dopamine release (Threlfell et al., 2010).

Glutamate

DA release can be modulated by striatal glutamate receptors, potentially directly and indirectly. Striatal glutamate arises principally from corticostriatal and thalamostriatal afferents, but populations of at least dopamine neurons and striatal ChIs also express vesicular glutamate transporters vGlut2 (Poulin et al., 2020) and vGlut3 respectively (Higley et al 2011) and are capable of striatal glutamate co-transmission (Hnasko et al., 2010)(reviewed in Tritsch and Melani 2025 this volume) and actions on striatal cell types, including ChIs (Chuhma et al., 2023). Dopamine axons have been suggested to lack ionotropic glutamate receptors (Bernard & Bolam, 1998; Chen et al., 1998), although axonal growth cones in development have been shown to express NMDA receptors (Schmitz et al., 2009). Dopamine axons

express the metabotropic glutamate receptor, mGluR1, in the primate brain at least (Paquet & Smith, 2003), and correspondingly glutamate spillover after tetanic stimulation in mouse inhibits dopamine release via mGluR1 (Zhang & Sulzer, 2003).

The effects of ionotropic glutamate receptors (NMDA and AMPA receptors) on striatal dopamine release (Kulagina et al., 2001; Leviel et al., 1990; Moghaddam & Gruen, 1991; Moghaddam et al., 1990; Wu et al., 2000) seem likely to be indirect and act on dopamine via other mediators. ACh is particularly pertinent here. ChIs express, and are modulated, by ionotropic glutamate receptors (Bloomfield et al., 2007) (**Figure 1**), and targeted optogenetic activation of glutamatergic corticostriatal or thalamostriatal inputs can indirectly support dopamine release via activation of NMDA and/or AMPA receptors on ChIs, increased ChI firing rates, and downstream activation of nAChRs on dopamine axons (Kosillo et al., 2016). This exemplifies the action that ACh can play as intermediary to the actions of other modulators on dopamine output. An additional means through which striatal ionotropic glutamate receptors have been shown to regulate dopamine release involves generation of the gaseous neuromodulator hydrogen peroxide (H_2O_2). A glutamate-mediated inhibition of striatal dopamine can involve AMPA-R-dependent generation of H_2O_2 from striatal spiny projection neurons (SPNs) (reviewed elsewhere; Lee et al., 2015) which subsequently activates ATP-sensitive K^+ (K_{ATP}) channels on dopamine axons, causing inhibition of dopamine release (Avshalumov et al., 2003; Avshalumov et al., 2008; Avshalumov & Rice, 2003; Bao et al., 2009; Chen et al., 2001). Those studies were performed in guinea pig striatal slices, but inhibition of striatal dopamine release by endogenous H_2O_2 has also been observed *in vivo* in rats (Spanos et al., 2013).

GABA

The striatum is a highly enriched in GABA transmission, comprising ~98% GABAergic SPNs and diverse GABAergic interneurons (Tepper et al., 2018). The axonal arbour of an average dopamine neuron in rats can be calculated to innervate a striatal region that contains ~74,000 GABAergic neurons (Oorschot, 1996). Additionally, striatal GABA may be also be supplied by canonically non-GABAergic sources, through co-release from dopamine axons and ChIs (Lozovaya et al., 2018; Tritsch et al., 2012) (reviewed in Tritsch and Melani 2025 this volume). A wealth of microdialysis and FCV studies *in vivo* and *ex vivo* show that striatal GABA modulates dopamine release (reviewed in Roberts et al., 2021). Ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors are abundant in the striatum, on SPNs and interneurons (Fujiyama et al., 2000). Recent immunohistochemical evidence has revealed for the first time that dopamine axons express at least α3-$GABA_A$ receptor subunits (Patel et al., 2024). There is not yet anatomical confirmation of $GABA_B$ receptors on dopamine axons, although ultrastructural immunocytochemical evidence shows $GABA_B$ receptors on structures that resemble (but were not confirmed as) dopamine axons (Charara et al., 1999).

In vivo microdialysis and acute slice FCV studies in rodents show that $GABA_A$ and $GABA_B$ receptor agonists can inhibit dopamine release (Brodnik et al., 2018; Pitman et al., 2014; Schmitz et al., 2002; Smolders et al., 1995), while antagonists can enhance dopamine release evoked by a single pulse (Lopes et al., 2019; Patel et al., 2024; Roberts et al., 2020). GABA receptor activation can slightly increase the ration of dopamine release evoked by pulse trains compared to single pulses, showing that GABA is not just regulating dopamine signal amplitude, but also its activity-dependence (Lopes et al., 2019; Roberts et al., 2020). Although $GABA_A$ and $GABA_B$ receptors are also expressed on ChIs (Waldvogel et al., 2004; Yung et al., 1999), GABA-mediated modulation of dopamine release persists even in the presence of nAChR antagonists (Lopes et al., 2019), indicating that tonic GABAergic inhibition of dopamine does not require a change to ACh release from ChIs but can be through direct actions on dopamine axons. An electrophysiological study involving patching of dopamine axons, identified that $GABA_A$-receptors operate on dopamine axons to regulate membrane potential and propagation of action potentials through a combination of sodium channel inactivation and shunting inhibition, confirming a direct action of GABA on dopamine axon function (Kramer et al., 2020).

The source(s) of GABA responsible for GABAergic inhibition of dopamine seem to be multiple. Tonic inhibition of dopamine release has been shown to be a canonical glutamic acid decarboxylase (GAD)-dependent neuronal source (Roberts et al., 2020), while another study has provided proof of principle that activation of a subtype of GABA interneuron (low threshold spiking) can inhibit evoked dopamine release (Holly et al., 2021). The potential for GABA co-release from dopamine axons to serve as a form of autoregulation of dopamine release is debated. Dopamine axons lack the conventional molecular machinery for GABA synthesis and storage, including GAD and vesicular GABA transporter (vGAT) (Kim et al., 2015; Tritsch et al., 2014). An alternative mechanism for non-canonical GABA synthesis in dopamine axons has been proposed, a pathway involving catalysis by aldehyde dehydrogenase (ALDH)-1a1 (Kim et al., 2015). However, other evidence indicates that dopamine axons accumulate GABA via uptake of striatal GABA from the extracellular space by GABA transporter-1 (GAT1) (Melani & Tritsch, 2022; Tritsch et al., 2014)(reviewed in Tritsch and Melani 2025 this volume). The GABA source responsible for tonic GABAergic inhibition of dopamine therefore cannot then readily be specified by the finding that it is GAD-but not ALDH-dependent (Roberts et al., 2020). However, a recent FCV study provided evidence that GABA co-release evoked from dopamine axons can participate in an "autoinhibition" of dopamine release via $GABA_A$ receptors: in striatal slices from mice with knockout of GAT1 specifically in dopamine axons, inhibition of dopamine release by $GABA_A$ receptors during by pulses trains was lost (Patel et al., 2024).

A further cell type, astrocytes, have now been identified as a major player in the striatal circuits that determine how GABA shapes dopamine transmission (**Figure 1**). GATs (GAT1 and GAT3) on striatal astrocytes support dopamine release level by limiting extracellular GABA levels and tonic inhibition of dopamine (Roberts et al., 2020). These findings also exemplify how neuromodulator levels

and their actions can be meaningfully shaped by mechanisms regulating both their release and their uptake.

Finally, in addition to direct effects on dopamine axons, indirect effects of GABA receptors can also be detected: With prolonged striatal stimulation, $GABA_A$ receptor activation can enhance dopamine release (Avshalumov et al., 2003) by inhibiting AMPA-dependent H_2O_2 generation in SPNs described above (see *Glutamate*).

Adenosine

Striatal adenosine signals can be detected using FCV (Wang & Venton, 2019) or by imaging of a genetically encoded fluorescent adenosine sensor $GRAB_{Ado}$ (Roberts et al., 2022). The exact source of striatal adenosine is still undefined, but it is suggested to arise from catabolism of ATP from neuronal sources (Latini & Pedata, 2001) and non-neuronal sources including astrocytes (Corkrum et al., 2020). Adenosine receptors A1 ($G_{\alpha i}$-coupled) and A2A ($G_{\alpha s}$-coupled) are expressed throughout the striatum (Glass et al., 1996; Mahan et al., 1991; Rivkees et al., 1995). Several rodent studies *in vivo* and *ex vivo* in brain slices have shown that A1 receptor agonists inhibit striatal dopamine release (Gołembiowska & Żylewska, 1998; Jin et al., 1993; Okada et al., 1996; Roberts et al., 2022; Ross & Venton, 2015), although the expression and presence of A1 receptors by dopamine neurons or dopamine axons has not been confirmed, as 6-OHDA lesion has no effect on ligand-binding to A1 receptors (Alexander & Reddington, 1989) and immunohistochemistry studies show no A1 receptor co-localisation with tyrosine hydroxylase (Rivkees et al., 1995). However, one study with rat striatal synaptosomes reports A1 receptor expression on a fraction of dopamine axons (Borycz et al., 2007).

A1 receptors are however expressed on ChIs (Dixon et al., 1996), and A1 receptor agonists inhibit ACh release (Brown et al., 1990; Kirk & Richardson, 1994), suggesting that these receptors may inhibit dopamine release indirectly. However, a FCV study in mouse brain slices reports that A1 receptor-mediated inhibition of dopamine release persists in the presence of a nAChR antagonist or GABA receptor antagonists (Roberts et al., 2022), seemingly excluding a role for A1 receptors on ChIs or GABA neurons in this regulation of dopamine release. Furthermore, the activation of A1 receptors not only reduced dopamine release evoked by single pulses but correspondingly increased the ratio of release by pulses trains vs single pulses, indicating not just a general suppression of dopamine release level, but a reduction to dopamine release probability that enables a relief of short-term depression, and enhanced activity-dependence after A1 receptor activation. That study further reports a tonic level of inhibition of dopamine release by striatal A1 receptors that is limited by the activity of the astrocytic equilibrative nucleoside transporter 1 (ENT1; Roberts et al., 2022). These findings again place astrocytes as a key component of the striatal circuitry that determines the neuromodulation of dopamine (**Figure 1**).

A2A receptors also modulate striatal dopamine, with initial evidence paradoxically suggesting an inhibition of dopamine release despite $G_{\alpha s}$ coupling (Gołembiowska & Żylewska, 1998; Jin et al., 1993). However, *in vivo* microdialysis has demonstrated that A2A receptor agonists increase dopamine release, and this effect is only revealed when the high affinity A1 receptors are blocked (Okada et al., 1996). The tendency for A2A receptors to heterodimerize with A1 receptors and a variety of other receptors, including dopamine D_2 receptors likely plays a key role in influencing the outcome of receptor activation on dopamine transmission (Ferré et al., 2007). Heterodimerisation of adenosine receptors, and of other GPCRs remains a likely additional source of complexity in understanding neuromodulation across modulator categories and brain regions.

Norepinephrine

Norepinephrine (NE) afferents from the locus coeruleus, and potentially the ventral medulla, provide only a sparse striatal innervation, predominantly to ventral striatum (Berridge et al., 1997; Zerbi et al., 2019). In some contrast, NE receptors are readily detectable throughout the striatum, particularly α1, α2 and β1 adrenoceptors (Paschalis et al., 2009; Pisani et al., 2003; Rommelfanger et al., 2009). *In vivo* microdialysis studies show that adrenoceptors can modulate striatal dopamine release, although results are conflicting (Saigusa et al., 2012; Tuinstra & Cools, 2000) and the circuitry involved remains poorly defined. Adrenoceptors can modulate excitability of striatal neurons, including ChIs, that can be excited by β1 adrenoceptors (Pisani et al., 2003), and might thereby indirectly modulate axonal dopamine release via changes in ACh release and nAChR activity.

Serotonin

Serotonin (5-HT) innervation of striatum is far more abundant than NE and extensive literature indicates that it locally regulates dopamine release (**Figure 1**). 5-HT neurons project to the striatum from the dorsal raphe nucleus and 5-HT exerts its effects through diverse striatal G-protein coupled 5-HT receptors that can promote or inhibit striatal dopamine release, reviewed elsewhere (reviewed in Navailles & De Deurwaerdère, 2011; Peters et al., 2021). These mechanisms are believed to be at least partly direct, via 5-HT receptors hypothesized to be on dopamine axons, but might also be indirect including via ChIs, as ChIs express and respond to multiple types of 5-HT receptors (Bonsi et al., 2007). However, a role for ChIs in mediating 5-HT control of dopamine has not yet been tested. Interestingly, 5-HT axons themselves are considered to become a site for release of dopamine in response to L-DOPA medication after dopamine neuron degeneration in Parkinson's disease (Mosharov et al., 2015; Zhou & Dani, 2008). In Parkinson's, the modulator mechanisms that operate on 5-HT axons, and not dopamine axons, might then dominate as those shaping dopamine output, and so should be further delineated.

Cannabinoids

The endogenous cannabinoids (endocannabinoids, eCBs) 2-arachidonoyl-glycerol (2-AG) and anandamide (AEA) are retrograde neuromodulators that generally inhibit neurotransmitter release, typically via CB1 receptors (reviewed in Covey et al., 2017). CB1 receptor mRNA is abundantly expressed in the striatum, with the highest expression in the dorsolateral striatum and decreasing along a ventromedial gradient (Matsuda et al., 1993). Immunohistochemistry and *in situ* hybridization studies do not detect CB1 receptors on dopamine axons (Julian et al., 2003), but locate them to other striatal neurons and afferents (Martín et al., 2008; Mateo et al., 2017). FCV studies *in vivo* and *ex vivo* show that CB1 receptor activation does not modulate single pulse-evoked dopamine release, but inhibits dopamine release evoked by pulse trains (Cheer et al., 2004; O'Neill et al., 2009; Sidló et al., 2008). The stimulus-dependence of this action might reflect an action on dopamine release that is indirect, involving an action on other circuits requiring activation, a hypothesis also supported by the absence of CB1 receptors on dopamine axons (Julian et al., 2003). One potential mechanism is the inhibition of GABA release by CB1 receptors on GABAergic interneurons and SPNs (Martín et al., 2008), which in turn increases H_2O_2 generation and subsequent activation of K_{ATP} channels on dopamine axons (see GABA section; Sidló et al., 2008). Another possible mechanism is modulation of ChIs and ChI-gated changes to dopamine release via nAChRs (Cachope et al., 2012; Threlfell et al., 2012). CB1 receptors are not present on ChIs, but are on glutamatergic afferents that regulate ChI activity (Mateo et al., 2017), through which CB1 receptor activation limits ChI-dependent modulation of dopamine release at nAChRs (see Glutamate section; Kosillo et al., 2016; Mateo et al., 2017).

Gaseous Neuromodulators: Hydrogen peroxide and nitric oxide

There is evidence for at least striatal H_2O_2 and nitric oxide (NO) shaping dopamine release, as discussed above for H_2O_2 (see *Glutamate*, *GABA*). Electron microscopy studies show that nitric oxide (NO) synthase-containing striatal interneurons form synapses onto dopamine axons in the NAc (Hidaka & Totterdell, 2001). Exogenous administration of NO enhances dopamine release in the NAc through a mechanism independent of nAChRs, and also enhances the frequency dependence of dopamine release through a nAChR-dependent mechanism (Hartung et al., 2011). *In vivo* microdialysis evidence suggests that NO can enhance striatal dopamine levels by inhibiting DAT activity (Kiss et al., 1999).

Neuropeptides: Opioids

Opioid peptides are enriched in the striatum, with dynorphin (selective for κ-opioid receptors) expressed in D_1 receptor-expressing SPNs and enkephalin (selective for μ- and δ-opioid receptors) expressed in D_2 receptor-expressing SPNs. Anatomical evidence shows that μ- and δ-opioid receptors are absent on dopamine axons but are expressed on GABAergic SPNs and ChIs (Trovero et al., 1990), while κ-opioid receptors are present on dopamine axons (Svingos et al., 2001). FCV studies report that all three opioid receptors inhibit striatal dopamine release (Schlösser et al., 1995), but the inhibition by μ- or δ-opioid

receptors is indirect via inhibition of ChI activity and subsequent ACh release (Arenas et al., 1990; Britt & McGehee, 2008; Ponterio et al., 2013). κ-opioid receptor modulation of dopamine occurs in a direct manner (Britt & McGehee, 2008) (**Figure 1**).

Microdialysis experiments have reported bidirectional effects of μ- and δ-opioid receptors which are region-specific. μ-opioid receptor agonists reduce dopamine in rostral and caudal dorsal striatum, but increase dopamine in medial dorsal striatum (Campos-Jurado et al., 2017), while μ- or δ-opioid receptor agonists increase dopamine in NAc core, but decrease dopamine in NAc shell (Alcantara et al., 2001; Gómez-A et al., 2018; Hipólito et al., 2008). These divergent outcomes suggest that opioid circuits modulating dopamine differ in specific striatal regions, and we might also expect these effects to co-vary with striosomal versus matrix location of region recorded, given that μ-opioid receptors are enriched specifically in striosomes (Mansour et al., 1995).

Neuropeptides: Neurotensin

Neurotensin (NTS) is an abundant neuropeptide in the CNS. A recent study using NTS-cre;GFP mice to map NTS neurons in mouse brain showed that NTS-expressing neurons are particularly abundant in NAc, and are also present in dorsal striatum (Schroeder et al., 2019). Several immunohistochemical studies in rat and cat report NTS expression in both enkephalin-positive SPNs in the dorsal striatum and NAc (Sugimoto & Mizuno, 1987), as well as TH-positive dopamine neurons in the VTA and SNc (Bayer et al., 1991; Seroogy et al., 1988). NTS acts at G_q-coupled NTS1 and NTS2 receptors, with NTS1, also known as the high-affinity receptor, considered the main target of NTS action in the striatum. Ligand binding studies in rat suggest that NTS receptors are present on dopamine axons, as they are lost following 6-OHDA lesion of the nigrostriatal or mesolimbic dopamine pathways (Quirion et al., 1985; Schotte & Leysen, 1989). These studies also indicate that in the DLS, NTS receptors are located solely on dopamine axons, but in the NAc they are also located post-synaptically on striatal neurons.

FCV studies in striatal slices have shown that NTS enhances dopamine release evoked by pulse-trains, but has no effect on single pulse-evoked dopamine release (Fawaz et al., 2009; Singhal et al., 2023). NTS-mediated excitation of dopamine release is thought to be mediated via inhibition of D_2 autoreceptors on dopamine axons (Fawaz et al., 2009). *In vivo* microdialysis studies have revealed that while exogenous NTS at high concentrations enhances dopamine release, in agreement with FCV studies, low concentrations of NTS inhibit dopamine release, likely via activation of high-affinity NTS1 receptors on GABAergic neurons (Ferraro et al., 1997; Tanganelli et al., 1994). Indeed, these studies have also shown that NTS increases striatal GABA release.

Neuropeptides: Substance P

Substance P is a neuropeptide released from D_1 receptor-expressing SPNs and is enriched in striosomes. The receptors for substance P are known as neurokinin-1 receptors (NK1Rs), which are expressed by ChIs in the striatum (Gerfen, 1991) and midbrain dopamine neurons in the SNc and VTA. It is unclear if they are present on striatal dopamine axons (Lessard & Pickel, 2005).

The initial reports on the effect of substance P on striatal dopamine were conflicting. However, a FCV study in striatal slices combined with immunolabeling of mu-opioid receptors (indicating striosomes) revealed that substance P has intriguing bidirectional effects on dopamine release depending on striosome-matrix location: substance P enhances dopamine release in striosomes, decreases dopamine in peristriosomal border regions and has no effect in the matrix (Brimblecombe & Cragg, 2015). NK1Rs are known to heterodimerize with other receptors, such as μ-opioid receptors (Pfeiffer et al., 2003) which are highly expressed in striosomes (Mansour et al., 1995), and the effect of substance P at NK1Rs might therefore depend on the interaction with other receptors that vary within the striosomal-matrix axis. Effects of substance P prevail when nAChRs are occluded, suggesting a mechanism of action independent of any actions on ChIs (**Figure 1**), but roles of NK1Rs on ChIs are uncharacterized.

Neuropeptides: Cholecystokinin

Cholecystokinin (CCK) is contained in a population of midbrain dopamine neurons in both SNc and VTA projecting to dorsolateral striatum and NAc (Hökfelt et al., 1985). CCK_1 and CCK_2 receptors, previously classified as CCK_A and CCK_B receptors, are G_q-coupled receptors that are richly expressed in striatum but are not reported to be enriched in dopamine neurons. CCK enhances K^+-evoked dopamine release in posterior NAc via CCK_1 receptors and inhibits dopamine release in anterior NAc via CCK_2 receptors (Marshall et al., 1991). The mechanism for this modulation is unclear, although studies report that CCK increases both ACh and GABA release in the striatum (Petkova-Kirova et al., 2012; Rakovska, 1995), making them potential candidates for mediating an impact of CCK on dopamine release.

Neuropeptides: Corticotropin-releasing factor

Corticotropin-releasing factor (CRF) is a neuropeptide released in response to stress, which acts at G_s-coupled CRF receptors CRFR1 and CRFR2. In the NAc, immunohistochemistry shows that CRF is present in ChIs and dopamine axons (Lemos et al., 2012). CRF increases dopamine release through coactivation of CRFR1 and CRFR2 (Lemos et al., 2012). Additionally, CRF also increases ACh release (Chen et al., 2012), and a recent study shows that CRF at CRFR1 increases ChI firing in dorsolateral striatum and NAc which activates downstream M5-mAChRs on dopamine axons to increase dopamine release (Lemos et al., 2019).

Neuropeptides: Insulin

Insulin receptors are expressed widely in the brain, including in the striatum with particularly high levels in the NAc (Werther et al., 1987), where they are reported to be functionally present on dopamine axons and ChIs (Stouffer et al., 2015). Striatal insulin can modulate dopamine release in rat striatum both directly or indirectly via exciting ChIs and promoting ACh action at nAChRs (Stouffer et al., 2015).

Neurotrophins: Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF), supplied from midbrain dopamine and corticostriatal glutamate afferents (Altar et al., 1997), acting at tyrosine kinase-linked TrkB receptors has been reported to enhance dopamine release in striatum (Goggi et al., 2002). Furthermore, in BDNF-deficient mice there is an increase in striatal dopamine content but decreased electrically-evoked dopamine release. This deficit in dopamine release can be restored through BDNF application (Bosse et al., 2012; Cordeira et al., 2010).

Neurotrophins: Glial-derived neurotrophic factor

Glial-derived neurotrophic factor (GDNF) is present throughout the striatum and, despite a name suggestive of a glial origin, one key immunohistochemical study has reported that striatal GDNF mRNA is particularly enriched in parvalbumin-positive GABAergic interneurons, with some expression also found in ChIs and somatostatin-positive GABAergic interneurons (Hidalgo-Figueroa et al., 2012). Acting at its canonical receptor, Ret, GDNF can regulate dopamine release and uptake (reviewed in Kramer & Liss, 2015). Immunohistochemistry in 6-OHDA lesioned mice show that the GDNF receptor Ret is localised on striatal dopamine axons (Araujo et al., 1997). *In vivo* microdialysis studies in monkey and rat show that GDNF increases K^+-evoked striatal dopamine release (Gash et al., 1995; Salvatore et al., 2004). In cultured dopamine neurons, GDNF also increases the quantal size of dopamine release from axonal varicosities as well as axonal outgrowth (Pothos et al., 1998). Furthermore, overexpression of GDNF levels in mice increases the numbers of dopamine axons in the striatum and increases dopamine release (Kumar et al., 2015). GDNF acting via Ret also regulates DAT surface expression and Ret-deficient mice have elevated DAT activity, indicating that GDNF is key determinant of DAT trafficking and activity (Zhu et al., 2015).

Concluding Remarks

Evidently, diverse striatal modulators can bidirectionally shape dopamine signalling, offering facilitation or inhibition, depending on the modulator and context. Some modulators change the short-term plasticity of dopamine release probability and so will differently influence dopamine release by different firing rates. ACh is a particularly notable modulator of dopamine release, exerting profound effects on axonal excitability and integration. Not all modulators of dopamine act directly on dopamine

axons, with ChIs acting as intermediaries for at least glutamate, cannabinoids, NO, opioids and insulin, which in turn shape dopamine via changes to ACh release and activation of nAChRs on dopamine axons. Serotonin, NE, and multiple other neuropeptides also seem likely to be able to shape dopamine release through modulation of ChIs, suggesting that ChIs are positioned to orchestrate the impact of a spectacular range of neuromodulators on striatal dopamine release. Action on ChIs must therefore be considered to understand regulation of dopamine of dopamine function by any modulator. For those modulators that can act directly on dopamine axons, the mechanisms underlying modulation of dopamine release involve changes to axonal excitability (e.g. $GABA_A$-mediated shunting inhibition (Kramer et al., 2020)), and are likely also to modify entry of Ca^{2+} that supports exocytosis and its dynamic release probability, but to date, specific mechanisms remain poorly defined, and require further delineation. Separately, a role for astrocytes is increasingly being appreciated in governing the striatal tone of neuromodulators that shape dopamine release, and further new insights into the role of astrocytes in striatal networks are likely to emerge in the coming years.

The recent development of new genetically encoded fluorescent sensors for modulators spanning all categories (Wu et al., 2022) is likely to catalyse new understanding of the dynamic availability of the neuromodulators themselves, to inform knowledge of when they might interact with dopamine. Additional next steps for the field are to identify the functional consequences of how an even fuller breadth of neuromodulators regulate both dopamine and ACh signalling to govern striatal function and ultimately, dysfunction, to help realise their potential for treatment of dopaminergic disorders.

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