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Direct dopamine terminal regulation by local striatal microcircuitry

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Abstract

Regulation of axonal dopamine release by local microcircuitry is at the hub of several biological processes that govern the timing and magnitude of signaling events in reward-related brain regions. An important characteristic of dopamine release from axon terminals in the striatum is that it is rapidly modulated by local regulatory mechanisms. These processes can occur via homosynaptic mechanisms - such presynaptic dopamine autoreceptors and dopamine transporters - as well heterosynaptic mechanisms such as retrograde signaling from postsynaptic cholinergic and dynorphin systems, among others. Additionally, modulation of dopamine release via diffusible messengers such as nitric oxide and hydrogen peroxide, allows for various metabolic factors to quickly and efficiently regulate dopamine release and subsequent signaling. Here we review how these mechanisms work in concert to influence the timing and magnitude of striatal dopamine signaling, independent of action potential activity at the level of dopaminergic cell bodies in the midbrain, thereby providing a parallel pathway by which dopamine can be modulated. Understanding the complexities of local regulation of dopamine signaling is required for building comprehensive frameworks of how activity throughout the dopamine system is integrated to drive signaling and control behavior.

Abstract

Regulation of axonal dopamine release by local microcircuitry is at the hub of several biological processes that govern the timing and magnitude of signaling events in reward-related brain regions. Dopamine release at terminals in the striatum can be modulated by a variety of

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mechanisms, including homosynaptic mechanisms intrinsic to the cell itself and heterosynaptic mechanisms that integrate activity of local microcircuitry. Together, these mechanisms work in concert to dynamically regulate dopamine release, uptake and repackaging for future release events, and thus exert precise control over dopaminergic activity and drive subsequent behaviors. Here we review how these mechanisms work together to influence the timing and magnitude of striatal dopamine signaling, independent of action potential activity at the level of dopaminergic cell bodies in the midbrain, thereby providing a parallel pathway by which dopamine can be modulated.

Introduction

Dopamine cell bodies in the midbrain send long-range projections to many targets in cortical and limbic structures allowing for dopaminergic modulation of neuronal function across the brain (Chen & Bonci 2017; Russo & Nestler 2013). The timing and magnitude of dopamine release is thought to relay information fundamental for guiding organismal behavior, with theories ranging from hypothesizing that phasic dopamine and accompanying release encodes reward prediction error, to incentive value or even representations of an internal clock (Schultz *et al.* 1997; Meck 2006; Berridge 2007). These facets of release are tightly controlled by a collection of receptor and transporter systems expressed at the presynaptic membrane. In the mesolimbic dopamine system, where dopamine is released from terminals in the nucleus accumbens (NAc), these include dopamine transporters (Richardson *et al.* 2016), dopamine type-2 autoreceptors (D2Rs) (Benoit-Marand *et al.* 2011), heteroreceptors (Zhang & Sulzer 2012) including channels regulating ion flux (Brimblecombe *et al.* 2015; Martel *et al.* 2011) and nicotinic acetylcholine receptors (Grady *et al.* 2007), and other signaling molecules such as nitric oxide (NO) (West *et al.* 2002) as well as steroid and sex hormones (Becker & Chartoff 2019). Direct regulation of dopamine release at the level of the terminal - through effectors located directly within or on dopamine terminals – is a critical component of dopamine release regulation and associated signaling.

The role of dopamine release is often discussed as an all-or-nothing process that compares how much dopamine is released relative to the baseline, ignoring the granularity of the signal regarding how the magnitude, spread and duration is shaped by the local microenvironment. These properties likely contain critical information that extends far beyond just the relative peak concentration of release events. The contribution of local microcircuitry is fundamental in regulating the timing of signaling, both pre- and post-synaptic, as well as the interactions between basal dopamine levels and stimulus-dependent signaling downstream. When accounting for these factors in sum, dopaminergic microcircuitry can exhibit a robust dynamic range, and therefore, there is likely more complex information within these signaling domains that allows for more nuance in what is being encoded. Here we review the current research on the complex mechanisms regulating the dynamics of dopamine release at its projection targets. Ultimately, mechanisms that elicit and shape dopamine release at the terminal may represent novel avenues for therapeutic interventions targeting striatal dopamine dysregulation in disease and as such an understanding of these complex regulatory mechanisms is critical to moving the field forward.

1. Homosynaptic Regulation at the Terminal

Dopamine terminals in reward-related brain regions, such as the NAc are regulated by a number of transmitters supplied by locally-projecting neurons (heterosynaptic - see section 2) or through responses to dopamine itself (homosynaptic - discussed in the present section). We will discuss the three following critical processes that govern release magnitude and temporal dynamics: (1) **alterations in release probability and release pool dynamics** (2) **autoreceptor-mediated feedback mechanisms**, and (3) **changes in the function and expression levels of transporters controlling dopamine reuptake and repackaging**. These processes all work to modulate the magnitude, onset, and duration of dopamine levels in the extracellular space.

1.1. Regulation of dopamine release

Early observations demonstrated that a single vesicle filled with neurotransmitter molecules represents the elementary unit of synaptic transmission (Katz 1971). Recent work has shown that the magnitude of release events the central nervous system can be modulated by a number of factors, including neurotrophic factors and neurotransmitter synthesis (Pothos *et al.* 2000; Pothos *et al.* 1998). Thus, the regulation of dopamine release is a potent mechanism by which dopamine terminals can be regulated. One common mechanism that impacts the magnitude and onset of dopamine release is related to changes in release mechanisms within the terminal itself, including changes in the distribution of various vesicle pools (section 1.1.1) and changes in the conductance or expression of calcium channels on presynaptic dopamine terminals (section 1.1.2) (Figure 1A). Plasticity in these mechanisms may allow for differential transformations between upstream action potential activity and downstream release, both across time/experience and between distinct terminals arising from the same soma.

1.1.1. Vesicle pool effects—Dopamine is released from multiple separate pools or compartments (Ewing *et al.* 1983; Javoy & Glowinski 1971; del Castillo & Katz 1954). These pools can most simply be divided into three distinct pools: the readily releasable pool, the recycling pool and the reserve pool (Rizzoli & Betz 2005).

a. *Readily releasable pool*. The readily releasable pool contains recently synthesized dopamine and is released first following activation by action potentials (Besson *et al.* 1969). The structure of this pool ensures immediate exocytosis of neurotransmitter in response to depolarization in the fast-acting synapse, though in response to continued activity the magnitude of this pool declines. However, this pool can be quickly refilled from the other pools of dopamine (Yavich & MacDonald 2000). Plasticity in this refilling process does indeed occur, as evidence showed that high-frequency stimulation repeated at 5 second intervals significantly delayed the decline in dopamine (Wang & Kaczmarek 1998; Stevens & Wesseling 1998). This effect is perhaps due to increased rate of refill from the reserve compartment, which has been proposed for other types of synapses (Richards *et al.* 2003). Previous work has shown that multiple psychostimulants can elicit increased dopamine release via mobilization of secondary reserves of dopamine (Venton *et al.* 2006; Shore 1976). Further, the

distribution of dopamine between the different pools may be related to individual differences in responding for cocaine (Verheij & Cools 2011; Verheij *et al.* 2008). This dopamine mobilization by cocaine is synapsin - and dopamine transporter (DAT) -dependent (Venton *et al.* 2006; Kile *et al.* 2010). Importantly, in non-dopaminergic systems, calcium signaling has been demonstrated to play a role in the upregulation of release magnitude due to docking of reserve pool vesicles following priming events (Wang *et al.* 2016; Thanawala & Regehr 2013) an effect that may play a similar role in dopaminergic terminals.

At glutamatergic synapses, plasticity processes like LTD have been shown to be related to decreases in the readily releasable pool (Goda & Stevens 1998). Additionally, inhibition of the mammalian target of rapamycin (mTOR), which plays a role in activity-dependent plasticity, within the presynaptic bouton has been shown to induce the formation of autophagic vacuoles which sequester and degrade dopamine-containing vesicles, thereby providing another mechanism for decreasing the size of the pool and subsequently release (Schmitz *et al.* 2003). Ultimately, the releasable pool is maintained by both synthesis and reuptake-dependent vesicular repackaging, and therefore is inextricably linked with other presynaptic agents, such as transporters and synthesis/degradation enzymes (sections 1.2 and 1.3).

b. *Recycling pool.* The recycling pool consists of a mobile pool of dopamine, composing roughly 10–20% of available dopamine (Rizzoli & Betz 2005; Denker & Rizzoli 2010). This pool exists to meet the high demand of the cell, as *de novo* synthesis of vesicles from the soma is a much slower process (Chanaday *et al.* 2019). However, it should be noted that more recent studies indicate that the distinctions between the recycling pool and the reserve pool are less clear, proposing that vesicles eventually mature from the recycling pool to the reserve pool over a discrete period of time (Kamin *et al.* 2010; Denker & Rizzoli 2010). This maturation process then sets up the possibility that this recycling process may then be involved in aspects of terminal plasticity.

c. *Reserve pool.* Finally, it is also important to consider the reserve pool. The reserve pool represents the largest pool of dopamine, consisting of roughly 80–90% of the available dopamine. These reserve pools are regulated by the synapsin protein family, the loss of which prevents cocaine augmentation of dopamine release following long simulations (Venton *et al.* 2006). Facilitation of shifting from the reserve pool to the active zone of the terminal is thought to be dependent on calcium influx, as well as actin polymerization status via interactions with alpha-synuclein (Bellani *et al.* 2010). The size of the reserve pool is a key determinant in establishing release magnitude following long stimulation paradigms. Moreover, effects on the reserve pool may underlie part of the physiological response to psychostimulants, as long duration stimulation of the dorsal striatum has been shown to elicit reduced dopamine release after administration of amphetamine (Covey *et al.* 2013).

Together, these studies demonstrate that the distribution of dopamine between the different vesicle pools is one of several dynamic processes that allows for regulation of release. Indeed, shifts in the release pool distribution that are important for release have been shown to occur when there are perturbations in dopamine clearance mechanisms (Jones *et al.* 1999), and may in fact serve as a compensatory mechanism following persistent stimulation and/or uptake blockade (as would be seen with stimulant use (Calipari *et al.* 2014)), or simply a way to shift release efficiency following different experiences. However, the precise conditions that result in release pool distribution shifts are not well understood and require further study.

1.1.2. Calcium regulation of dopamine release—Calcium entry into the bouton through voltage-gated calcium channels bears the primary responsibility of initiating synaptic transmission at conventional synapses. These channels interact functionally with other ion channels to modulate release (Martel *et al.* 2011). This is a key process that can be regulated via numerous mechanisms to enhance release. For example, calcium channels can be enhanced via upregulated expression levels or via changes in conductance. Further, the relationship between terminal depolarization and neurotransmitter release can change over repeated stimulations, an effect that is driven by changes in the sensitivity of calcium binding proteins for calcium itself, also altering the relationship between calcium and exocytotic release (Hsu *et al.* 1996). Together, these mechanisms allow for experience-dependent plasticity in calcium systems that are critical for neurotransmitter release.

Significant heterogeneity exists in the presence of channel types and function at the dopaminergic terminal across various brain areas (Brimblecombe *et al.* 2015). There are multiple types of calcium channels, many of which have differential effects on dopamine terminals and dopamine release. Regarding dopamine regulation, N-Type (CAV2.2) has the largest effect on dopamine release where blocking these channels almost completely eliminates evoked dopamine release from terminals in the ventral striatum (Phillips & Stamford 2000; Brimblecombe *et al.* 2015). P/Q type (CAV2.1) calcium channels are also a critical regulators of dopamine release, where blocking these channels significantly reduces release, but does not completely abolish it. Blocking T-type channels modestly reduces release, but much smaller than the previously mentioned subtypes. Finally, it is likely that L-type calcium channels (CAV1.2/1.3/1.4) are present on dopamine terminals in the NAc, though pharmacological blockade has no effect on dopamine release in slice voltammetry experiments (Brimblecombe *et al.* 2015), which calls into question their functional role in direct release regulation as well as presence directly on dopamine terminals. Importantly, all calcium channels present on the membrane of terminals are capable of regulating calcium flux through posttranslational modifications, such as those that can alter conductance or more broadly via expression; thus, implicating these channels as potential mediators of experience-dependent plasticity at dopamine synapses. In addition to CAV 1.2, 1.3, 1.4, 2.1, and 2.2, TRP channels are also potent regulators of calcium signaling and have been suggested to have a role in plasticity within this circuit (Wescott *et al.* 2013; Fowler *et al.* 2007). The ability to regulate calcium following experience-dependent plasticity is critical for release, given the clear relationship between the size of the readily releasable pool and calcium (Thanawala & Regehr 2013).

Calcium regulation of release through voltage gated calcium channels is a critical step in action potential-dependent release; however, calcium regulation of intracellular signaling and release can also occur through not only calcium channels, but a variety of ligand-gated receptors that are permeable to calcium. For example, some nicotinic acetylcholine receptors are highly calcium permeable (Séguéla *et al.* 1993; Lendvai & Vizi 2008). Therefore, it is conceivable that any changes in nicotinic receptor density or subunit composition resulting from plasticity mechanisms or sex-dependent effects may be related to changes in calcium influx in the terminal that results from acetylcholine binding and associated channel opening. Broadly, these heterosynaptic receptor mechanisms are described in more detail below (section 2), and these findings indicate that they may serve as a critical component of release regulation via modulation of calcium influx into dopamine terminals.

Together, interactions between releasable pool organization, calcium dynamics, and release machinery all interact to alter the magnitude of dopamine release events directly at terminal projections in the striatum. This is a critical component allowing for release to scale, allowing for a dynamic system that can change on a rapid or prolonged time scale.

1.2. Autoreceptor-mediated feedback mechanisms

In addition to calcium channels, release can also be regulated via G-protein coupled receptors that are located on dopamine terminals. This group of receptors is comprised of both heteroreceptors (described in detail in section 2) and autoreceptors. D2Rs are autoreceptors that provide inhibitory feedback to curtail signaling at times of heightened extracellular dopamine levels, thereby profoundly regulating both the temporal dynamics of extracellular dopamine levels and the magnitude of evoked dopamine release events. Of the receptors expressed on dopamine terminals in the striatum, D2Rs are among the most studied and have been well characterized. They are located both at the level of the cell-body in the VTA as well as directly on terminals in striatal regions where they act to downregulate tyrosine hydroxylase (TH) expression and cellular activity, leading to decreases in dopamine production and release (Ford 2014; Palij *et al.* 1990; Kennedy *et al.* 1992; Benoit-Marand *et al.* 2001; Benoit-Marand *et al.* 2011; Phillips *et al.* 2002; Rouge-Pont *et al.* 2002; Anzalone *et al.* 2012; Schmitz *et al.* 2002). Mechanistically, these receptors are G_i-coupled and early work showed that D2R-mediated decreases in dopamine neuron excitability occur via activation of inwardly rectifying potassium (K^+) channels – both GIRK and Kv channels - and via inhibiting P/Q and N-type calcium channels (Cardozo & Bean 1995). However, more recent work has shown that while D2R-activation may alter calcium currents, though these effects on calcium currents are downstream of initial K^+ channel effects (Congar et al. 2002). Indeed, there is a wealth of evidence demonstrating that the ability of D2Rs to reduce terminal dopamine release occurs through functional interactions with K^+ channels, as D2R-mediated reductions in dopamine overflow can be attenuated by bath application of Kv1.1/1.2/1.6 blockers, with a smaller role played by interactions with GIRK channels (Fulton *et al.* 2011; Martel *et al.* 2011; Congar *et al.* 2002). Additionally, D2R activation results in observable increases in Kv1.2 mediated currents, and germline loss of Kv1.2 as well as selective blockage of Kv1.2 prevent D2R-mediated dopaminergic release regulation further highlighting the role that potassium channels play in this process (Fulton *et al.* 2011).

Aside from acute regulation of terminal excitability and associated release, activation of D2Rs has been shown to drive posttranslational modifications to other regulators, such as DAT and vesicular monoamine transporter-2 (VMAT2), leading to lasting alterations in transporter function and associated repackaging efficiency (Meiergerd *et al.* 1993; Belin *et al.* 2007), an effect that alters the timing of dopamine release. Similarly, chronic activation of D2Rs can also induce morphological changes in dopaminergic axon growth and alterations in plasticity across multiple striatal subregions (Fasano *et al.* 2010; Parish *et al.* 2001; Parish *et al.* 2002; Tripanichkul *et al.* 2003; Giguère *et al.* 2019). These changes have important implications for subsequent terminal release events and dopamine-mediated plasticity of other cell types across the brain as well.

Region-specific D2 regulation.—D2Rs are critical regulators of dopamine release across the entire striatum; however, their efficacy in reducing dopamine release has been shown to differ depending on the striatal subregion. D2Rs are more efficacious at reducing dopamine release in dorsal striatal regions and their efficacy reduces in a stepwise function from dorsolateral striatum down to medial shell (Rothblat & Schneider 1997). However, it should be noted that this observation has been contested by more recent studies, which demonstrate that D2 agonists have similar inhibitory effects in the dorsal striatum, NAc core and NAc shell (Maina & Mathews 2010; Holloway *et al.* 2019). Region-specificity in function may be due to interactions with other regulators mentioned here, as recent evidence has highlighted that activation of D2Rs in the dorsal striatum, but not the ventral striatum, increases DAT phosphorylation and surface trafficking (Gowrishankar *et al.* 2018). Taken together, this potential heterogeneity provides a region-specific regulatory mechanism allowing for different relationships between release dynamics and timing between regions – an effect that may allow for region-specific behavioral regulation.

1.3. Changes in the function and expression levels of transporters

One of the most critical regulators of dopamine signaling is the speed at which it is cleared from the extracellular space and repackaged for future release events. Below we outline how transport regulation plays a key role in dopamine terminal regulation through the major regulators of this process: DAT and VMAT2.

1.3.1. Dopamine transporter (DAT)—Mounting evidence has demonstrated that the DAT represents a critical regulator of terminal release and plasticity via regulation of the temporal dynamics of dopamine in the extracellular space (Condon *et al.* 2019). DAT is a low capacity, high affinity transporter expressed on dopamine neurons and can be found on dopamine cell bodies, their dendrites, and their axonal projections (Ciliax *et al.* 1995; Freed *et al.* 1995). It is comprised of 12 transmembrane domains with both the N- and C-terminal located intracellularly (Giros & Caron 1993; Uhl & Kitayama 1993). DAT is a member of the Na+/Cl- transporters and that uses the Na+ concentration gradient created by the Na+/K + ATPase to transport dopamine from the extracellular space to the intracellular space. In the striatum, the DAT is the primary method of clearing out dopamine from the extracellular space (Jones *et al.* 1998; Chen & Reith 2000; Giros *et al.* 1996). As such, any changes in DAT expression or function can have profound consequences on the timing and duration of dopamine's interactions with receptors after release events.

DAT is a target of many psychotropic drugs such as cocaine, methamphetamine, and amphetamine (Baumann *et al*. 2012; Rothman *et al*. 2001; Belovich *et al*. 2019; Cartier *et al*. 2015; Hamilton *et al*. 2014) and therefore has been well-studied for its role in substance use disorder, motivation, and dopamine signaling. Impaired clearance resulting from inhibition of the DAT by compounds such as cocaine produce elevated levels of dopamine in the extracellular space for prolonged periods of time, and consequently increases in postsynaptic dopamine receptor activation on target cells downstream. Similar findings have been reported with other approaches such as genetic downregulation of DAT, where mice lacking the DAT showed elevated extracellular dopamine and an extended half-life of dopamine in the extracellular space. Importantly, these mice also had a decreased releasable pool of dopamine despite an elevated rate of dopamine synthesis (Jones *et al*. 1998), highlighting the critical role that DAT plays in vesicular repackaging. Thus, DAT is involved not only in clearance rates, but also serves as an important step in packaging dopamine into vesicles by bringing released dopamine back into the presynaptic cell and facilitating its repackaging into vesicles through interactions between specific synaptic vesicle proteins and the N-terminus of the DAT (Egaña *et al*. 2009).

The N and C termini of DAT can both be post-translationally modified to alter its membrane stability and function (Sweeney *et al*. 2017; Hamilton *et al*. 2014; Belovich *et al*. 2019; Cartier *et al*. 2015). Protein kinase C (PKC) has been shown to phosphorylate the DAT, cause internalization, and decrease transport kinetics (Moritz *et al*. 2015; Foster *et al*. 2008; Loder & Melikian 2003). PKC activity is also involved in amphetamine-mediated dopamine efflux along with CaMKII, Akt, and PI-3 kinase (Fog *et al*. 2006; Wei *et al*. 2007). While phosphorylation of DAT by PKC can decrease DAT activity, phosphorylation by other kinases such as ERK1/2 can increase DAT activity (Morón *et al*. 2003). The phosphatases PP1 and PP2A associate with DAT and are responsible for dephosphorylation of specific phosphorylation sites on the DAT (Foster *et al*. 2012). Further, inhibition of PP2A activity decreases dopamine uptake (Bauman *et al*. 2000). All of the above effectors - ERK, PKC, PP1, PP2A, CaMKII, Akt, and PI3K - are directly linked to activity-dependent signaling, providing a potential mechanism by which changes in terminal excitability can regulate clearance on a rapid timescale. Indeed, changes in membrane potential alter DAT membrane expression and dopamine clearance via rapid DAT trafficking on a second timescale, through interactions Rit2 (Richardson *et al*. 2016; Fagan *et al*. 2020; Sweeney *et al*. 2020). Additionally, increasing dopamine neuron activity increased phosphorylated-ERK, DAT phosphorylation and threonine53 (known to be phosphorylated by ERK) as well as functionally increased in the maximal rate of reuptake (V_{max}) (Foster *et al*. 2012; Calipari *et al*. 2017).

Several receptors are also involved in regulating DAT function and expression. For example, DAT has direct protein-protein interactions with the D2R and co-expression of D2Rs increases DAT membrane expression and subsequent uptake in cultured neurons (Mayfield & Zahniser 2001; Lee *et al*. 2007). However, conditional loss of the D2R in dopamine neurons does not alter dopamine kinetics (Giguère *et al*. 2019). These data suggest that the D2R-mediated mechanisms can regulate DAT function quickly and transiently, but D2Rs are not necessary for basal DAT activity. Activation of κ-opioid receptors (KORs) also increases dopamine uptake through DAT regulation (Thompson *et al*. 2000) while activation of

mGluR5 receptors decreases the maximal rate of dopamine update (V_{max})(Page *et al.* 2001), suggesting that Gi (KOR) and Gq (mGluR5) mediated signaling exert opposing actions on DAT-mediated clearance rates.

Region-specific DAT regulation.: DAT expression, like D2Rs, shows region-specific effects on dopamine signaling. Dopamine clearance is highest in dorsal striatal regions and clearance rates decrease across a gradient from dorsolateral striatum down to medial shell. This region-specific DAT regulation is important as psychostimulant drugs, which inhibit transporter function, can have region-specific efficacy. For example, the effects of amphetamine are largest in the dorsal striatum due to the higher density of DAT in the region (Ramsson *et al.* 2011; Siciliano *et al.* 2014).

1.3.2. Vesicular monoamine transporter-2 (VMAT2)—

While DAT clears dopamine from the extracellular space, VMAT2 clears dopamine from the cytosolic space and sequesters it into synaptic vesicles (Erickson *et al.* 1992; Liu *et al.* 1992). This serves two important functions: 1) by sequestering dopamine in vesicles it protects the cell from free radicals formed by the oxidation of dopamine during its enzymatic degradation by monoamine oxidases in the cytosol (Liu & Edwards 1997; Liu *et al.* 1992) and 2) it allows the dopamine to be recycled and to be prepared for re-release. This transporter has 12 transmembrane domains with N- and C- terminals in the cytosol and several potential sites for posttranslational modification, including phosphorylation and glycosylation sites (Schuldiner *et al.* 1995). This transporter relies on the H+ gradient created by the H+ ATP-ase, which works to sequester H+ ions in the vesicles and create a proton gradient. Conversely, VMAT2 functions as an antiporter, transporting 2 H+ molecules out of the vesicle for each dopamine molecule it transports into the vesicle [VMAT2 function reviewed in (Eiden & Weihe 2011)]. Inhibition of VMAT2 function via pharmacological methods, such as application of reserpine, leads to decreases in quantal dopamine release (Floor *et al.* 1995; Pothos *et al.* 1998). Increases in VMAT2 expression or function result in increased dopamine loading into vesicles which leads to increases in quantal release of dopamine as well as increases in release events, providing a critical role for VMAT2 in regulating the amount of dopamine released in the extracellular space (Pothos *et al.* 2000; Eiden & Weihe 2011; Lohr *et al.* 2014; Lohr *et al.* 2015). Along similar lines, multiple studies have shown that expression of VMAT2 is required for vesicular dopamine storage, with VMAT2 deficient mice showing significantly reduced dopamine release depending on the relative levels of VMAT expression (Patel *et al.* 2003; Mooslehner *et al.* 2001; Wang *et al.* 1997). Acute blockade of VMAT2 function with reserpine also diminishes dopamine release as measured by voltammetry, suggesting that this blockade significantly prevents pool refilling (Kuhr *et al.* 1986). Additionally, expression of VMAT2 can be regulated in an activity-dependent manner and function can be altered by N-terminal glycosylation by CREB (Watson *et al.* 2001; Yao *et al.* 2004)(Watson et al. 2001; Yao, Erickson, and Hersh 2004). Thus, VMAT2 regulation also represents a critical factor that dictates the amount of stimulus-dependent dopamine release and can allow for dynamic changes as cellular activity changes.

Taken together, transporters exert important effects on the functioning of the dopamine terminals. They exert strong influence over extracellular and intracellular dopamine levels, releasable pool volume, release magnitude, and duration of dopamine's presence in the extracellular space.

2. Heterosynaptic Regulation at the Terminal

In addition to homosynaptic mechanisms that regulate dopamine release independent of other local circuitry, there is complex microcircuitry in the NAc whereby ligands can be released from non-dopaminergic populations and bind to receptors located directly on the dopamine terminal (Figure 1B). In addition to the dopamine terminals originating from the VTA that are described above, the striatum contains several types of postsynaptic neurons including GABAergic medium spiny projection neurons as well as a diverse population of interneurons (e.g. parvalbumin, somatostatin, cholinergic). Regulation of the levels of released ligands - via changes in the excitability of interneuron populations - along with regulation of the expression and function of the receptors for these ligands can dynamically influence the magnitude and frequency of synaptic dopamine release. Below we review the regulators that directly influence release at dopamine terminals through monosynaptic connections – i.e. via transmitters/molecules that signal through receptors/effectors that are located directly on or within dopamine terminals.

2.1. G-protein coupled receptors (GPCRs) and ligand-gated ion channels

Dopamine terminals in the striatum express several classes of heteroreceptors that can be classified as ligand-gated ionotropic receptors or G-protein coupled receptors (GPCRs). Ligand-gated receptors – such as nicotinic acetylcholine receptors (nAChRs) (Quik *et al.* 2007), and GABA-A receptors (Brodnik *et al.* 2019) - bind to neurotransmitter an allow for the passage of ions that can increase or decrease release probability and terminal excitability. Similarly, GPCRs located on terminals can also alter release, membrane excitability, function of transporters, and dopamine synthesis (Huang & Thathiah 2015) through initiation of intracellular cascades that can cause a variety of effects, including increases or decreases in cAMP production, opening of inward rectifying potassium channels that cause hyperpolarization, changes to kinase function and increases or decreases in gene expression. Dopamine terminals express many classes of GPCRs, including: D2Rs (Ford 2014; Chesselet 1984), the kappa opioid receptors (KOR) (Svingos *et al.* 2001; Ronken *et al.* 1993a), GABA-B receptors (Lopes *et al.* 2019; Ronken *et al.* 1993a), as well as metabotropic glutamate receptors (mGluR) (Kuwajima *et al.* 2007; Manzoni *et al.* 1997). Generally, these receptors can be classified as excitatory or inhibitory based on the 2nd messenger system they activate. Receptors that couple to excitatory G proteins - G_s or G_q - tend to increase activity of the cell by increasing cAMP production, increasing calcium levels and increasing gene expression (Huang & Thathiah 2015). Conversely, receptors that couple to inhibitory G proteins - $G_{i/o}$ - tend to decrease the activity of the cell by inhibiting cAMP production, activating GIRK channels (and/or other inwardly rectifying channels), inhibiting calcium channels, and increasing or decreasing gene expression. Below we outline ligand-gated receptors and GPCRs that have been shown to directly regulate dopamine release at terminals:

2.1.1. K-opioid receptors (KORs)—Another major regulator of dopamine release occurs via KORs. These GPCRs are located on dopamine terminals and act as a negative regulator of dopamine release through direct G_i signaling cascades that affect release probability and dopamine synthesis, as well as through interactions with the DAT that alter clearance rates (Britt & McGehee 2008; Thompson *et al.* 2000). Dynorphin, the endogenous ligand of KORs, is released from postsynaptic D1 receptor containing medium spiny neurons (MSNs) and acts to reduce dopamine release when high levels of D1 MSN activation occur. To this end, terminals can be regulated via changes in local dynorphin tone in an experience-dependent fashion. For example, repeated drug exposure and stress have both been shown to alter both dynorphin levels as well as KOR regulation - effects that converge to regulate tonic dopamine levels within the synapse (Karkhanis *et al.* 2015; Karkhanis *et al.* 2016; Bruchas *et al.* 2010; Land *et al.* 2008; Crowley & Kash 2015).

Region-specific KOR regulation.: Additionally, like with other regulatory mechanisms, expression of these receptors follows a region specificity, such that the NAc shell displays a "patchy" or clustered expression pattern (Svingos *et al.* 1999; Mansour *et al.* 1994), while the caudate-putamen shows dense expression in the medial and ventral portion (Steiner & Gerfen 1996; Steiner & Gerfen 1998). When total receptor availability or functional effects on dopamine release are compared, studies have found greater KOR availability/function within the NAc compared to dorsal regions of the striatum, an effect that has been demonstrated in both rodents and non-human primates (Siciliano *et al.* 2015; Le Merrer *et al.* 2009).

2.1.2. Metabotropic glutamate receptors (mGluRs)—While it is well-known that glutamate has robust actions on dopamine signaling within the striatum, how exactly glutamate exerts these actions has been a matter of controversy. Early work showed that exogenous application of L-glutamic acid increased spontaneous release of dopamine in striatal slices, though whether this was mediated through ionotropic or metabotropic receptors was unknown (Giorguieff *et al.* 1977). Local infusion of a glutamate reuptake inhibitor into the NAc resulted in increased extracellular dopamine in the NAc of rats as measured by microdialysis (Segovia & Mora 2001), which is consistent with human imaging studies (Gleich *et al.* 2015). Exactly which receptors were present on dopamine terminals was a matter of much debate until electron microscopy confirmed the presence of mGluR1a on dopaminergic terminals (Paquet & Smith 2003). In line with this evidence, previous work has shown that intrastriatal injection of the mGluR group I and II agonist 1*S*,3*R*-ACPD results in a behavioral phenotype that can be directly correlated with increased tissue levels of dopamine and its metabolites (Sacaan *et al.* 1992). However, there are limited studies that have outlined the precise mechanisms by which these receptors directly regulate dopamine release. Work from Sulzer and colleagues has shown that blockade of glutamatergic uptake in slice decreases dopamine release through mGluR1 activation, involving a mechanism involving phospholipase C and activation of calcium-dependent potassium channels (Zhang & Sulzer 2003). Interestingly, this glutamate appears to come from spillover from nearby corticostriatal glutamatergic synapses (Zhang & Sulzer 2003). The localization of these receptors on dopamine terminals and subsequent activation provides yet another potential

mechanism by which glutamatergic inputs into the striatum may be able to directly regulate dopamine terminals independent of local microcircuitry.

2.1.3. GABA receptors—There are a variety of sources of GABA within the striatum such as parvalbumin and somatostatin interneurons, and GABAergic MSNs (Brog *et al.* 1993; Pennartz *et al.* 1994). Locally released GABA acts to reduce dopamine release, either through G_i-coupled GABA-B receptors or ionotropic GABA-A receptors (Pitman *et al.* 2014; Ronken *et al.* 1993b; Brodnik *et al.* 2019). Indeed, these effects on dopamine release can occur through either GABA-A and GABA-B receptors as agonism of either receptor subtype reduces dopamine release (Pitman *et al.* 2014; Brodnik *et al.* 2019). However, GABA-A receptor-mediated reductions in dopamine release can be blocked with a GABA-B receptor antagonist, suggesting that GABA-A effects occur through a polysynaptic mechanism, rather than through direct effects on terminals (Brodnik *et al.* 2019). Thus, striatal GABA can inhibit dopamine release through both GABA-A and GABA-B receptors; however, there is some debate as to the localization of these receptors on local circuitry and terminals (Lopes *et al.* 2019; Pitman *et al.* 2014; Brodnik *et al.* 2019) .

2.1.4. Nicotinic acetylcholine receptors (nAChRs)—One of the most studied circuits in regard to local striatal regulation of dopamine release is acetylcholine release from cholinergic interneurons and the associated activation of nAChRs. nAchRs are pentameric ligand-gated iononotropic receptors that are activated by the endogenous ligand acetylcholine and are also the primary site of action for the exogenous ligand nicotine. As such these local circuit regulation mechanisms have been of interest in our understanding of substance use disorder, and much of our basic understanding of this process has originated from studies investigating how nicotinic agonists and antagonists affect dopamine release (Fennell *et al.* 2019; Lim *et al.* 2014; Yorgason *et al.* 2017; Kosillo *et al.* 2016; Shin *et al.* 2017; Collins *et al.* 2016; Cachope *et al.* 2012; Threlfell *et al.* 2012). In the striatum, dopamine is released in tonic (slow and regular) and phasic (short, burst/spikes) frequency patterns (Liss & Roeper 2010) that are subject to heavy modulation by these cholinergic systems (Rice & Cragg 2004). Normally, when increasing electrical stimulation frequencies are applied to dopamine terminals in brain slices, the total amount of dopamine release stays relatively stable; however, when acetylcholine is blocked by a nAChR antagonist, dopamine release is robustly responsive to stimulation frequency (Rice & Cragg 2004; Zhang & Sulzer 2004). These results have led to the hypothesis that acetylcholine in the striatum acts as a low-pass filter at dopamine terminals. In other words, in basal conditions where tonic acetylcholine is present high frequencies stimulations are “filtered out”, but when acetylcholine is blocked, or reduced via endogenous mechanisms, this filter is lifted (Rice & Cragg 2004; Zhang & Sulzer 2004).

The above examples focus on how signaling through nAchRs can alter dopamine release; however, these effects are beginning to be further characterized based on the type and location of nAchRs in the striatum. nAChRs have a number of subtypes, and as such, the expression and subunit composition of nAChRs on dopamine terminals is of vast importance to activity-dependent regulation of dopamine neurotransmission (Threlfell & Cragg 2011). Neuronal nAChRs are composed of combinations of any of the 10 alpha ($\alpha 2 - \alpha 10$) and 3

beta (β2 -β4) subunits (McGehee & Role 1995; Karlin 2002; Karlin 1993) . Each receptor is composed of 5 of these subunits, typically in a heteromeric composition, though homomeric arrangements also exist. Thus, there are a large number of possible compositions which can vary greatly in their physiological and biophysical properties (Lim *et al.* 2014) . Within the NAc, the most commonly expressed receptors contain α4, α6, α7, β2 and β3 (Quik *et al.* 2007) and are most often broadly divided into two groups that are either α6 or non- α6 containing (Threlfell & Cragg 2011; Salminen *et al.* 2004).

These subtypes of nAchRs can confer different biophysical properties, which adds further complexity in addition to differences in cell-type specific expression in the striatum. nAChRs have been shown to be located on cholinergic interneurons (Azam *et al.* 2003), glutamatergic terminals in the NAc (Marchi *et al.* 2002), cell bodies of GABAergic interneuronal populations (Inoue *et al.* 2016), and dopaminergic terminals (Lim *et al.* 2014; Champtiaux *et al.* 2003). Their location on dopamine terminals permits complex local circuit regulation through cholinergic regulation depending on spatial localization and timing. The β2 subunit is thought to be expressed in all nAChRs on dopamine terminals within the striatum, and has been shown to be important for the rewarding effects of nicotine (Picciotto *et al.* 1998). Moreover, activation of these specific receptors enhances dopamine release via a calcium-dependent mechanism, showing their ability to directly alter effectors necessary for dopamine release and associated plasticity (Turner 2004). Importantly, α6β2 subunit containing nAChRs located on dopamine terminals have been shown to mediate differential behavioral and physiological responses to nicotine (Siciliano *et al.* 2017; Fennell *et al.* 2019) . Therefore, the type of nAChR subunits present play a particularly important and critical role in the direct modulation of dopamine release via acetylcholine release.

2.1.5. Heterosynaptic regulation of calcium flux—

While we discussed calcium channels as homosynaptic regulators of dopamine release above, it is important to note that many ligand-gated ion channels also often are highly permeable to calcium. Thus, calcium regulation via either homosynaptic or heterosynaptic mechanisms plays a significant role in activity-dependent dopamine release dynamics. In particular, nAChRs and NMDA, another ligand gated receptor, have both been demonstrated to be permeable to calcium (MacDermott *et al.* 1986). In fact, recent work showed that calcium entry through nAChRs leads to enhanced size of the ready releasable pool, which can subsequently result in increased quantal dopamine release (Turner 2004). Similarly, early work has shown that NMDA receptor activation can trigger dopamine release in the striatum, which may be mediated by increased calcium flux into the terminal, rather than other direct mechanisms (discussed in section 3.1) (Krebs *et al.* 1989; Krebs *et al.* 1991; Cheramy *et al.* 1996). Thus, modifications in calcium entry and synaptic regulation of this process can also play a critical role in regulating dopamine release dynamics across the striatum.

2.2. Heterosynaptic transport mechanisms: Organic cation transporter (OCT3)

The organic cation transporter 3 (OCT3) is a high capacity, low affinity transporter located on dopamine neurons (Mayer *et al.* 2018), surrounding non-dopaminergic neurons and astrocytes (Cui *et al.* 2009) that plays a smaller role than DAT in clearing dopamine from the extracellular space, but nonetheless does participate in dopamine temporal dynamics. OCT3

is a low affinity, high capacity system meaning that it does not efficiently bind dopamine but has the capacity to transport large amounts of substrate. Functionally, this transporter works to reduce excess extracellular dopamine to prevent toxicity and oxidative stress (Cui *et al.* 2009). Inhibition of this transporter by the steroid hormone corticosterone can affect dopamine transients *in vivo* and can extend effects of DAT-inhibitor drugs like cocaine (Graf *et al.* 2013). Other hormones, including gonadal hormones like 17β-estradiol (E2) and progesterone, may inhibit this transporter (Iversen & Salt 1970) but *in vivo* studies have not yet been conducted to determine if these effects occur in live animals. These hormonal effects point to the possibility of potential sex differences, however there is a surprising paucity of data regarding hormonal action on microcircuit regulation of dopamine dynamics.

Importantly, the ability of both steroid and sex hormones to selectively alter clearance through modulation of secondary uptake mechanisms provides an avenue for dopamine regulation in a context-specific fashion. Because low affinity transporters like OCT3 are only engaged in situations where there is high concentration of extracellular dopamine, this likely only plays a strong role in regulating dopamine signaling in certain situations (e.g. high intensity stimuli or drug effects) but not others (basal dopamine release). Thus, these mechanisms are likely more complicated than simply increasing or decreasing extracellular dopamine levels, and therefore understanding dopamine regulation moving forward will require an understanding of context-specific processes.

2.3. Non-canonical regulatory mechanisms: diffusible transmitters and hormones

In addition to modulation by the neurotransmitter mediated- and clearance based-mechanisms, there are several diffusible signaling mechanisms that play potent roles in modulating dopamine release, including nitric oxide, hydrogen peroxide (H_2O_2), and insulin. These signaling molecules, especially for hormonal control, allow for state-dependent regulation of dopamine release to modify signal transduction in different cellular environments.

2.3.1. Nitric oxide regulation of dopamine transmission—Nitric oxide is produced by a variety of neurons throughout the brain and its production is stimulated by elevated intracellular calcium levels through a calmodulin-dependent process [reviewed in (Vincent 2010)]. However, these neurons densely innervate neighboring neurons, supporting potential involvement of nitric oxide in the regulation of many systems, including dopamine terminals in the NAc. Indeed, sodium nitroprusside, which generates nitric oxide, dose-dependently increases the amount of [3H]-dopamine released from pre-loaded dopamine terminals (Hanbauer *et al.* 1992), and slows [3H]-dopamine uptake rates measured in striatal synaptosomes (Pogun *et al.* 1994). Further, administration of nitric oxide synthase inhibitors, which reduce nitric oxide production, decreases striatal dopamine release (Kiss et al. 1999), showing that the effects of nitric oxide are bidirectional. This relationship remains true for [3H]-dopamine electrically evoked from intact terminals in striatal slices (Sandor *et al.* 1995). It has been suggested that some of the effects of nitric oxide occur via direct inhibition of DAT, thereby slowing clearance to increase synaptic dopamine levels (Kiss et al. 1999; Kiss 2000). Indeed, the effects of nitric oxide on dopamine release can be blocked by nomifensine, a potent DAT inhibitor (Kiss *et al.* 1999). Together this provides a potent

mechanism by which activity-dependent regulation of postsynaptic neurons can cause significant plasticity to dopamine terminals to alter feedforward signaling in this circuit following activity – and associated calcium influx – in postsynaptic cells.

2.3.2. Hydrogen peroxide (H_2O_2) modulation of dopamine dynamics—The enzymatic breakdown of dopamine and other monoamine neurotransmitters results in the production of several by-products, including reactive oxygen species (ROS) such hydrogen peroxide (H_2O_2). While atypical production of ROS is considered a harmful effect of oxidative cellular stress, under normal physiological conditions these species can also serve as important diffusible chemical messengers. Early work in the hippocampus deduced that H_2O_2 may inhibit release via inactivation of presynaptic ion channels (Pellmar 1987). Similarly, within the dopaminergic terminal, endogenous production of H_2O_2 inhibits presynaptic dopamine release through a calcium-dependent mechanism (Chen *et al.* 2001). H_2O_2 is generated from enzymatic reactions within medium spiny neurons and results in retrograde signaling that inhibits terminal dopamine release through ATP-sensitive potassium channels (Rice 2011). More recent work, leveraging approaches to monitor fluctuations in H_2O_2 and dopamine release concurrently, has also demonstrated H_2O_2-induced inhibition of dopamine release in dorsal striatum (Spanos *et al.* 2013). Thus, H_2O_2 along with nitric oxide represent two diffusible molecules that are generated in the postsynaptic cells in the striatum that function as potent retrograde regulators of dopamine terminals.

2.3.3. Insulin—In addition to the other receptors mentioned within this review, the NAc also expresses a high density of insulin receptors which function to regulate the reinforcing aspects of food intake through direct modulation of dopamine terminals (Werther *et al.* 1987; Fordahl & Jones 2017; Stouffer *et al.* 2015). Circulating levels of insulin have indeed been shown to bidirectionally modify dopamine dynamics, through interactions with DAT and through DAT trafficking mechanisms. In normal/basal states, insulin activates PI3 kinase (PI3K), leading to increases in dopamine uptake rates (Carvelli *et al.* 2002), an effect that leads to more efficient repackaging of dopamine. However in low-glucose states, for example following chronic food restriction, low circulating insulin levels are concomitant with reduced dopamine uptake rates – thus prolonging the time that dopamine is present in the synaptic cleft following release (Zhen *et al.* 2006). Dietary manipulations that lead to insulin resistance have shown a similar phenotype (Fordahl & Jones 2017). Similarly, glucose clearance rate is negatively correlated with dopamine clearance rates (Fordahl & Jones 2017) and this effect can be reversed by dose-dependent bath application of insulin (Fordahl & Jones 2017), indicating that the effects of insulin on dopamine dynamics are rapid and direct. Other lines of research have shown that insulin also reduces somatodendritic dopamine release in the VTA, providing a mechanism that also influences terminal DA release (Mebel *et al.* 2012; Naef *et al.* 2019).

Thus, in addition to canonical regulatory mechanisms through neurotransmitter systems, a number of diffusible signaling molecules and hormones act directly on dopamine terminals to alter dopamine signaling in response to both internal states (hunger, satiety) and following experience-dependent post-synaptic plasticity. These mechanisms serve as a process by

which dopamine release, repackaging, and clearance can be modulated on either a rapid or more prolonged timescale to influence how incoming upstream signals induce dopamine release and associated downstream signaling.

3. Other candidate direct mechanisms

The sections above have outlined the receptor systems present directly on dopamine terminals that allow for direct monosynaptic regulation of dopamine release dynamics. However, there are a number of other systems that show robust dopamine terminal regulation independent of VTA activity - and as such may exert direct control; yet many of these effects have been debated to be through other indirect polysynaptic mechanisms and require further analysis to definitively define their circuit localization.

One important candidate mechanism concerns ionotropic glutamate receptors, such as the NMDA receptor, and whether they can directly modulate presynaptic dopaminergic terminal. Indeed, early work using push-pull cannulae and superfusion slice methods showed that activation of NMDA receptors resulted in increased dopamine release in the striatum (Krebs *et al.* 1989; Krebs *et al.* 1991; Cheramy *et al.* 1996). More recent work using *in vivo* voltammetric recordings demonstrated that intra-striatal infusion of an NMDA receptor **antagonist** reduces dopamine release (Borland & Michael 2004; Kulagina *et al.* 2001). However, *ex vivo* application of NMDA receptors **agonists** also reduced evoked accumbal dopamine release (Yavas & Young 2017; Wu *et al.* 2000), an effect that is blocked by application of an NMDAR antagonist. These opposing effects – where *in vivo* and *ex vivo* application of an antagonist and agonists have the same effect on dopamine release - suggest that there may be multiple circuit-based mechanisms responsible for these effects, and it has been suggested that these effects are unlikely to be mediated by direct modulation of terminal excitability (Yavas & Young 2017). A prominent theory is that NMDAR activation increases local glutamate spillover and leads to subsequent regulation of dopamine terminals through either activation of metabotropic glutamate receptors and/or cholinergic interneurons (Zhang & Sulzer 2003). Data suggests that both metabotropic glutamate receptors and nAChRs are key mediators of NMDAR-mediated effects, as antagonism of both receptors blocked NMDAR effects (Zhang & Sulzer 2003; Marchi & Grilli 2010). However, it is also possible that NMDAR activation increases in the activity of local cholinergic interneurons and acetylcholine release then activates nAChRs directly on dopamine terminals. However, activation of nAChRs negatively regulates the effect of NMDAR agonists on dopamine release via triggering internalization of NMDA receptors that are located directly on the dopaminergic terminals themselves, suggesting NMDA effects likely wok through other mechanisms (Salamone *et al.* 2014).

Neurotensin is a signaling peptide that binds to the G-protein coupled receptor neurotensin receptor 1 (NTSR1) and plays a role in regulating synaptic plasticity in the dopaminergic system (Binder *et al.* 2001; White *et al.* 2012). These receptors are present on both cell bodies in the VTA and SN, as well as presynaptically in the dorsal and ventral portions of the striatum (Nicot *et al.* 1994; Palacios & Kuhar 1981; Schotte & Leysen 1989; Quirion *et al.* 1985). With respect to presynaptic release regulation, exogenous application of neurotensin has been shown to potentiate evoked dopamine release in NAc slices (Hetier *et*

al. 1988). More recent voltammetric studies showed that phasic stimulation of dopaminergic terminal concurrent with exogenous neurotensin application results in augmented dopamine release (Fawaz *et al.* 2009). However, the effects are only observed with voltammetric recordings following multiple pulse, but not single pulse, stimulations. This is important to note as multiple pulse stimulation paradigms in *ex vivo* voltammetric studies allow for the recruitment of indirect circuit mechanisms, while single pulse stimulations largely isolate direct terminal effects. Thus, it is clear that neurotensin has potent regulatory effects on dopamine terminals in striatal regions; however, it is unclear whether this effect is monosynaptic or polysynaptic.

4. Expanding our understanding of dopamine release regulation

Taken together there are complex regulatory mechanisms that control dopamine release at the level of the terminal. The microcircuit mechanisms described here may allow for encoding of important information that extends computations beyond just the amount of relative release and may control dopamine release in microdomains. Indeed, there is evidence for differential dopamine release regulation and clearance kinetics within genetically defined patch and matrix compartments, even within a single defined region like the NAc core (Shu *et al.* 2013; Brimblecombe & Cragg 2017; Nastuk & Graybiel 1985; Jiménez-Castellanos & Graybiel 1989). Thus, moving forward it will be critical to understand how different release regulation that is driven by these monosynaptic connections alters behavior and signaling in unique ways.

Another important caveat is that a large majority of this work was conducted in male animals, despite seminal work showing significant local effects of gonadal hormones within mesolimbic systems (Becker 1999; Walker *et al.* 2006; Walker *et al.* 2000; Bazzett & Becker 1994; Cummings *et al.* 2014; Yoest *et al.* 2018; Lynch *et al.* 2002; Carroll & Smethells 2015; Anker & Carroll 2011). It should be noted that much of the work in males was conducted in *ex vivo* preparations which isolates the local circuits, and as such is advantageous for investigating direct mechanisms without confounding influences of long-range projection systems and other whole animal systems such as hormonal influences. However, it is difficult to disentangle how the organizational effects of sex may influence local microcircuitry and interact with the mechanisms described above. Along these lines, there is significant evidence of differences in distribution and size of dopamine cell bodies between the sexes, even early in development, suggesting that dopaminergic systems are at least in part differentially organized (Ovtscharoff *et al.* 1992). However, studies to explicitly test whether the reviewed mechanisms are present in females, the microcircuits are organized the same way between the sexes, or whether they affect dopamine release to a similar extent in both sexes have not been completed to date. Further, while work has focused on how sex interacts with aspects of substance use (Townsend *et al.* 2019; Siciliano 2019), depression (Ma *et al.* 2019), motivation and the dopaminergic mechanisms underlying these phenotypes (Becker & Koob 2016; Brady *et al.* 2019), it remains mostly unclear how sex interacts with the specific local terminal regulatory mechanisms outlined in this review to drive these behaviors. Taken together, lack of understanding of how terminal dopamine is modulated in both males and females will further impede the development of pharmaceuticals to many

neuropsychiatric conditions involving dopamine dysfunction, including substance use disorder (Correa-De-Araujo 2006).

Finally, there has been a significant body of work that has sought to link dopamine to its role in motivated behavior, and as such, has supported dopamine's role in reinforcement learning, motivation, and disorders associated with these behaviors (Dayan 2009; Berridge 2012; Berke 2018; Watabe-Uchida *et al.* 2017; Keiflin & Janak 2015; Ahmed 2018). However, discerning the exact contributions of the above described microcircuit mechanisms to dopamine release events during learning has remained elusive due to technical limitations. Early studies were conducted using microdialysis methods, which provided valuable insights but lacked the resolution to dissociate effects on dopamine release that occurred directly at the dopamine terminal from effects upstream in the VTA. Still other studies have utilized transgenic mouse lines (Lammel *et al.* 2015) or blocked entire receptor systems (Roberts *et al.* 1977; Mahler *et al.* 2019), both of which make it difficult to disentangle cell body mechanisms from terminal regulation. While the VTA to NAc projection is intimately involved with reward learning, activity in this circuit can result in an array of dopamine release mechanisms – reviewed above-, and how these distinct mechanisms contribute to learning processes has yet to be established. Moreover, the variety of mechanisms and resulting dopamine signal may differentially encode aspects of contingencies, and as such, achieving a precise understanding how these microcircuits evoke dopamine and in what specific contexts they are invoked is critical to understanding how this release controls downstream signaling and achieves behavioral control.

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List of Abbreviations

ACh	acetylecholine
ChAT	choline acetyltransferase
DAT	dopamine transporter
D2R	dopamine type-2 atuoreceptor
ERK	extracellular signal-related kinase
E2	17β-estradiol
Glu	glutamate
GABAR	GABA receptor
GPCR	G-protein coupled receptor

H_2O_2	hydrogen peroxide
IR	insulin receptor
KOR	K-opioid receptor
MSN	medium spiny neuron
mTOR	mammalian target of rapamycin
mGluR	metabotropic glutamate receptor
NAc	nucleus accumbens
nAChR	nicotininc acetylcholine receptor
NO	nitric oxide
NT	neurotensin
NTSR1	neurotensin receptor 1
OCT3	organic cation transporter 3
PI3K	phosphoinositide 3-kinase
PKC	protein kinase C
PPAR	peroxisome proliferator-activated receptor
PV	paralbumin
ROS	reactive oxygen species
SN	substantia nigra
SST	somatostatin
VMAT	vesicular monoamine transporter
V_{max}	maximal rate of dopamine reuptake
VTA	ventral tegmental area

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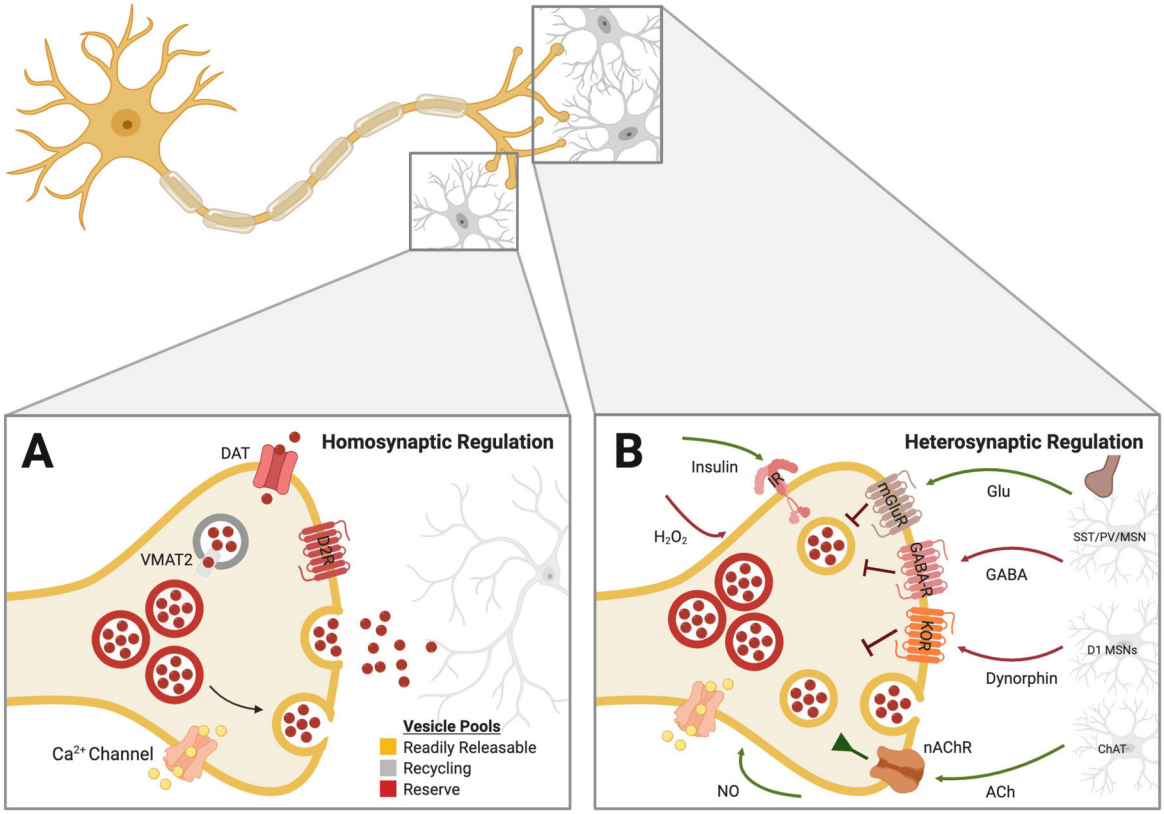

Figure 1. Homosynaptic and heterosynaptic regulators of presynaptic dopamine release in the striatum.

Dopamine release at the terminal can be elicited and modulated through mechanisms intrinsic to the cell itself, as well as via substrates released from postsynaptic cells and presynaptic inputs from non-dopaminergic systems. A. Fluctuations in the functionality of transporters, changes in the size of the various vesicle pools and activity of autoreceptors, all termed homosynaptic regulators, each have established roles in determining the amplitude of evoked dopamine release events. B. Several neurotransmitters from local microcircuitry, such as glutamate (Zhang and Sulzer 2003), GABA (Brog et al. 1993; Pennartz et al. 1994), dynorphin (Britt and McGehee 2008; Thompson et al. 2008), and acetylcholine (Collins et al. 2016; Kosillo et al. 2016; Shin et al. 2017; Yorgason et al., 2017), as well as diffusible retrograde signaling molecules like hydrogen peroxide (Chen et al. 2001) and nitric oxide (Kiss et al. 1999) can all exert influences on dopamine release at the axon terminal. ACh = acetylecholine; ChAt = choline acetyltransferase; DAT = dopamine transporter; GABA-R = GABA receptor ; Glu = glutamate; IR = insulin receptor; KOR = kappa opioid receptor; nAChR = nicotinic acetylcholine receptor; NO = nitric oxide; mGluR = metabotropic glutamate receptor; MSN = medium spiny neuron; SST = somatostatin; PV = paralbumin; VMAT = vesicular monoamine transporter.