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Invited review

Endocannabinoid modulation of dopamine neurotransmission

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ABSTRACT

Dopamine (DA) is a major catecholamine neurotransmitter in the mammalian brain that controls neural circuits involved in the cognitive, emotional, and motor aspects of goal-directed behavior. Accordingly, perturbations in DA neurotransmission play a central role in several neuropsychiatric disorders. Somewhat surprisingly given its prominent role in numerous behaviors, DA is released by a relatively small number of densely packed neurons originating in the midbrain. The dopaminergic midbrain innervates numerous brain regions where extracellular DA release and receptor binding promote short- and long-term changes in postsynaptic neuron function. Striatal forebrain nuclei receive the greatest proportion of DA projections and are a predominant hub at which DA influences behavior. A number of excitatory, inhibitory, and modulatory inputs orchestrate DA neurotransmission by controlling DA cell body firing patterns, terminal release, and effects on postsynaptic sites in the striatum. The endocannabinoid (eCB) system serves as an important filter of afferent input that acts locally at midbrain and terminal regions to shape how incoming information is conveyed onto DA neurons and to output targets. In this review, we aim to highlight existing knowledge regarding how eCB signaling controls DA neuron function through modifications in synaptic strength at midbrain and striatal sites, and to raise outstanding questions on this topic.

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Contents

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1. Introduction

The dopamine (DA) molecule is a major CNS neurotransmitter that has been the focus of extensive study due to its prominent involvement in core behavioral processes – including motor control, motivation, learning, and memory – and contribution to several neuropsychiatric disorders – including Parkinson's disease, schizophrenia, and drug addiction (Iversen et al., 2010). DA influences behavioral output by modulating basal ganglia circuit function. This occurs in large part through actions in the striatum, the primary input nucleus of the basal ganglia and predominant afferent target of midbrain DA cell bodies (**2. Midbrain-forebrain DA circuits**). Research into this mesostriatal DA circuit has revealed a crucial regulatory role for the endocannabinoid (eCB) system, a vast signaling network that controls synaptic transmission throughout the brain and periphery (**3. Brief primer to endocannabinoid signaling**). Notably, many behaviors and disease states that have traditionally been conceptualized as 'DA-dependent' are now understood to arise from interactions between the eCB and DA systems, including motor control or motor disorders (García et al., 2016) and reward seeking or addiction (Parsons and Hurd, 2015). Regulation of DA neurotransmission by eCBs arises through modulation of DA neuron effector sites in the striatum (**4. Endocannabinoid control of striatal function**), DA neuronal activity at midbrain cell bodies (**5. Endocannabinoid control of midbrain DA neurons**), and DA release at axon terminal endings (**6. Endocannabinoid control of terminal DA release**). Recent work indicating additional mechanisms by which eCB signaling controls DA function (**7. CB2 receptor regulation of DA function**) suggests these two systems are even more unified than previously thought. While several questions remain regarding the precise location and mechanisms by which eCBs and DA neurons communicate, it is clear that an understanding of DA neurotransmission cannot be fully realized independently of its relationship with eCB signaling.

2. Midbrain-forebrain DA circuits

The defining feature of a dopaminergic neuron is an ability to synthesize DA and release it both locally and at distal axon terminals (Subramaniam and Roeper, 2017; Sulzer et al., 2017). DA is synthesized by tyrosine hydroxylase and aromatic L-amino acid decarboxylase in neuronal cytosol, and packaged into synaptic and dense core vesicles via the vesicular monoamine transporter (VMAT) (Andén, 1967; Carlsson et al., 1958; Scherman et al., 1988). Vesicular release occurs in a calcium-dependent manner from both somatodendritic and axonal compartments (Beart et al., 1979; Beckstead et al., 2004; Besson et al., 1969; Bustos and Roth, 1972). Dopaminergic cell bodies originate within discrete midbrain nuclei known as the retrorubral field (A8), substantia nigra pars compacta (SNc, A9), and ventral tegmental area (VTA, A10) (Hillarp et al., 1966). Dopaminergic neurons densely innervate the dorsal and ventral striatum (i.e., nucleus accumbens, NAc), and project more sparsely to certain cortical subregions including the hippocampus and prefrontal cortex, thus comprising the mesocorticolimbic DA system. DA affects target neurons via 5 subtypes of G protein-coupled receptors (GPCRs) that come in two general classes, those that predominantly couple to $G\alpha_{s/olf}$ heterotrimeric G proteins (D1 and D5 receptors), and those that predominantly couple to $G\alpha_{i/o}$ G proteins (D2-D4 receptors) (Lachowicz and Sibley, 1997; Neve et al., 2010). Thus, DA is a 'pure' neuromodulator that exerts slow control over fast neurotransmission, in contrast to many other neurotransmitter systems that have both fast-acting ionotropic and slower acting GPCR-mediated actions.

Receptor activation dissociates the G protein heterotrimeric complexes to liberate Gα and Gβ/γ subunits (Latek et al., 2012). $G\alpha_s$ stimulates adenylyl cyclase (AC), which activates a variety of intracellular signaling systems that depolarize neurons, while $G\alpha_{i/o}$ liberation inhibits AC and suppresses these systems. Gβ/γ subunits also have signaling functions, including activation of phospholipase C (PLC) and modulation of certain ion channels that ultimately suppresses neuronal activity (Oldham and Hamm, 2006). This includes activation of G protein-coupled Inwardly-Rectifying Potassium (GIRK) channels and inhibition of voltage-gated calcium channels (VGCCs) (Betke et al., 2012). Once released, extracellular DA is subject to a number of regulatory mechanisms. The DA transporter (DAT) mediates fast DA re-uptake at cell bodies, dendrites, and axon terminals, and constitutes the main mechanism controlling DA concentrations at extrasynaptic sites, although the norepinephrine transporter also supports DA re-uptake in the prefrontal cortex (Carboni et al., 1990). DA degradation is primarily catalyzed by monoamine oxidase in striatum, and in some regions catechol-*o*-methyltransferase plays a dominant role.

DA neuron somata and dendrites are activated, inhibited, and modulated by several neurotransmitter systems arising from numerous brain regions, as recently reviewed (Sulzer et al., 2016; Paladini and Tepper, 2017). For the purposes of this review, we highlight here prominent inputs that control DA neurotransmission and explain in subsequent sections how these inputs are regulated by endocannabinoid (eCB) signaling. In general, glutamatergic inputs excite midbrain neurons through activation of ionotropic, and to some extent metabotropic, glutamate receptors on somatodendritic regions (Morikawa et al., 2003). However, the M5 metabotropic glutamate receptor, the only one reported to be expressed by midbrain DA neurons, exerts complex effects on terminal DA release (see below). GABAergic inputs generally inhibit DA function via $GABA_A$-type anion-fluxing ionotropic receptors and $GABA_B$-type Gi/o-coupled metabotropic receptors, although notable differences exist in the anatomical and functional characteristics of the GABA receptor subtypes (for review see Paladini and Tepper, 2017). Midbrain DA neurons also receive prominent neuromodulatory inputs, including particularly dense projections from serotonergic neurons in the dorsal raphe (Watabe-Uchida et al., 2012), although these projections also release glutamate onto DA neurons in the VTA (Qi et al., 2014). Finally, autoregulation can occur via DA release at somatodendritic compartments or terminals, which provides feedback inhibition through presynaptic DA D2 receptor (D2-R) binding (Beart and McDonald, 1982; Beckstead et al., 2004; Ford et al., 2009).

DA neurotransmission is also modulated at release sites in the striatum by several afferent inputs (Cachope and Cheer, 2014), including cholinergic and glutamatergic sources, which can control terminal DA release independently of DA cell body input (Fig. 1). Acetylcholine (ACh) released from striatal cholinergic interneurons (CINs; Fig. 1B) binds ionotropic nicotinic ACh (nACh) receptors on DA terminals, which increases intracellular calcium flux (Zhou et al., 2001; Exley and Cragg, 2008) and elicits DA release in the NAc and dorsal striatum (Cachope et al., 2012; Threlfell et al., 2012). The nACh-R subtypes involved in this release are of the α4/6β2 variety with α4 perhaps predominating in dorsal striatum and α6 in NAc (Rapier et al., 1990; Zhou et al., 2001; Exley and Cragg, 2008; Cachope et al., 2012; Threlfell et al., 2012). CINs also target muscarinic ACh (mACh) GPCRs, which are of the $G_{q/11}$-coupled M5 subtype on DA terminals. Activation of M5 mACh-Rs in dorsal striatal (Foster et al., 2014) or NAc (Shin et al., 2015) brain slices inhibits DA released by electrical stimulation (Foster et al., 2014). In contrast, a non-specific mACh-R agonist, oxotremorine M, potentiates DA release in response to selective optogenetic stimulation of DA neuron axon projections, achieved through virally-mediated expression of channelrodopsin-2 in the VTA. This selective