# G protein-coupled receptor modulation of striatal dopamine transmission: Implications for substance use disorders

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**Abstract**

Dopamine transmission in the striatum is a critical mediator of the rewarding and reinforcing effects of commonly misused psychoactive drugs. G protein-coupled receptors (GPCRs) that bind a variety of neuromodulators including dopamine, endocannabinoids, acetylcholine, and endogenous opioid peptides regulate dopamine release by acting on several components of dopaminergic circuitry. Striatal dopamine release can be driven by both somatic action potential firing and local mechanisms that depend on acetylcholine released from striatal cholinergic interneurons. GPCRs that primarily regulate somatic firing of dopamine neurons via direct effects or modulation of synaptic inputs are likely to impact distinct aspects of behavior and psychoactive drug actions compared with GPCRs that primarily regulate local acetylcholine-dependent dopamine release in striatal regions. This review will highlight mechanisms by which GPCRs modulate dopaminergic transmission and the relevance of these findings to psychoactive drugs involved in substance use disorders.

## 1. Introduction

Dopamine transmission in the striatum plays critical roles in complex cognitive and behavioral processes including reward, motivation, reinforcement learning, effort, and responses to salience (Berke, 2018; Kutlu et al., 2021; Walton & Bouret, 2019). Dopamine neurons that project to striatal regions originate in the substantia nigra pars compacta (SNc), which densely innervates the dorsal striatum, and the ventral tegmental area (VTA), which projects to the ventral aspect of the striatum (the nucleus accumbens or NAc) and cortical areas that are important for executive functions (An et al., 2021; de Jong et al., 2022). Dopamine exerts several types of modulatory influence on striatal physiology (Yamada et al., 2016). Distinct populations of striatal projection neurons (SPNs; also known as medium spiny neurons) express D1 and D2 subtypes of dopamine receptors, which modulate their excitability and regulate neurotransmitter release. D2 receptors on striatal cholinergic interneurons are important regulators of firing patterns (Zhang & Cragg, 2017). In addition, dopaminergic transmission contributes to several forms of synaptic plasticity that influence corticostriatal transmission over longer time scales (Bamford et al., 2018).

Psychoactive drugs that are subject to misuse acutely increase dopamine release in striatal regions, although the mechanisms that mediate these transient increases in dopamine release vary depending on the molecular targets of each drug (Luscher et al., 2020). Drug-evoked dopamine release is an important mediator of the rewarding and reinforcing effects of psychoactive drugs, and is involved in many aspects of psychoactive drug misuse including behavioral reinforcement, habit formation, and aberrant responses to drug-associated stimuli (Koob & Volkow, 2016; Wise & Robble, 2020). GPCRs that regulate dopaminergic circuitry play various roles in psychoactive drug effects. Opioids and cannabinoids directly activate GPCRs, resulting in increased striatal dopamine transmission. In other cases, endogenous activation of GPCRs that inhibit dopamine release constrain the effects of psychoactive drugs (e.g., D2 dopamine receptors and kappa opioid receptors). Many GPCRs that modulate dopamine release in the striatum are current or proposed targets for treatment of substance use disorders based on their ability to reduce drug consumption in preclinical

models and in human subjects. Reducing the primary reinforcing value of psychoactive drugs by attenuating their ability to evoke dopamine release is one potential mechanism by which GPCR modulation can reduce drug consumption. GPCR manipulations that reduce dopamine transmission evoked by drug-associated stimuli also have the potential to inhibit drug seeking caused by aberrant incentive salience. Understanding how GPCRs modulate striatal dopamine transmission under normal conditions, and the relevance of GPCR actions to psychoactive drug effects in the context of recreational-type use and substance use disorders, is critical to understanding the neurobiology of psychoactive drug use and developing novel treatment strategies for substance use disorders.

This review will highlight several types of GPCRs that regulate dopamine release, including dopamine release evoked by psychoactive drugs, in striatal regions. We will focus on examples that demonstrate the diverse mechanisms by which GPCRs can regulate striatal dopamine release, including D2 dopamine receptors, metabotropic glutamate receptor 2 ($mGlu_2$), cannabinoid receptors (CB1 and CB2), muscarinic acetylcholine receptors (M1, M4, and M5), and opioid receptors (mu and kappa). For each receptor, we will review the synaptic mechanisms by which dopamine release is either enhanced or attenuated, and then highlight examples of how these receptors modulate psychoactive drug effects from a neurochemical and behavioral perspective.

## 2. Sites of GPCR-mediated modulation of dopamine transmission

Release of dopamine from midbrain dopamine neurons is regulated by a variety of intrinsic and extrinsic factors that influence action potential firing at the somatodendritic level and terminal release mechanisms in target regions. These factors include activation of GPCRs and ligand-gated ion channels, adaptive changes in gene expression, regulation of dopamine synthesis and vesical release mechanisms, altered capacity or kinetics of dopamine reuptake through dopamine transporters (DAT), and modulation of synaptic inputs. In the midbrain, $G\alpha_{i/o}$-coupled GPCRs (e.g., D2) can activate G protein-gated inwardly rectifying $K^+$ (GIRK) channels to hyperpolarize dopamine neurons (**Fig. 1** ) (Rifkin et al., 2017). Dopamine neurons receive both glutamatergic and GABAergic synaptic inputs, and presynaptic inhibition of these inputs via activation of inhibitory GPCRs (e.g., CB1) can modulate rates and patterns of dopamine neuron firing (**Fig. 1** ) (Wang & Lupica, 2014). In striatal target regions, GPCRs modulate dopamine release in a variety of ways that include enhancing or inhibiting vesicular release mechanisms, modifying surface expression and kinetics of DAT activity, and altering synthesis and vesicular dynamics (reviewed in Nolan et al., 2020; Sulzer et al., 2016).

In addition to dopamine release driven by somatic action potential firing, synchronous release of acetylcholine (ACh) from cholinergic interneurons (CINs) in both the dorsal striatum and NAc elicits dopamine release via activation of nicotinic ACh receptors in dopamine neuron axons (**Fig. 2** ) (Cachope et al., 2012; Threlfell et al., 2012). This form of local axo-axonal dopamine release is generated by triggering local action potentials (Kramer et al., 2022; Liu et al., 2022) and can be indirectly elicited by glutamatergic inputs to CINs that originate from intralaminar thalamic nuclei (Cover et al., 2019; Threlfell et al., 2012) and various cortical regions (Adrover et al., 2020; Kosillo et al., 2016; Mateo et al., 2017). Thus, GPCRs that regulate CIN excitability, ACh release from CINs, or glutamatergic input to CINs are all putative modulators of striatal dopamine release (**Fig. 2** ). Although the functional consequences of having multiple routes to dopamine release are not well understood, each pathway is likely to make unique contributions to behavior (e.g., Mohebi et al., 2019; Mohebi, 2022). Moreover, these mechanisms can interact with one another, with ACh-dependent mechanisms acting as a low-pass filter on simultaneously occurring somatic action potential-dependent dopamine release (Lovinger et al., 2022; Threlfell et al., 2012). GPCRs that differentially modulate these mechanisms of dopamine release could therefore modify interactions between these mechanisms as well.

## 3. Modulation of dopamine transmission by D2 autoreceptors

Dopamine release modulates the physiology of dopamine neurons and neurons in target regions by acting on GPCRs that include the $G\alpha_s$-coupled D1-like receptors (D1 and D5) and $G\alpha_{i/o}$-coupled D2-like receptors (D2,

D3, D4) (Martel & Gatti McArthur, 2020). D2 receptors are expressed in both axonal and somatodendritic regions of dopamine neurons, and are thus poised to exert negative feedback on dopamine release using several distinct mechanisms (reviewed in Ford, 2014; Nolan et al., 2020). Activation of somatodendritic D2 receptors expressed by VTA and SNc dopamine neurons produces hyperpolarization via activation of GIRK channels and can reduce firing rates (Beckstead et al., 2004; Courtney et al., 2012; Ford, 2014; Lacey et al., 1987). In terminal regions, activation of D2 autoreceptors inhibits dopamine release due to activation of $K^+$ currents and inhibition of voltage-gated calcium channels (Cardozo & Bean, 1995; Congar et al., 2002; Ford, 2014; Martel et al., 2011; Nolan et al., 2020; Stamford et al., 1991). In addition, D2 receptor activation can modulate dopamine transmission over a range of timescales via effects on synthesis and clearance. D2 activation reduces tyrosine hydroxylase activity and can increase activity of dopamine transporters, particularly in the context of strong D2 receptor activation (Anzalone et al., 2012; Benoit-Marand et al., 2011; Ford, 2014; Lee et al., 2007; Mayfield & Zahniser, 2001; Nolan et al., 2020; Wolf & Roth, 1990).

Converging lines of evidence from pharmacological, genetic, and human imaging studies provide substantial evidence that D2 receptors are involved in acute responses to psychoactive drugs and that adaptations in D2 receptor expression and function can occur following chronic drug use (reviewed in Jordan & Xi, 2021; Urban & Martinez, 2012; Volkow & Morales, 2015). Because D2 receptors are expressed by both dopaminergic and non-dopaminergic neurons, the majority of studies do not delineate specific roles for D2 autoreceptors vs. heteroreceptors expressed by various striatal neurons and neurons in other target regions (e.g., cortex). Conditional knockout mice are an important tool for interrogating cell-type specific receptor functions. Selective deletion of D2 receptors from dopamine neurons enhances dopamine release, increases locomotion while exploring a novel environment, and elevates motivation for natural rewards (Anzalone et al., 2012; Bello et al., 2011). In the context of psychoactive drug responsiveness, D2 autoreceptor deletion enhances responses to psychoactive drugs, including enhanced cocaine-induced dopamine release and psychomotor activation, conditioned place preference, acquisition of operant self-administration, and cocaine-paired cue reactivity (Anzalone et al., 2012; Bello et al., 2011; Holroyd et al., 2015). However, D2 autoreceptor deletion from the SNc of adult rats using RNA interference blunted locomotor responses to cocaine, suggesting that it could be important to consider the developmental effects, species dependence, and region specificity when using the conditional knockout approach (Budygin et al., 2016). Interestingly, human imaging studies suggest that midbrain D2/D3 receptor availability is inversely correlated with trait impulsivity, a potential vulnerability factor for psychoactive drug misuse (Buckholtz et al., 2010). Lower human D2/D3 receptor binding is also associated with enhanced amphetamine-induced striatal dopamine release, supporting the translational relevance of preclinical evidence for the autoinhibitory role of D2 receptors (Buckholtz et al., 2010). In addition to the potential for D2 autoreceptor expression or function to confer vulnerability to drug misuse, repeated exposure to drugs including psychostimulants and alcohol can alter D2-mediated modulation of dopaminergic transmission (Perra et al., 2011; Wolf et al., 1993).

## 4. Modulation of dopamine transmission by metabotropic glutamate receptor 2

$mGlu_2$ receptors are primarily expressed at presynaptic sites of glutamatergic synapses, where they reduce neurotransmitter release by inhibiting voltage-gated calcium channels (Kupferschmidt & Lovinger, 2015; Niswender & Conn, 2010). Activation of $mGlu_2$ reduces dopamine release in the dorsal striatum and NAc (reviewed in Johnson, 2021). However, $mGlu_2$expression is not detected in midbrain dopamine neurons, and $mGlu_2$ agonists do not reduce dopamine release or associated behavioral effects produced by direct stimulation of midbrain dopamine neurons (Pehrson & Moghaddam, 2010); these findings indicate that $mGlu_2$ modulates dopamine release indirectly. In*ex vivo* preparations, activation of $mGlu_2$ induces long-term depression of both cortical and thalamic glutamatergic inputs to the dorsal striatum, and also inhibits dopamine release driven by optogenetic stimulation of thalamostriatal afferents (Johnson et al., 2017; Johnson et al., 2020). $mGlu_2$ modulation of dopamine transmission in the dorsal striatum is occluded by nicotinic receptor blockade, supporting the idea that $mGlu_2$modulation of dopamine release is exclusively mediated by indirect, ACh-dependent mechanisms (Johnson et al., 2020). This mechanism appears to be engaged *in vivo* as well, as $mGlu_2$activation reduces operant responding for optogenetic stimulation of thalamostriatal

neurons, while $mGlu_2$ blockade increases response rates for thalamostriatal self-stimulation. Although $mGlu_2$ effects on cortically-driven dopamine release have not been directly evaluated, $mGlu_2$-mediated inhibition of cortical inputs to CINs in both the dorsal striatum and NAc represents another possible mechanism for modulation of dopamine transmission.

In addition to effects on basal dopamine transmission, $mGlu_2$ activation can reduce dopamine evoked by psychoactive drugs including amphetamine, nicotine, and cocaine, and likewise reduces associated behavioral effects including drug-induced locomotor activity (Arndt et al., 2014; Bauzo et al., 2009; D'Souza et al., 2011; Johnson & Lovinger, 2016; Pehrson & Moghaddam, 2010). Moreover, some effects of psychoactive drugs are altered in mice or rats lacking $mGlu_2$, including increased vulnerability to excessive drug consumption (reviewed in Jordan & Xi, 2021). $mGlu_2$ activation could therefore decrease the reinforcing properties of a variety of psychoactive drugs, and this is supported by observations that $mGlu_2$ activation reduces operant self-administration of drugs including alcohol (Augier et al., 2016), cocaine (Bauzo et al., 2009; Jin et al., 2010), methamphetamine (Crawford et al., 2013), and nicotine (Justinova et al., 2015; Li et al., 2016; Liechti et al., 2007). Interestingly, $mGlu_2$activation can also reduce cue-induced reinstatement of drug seeking, though it is unclear whether inhibition of cue-associated dopamine responses are attenuated by $mGlu_2$. Based on these findings, $mGlu_2$ positive allosteric modulators are currently being developed to treat several substance use disorders (reviewed in Caprioli et al., 2018; Johnson & Lovinger, 2020).

## 5. Modulation of dopamine transmission by muscarinic acetylcholine receptors

Metabotropic effects of acetylcholine, including regulation of dopaminergic transmission, are mediated by five subtypes of muscarinic acetylcholine receptors (M1-M5) that signal through $G\alpha_q$(M1, M3, M5) or $G\alpha_{i/o}$ (M2, M4) (Kruse et al., 2014). In the midbrain and striatum, these receptors exert complex regulatory control over dopamine release. Nonselective activation of muscarinic receptors increases extracellular dopamine levels in freely moving rats as measured by microdialysis (Smolders et al., 1997). In striatal slices, nonselective mAChR activation decreases dopamine release evoked by low-frequency electrical stimulation (Threlfell et al., 2010). Conversely, muscarinic receptor activation can enhance dopamine release evoked by high-frequency stimulation (Threlfell et al., 2010). Of the five muscarinic receptor subtypes, pharmacological and genetic approaches have identified roles for M1, M4, and M5 in modulating dopamine release; these receptors act through a variety of mechanisms, including direct modulation of somatic and terminal dopamine neuron activity and indirect mechanisms such as modulation of striatal acetylcholine and endocannabinoid (eCB) release. Muscarinic receptors contribute to reward-associated learning and behaviors in a variety of ways. For example, broad blockade of accumbal muscarinic receptors attenuates cue-induced dopamine release and prevents cue-induced invigoration of reward seeking in a Pavlovian-to-instrumental transfer (PIT) task (Collins et al., 2016). Thus, multiple muscarinic receptor subtypes are likely to play modulatory roles in responses to psychoactive drugs that enhance dopamine transmission.

### 5.1 M1 receptors

M1 receptors are the most abundant muscarinic receptor in the striatum (Weiner et al., 1990). Studies measuring dopamine transmission using*in vivo* microdialysis in the striatum of freely moving rats demonstrated that M1 antagonism decreases dopamine release, suggesting that M1 activity tonically augments dopamine transmission (De Klippel et al., 1993; Smolders et al., 1997). Although the exact mechanisms for M1-mediated facilitation of dopamine transmission are not clear, reduced dopamine reuptake due to PKC-dependent internalization of DAT is one putative contributor (Underhill & Amara, 2021). Circuit-level effects that increase striatal glutamate transmission to enhance nicotinic receptor-dependent dopamine release could also play a role.

Although M1 appears to facilitate dopamine release under normal conditions, studies evaluating the effect of chronic M1 agonist treatment on cocaine-induced dopamine show decreased cocaine-induced dopamine transmission. Concordantly, M1 agonist treatment facilitates the reallocation of behavior from cocaine rewards to food pellets in operant cocaine vs. food choice task (Weikop et al., 2020). In addition, despite evidence that M1 blockade reduces dopamine release, both nonselective and M1-preferring muscarinic antagonists produce

cocaine-like discriminative stimulus effects that are lost in mice lacking M1 receptors (Joseph & Thomsen, 2017). Based on these findings, enhancing M1 activity has been suggested as a putative treatment strategy for cocaine use disorder. Because M1 expression is not detected in dopamine neurons, further investigation will be required to determine the mechanisms by which M1 modulates dopamine transmission evoked by psychoactive drugs.

### 5.2 M4 receptors

M4 receptors are expressed by striatal neurons including spiny projection neurons and cholinergic interneurons but are not found on midbrain dopamine neurons. Mice lacking M4 receptors have elevated accumbal dopamine levels, suggesting that M4 tonically inhibits dopamine release (Tzavara et al., 2004). Interestingly, the non-selective muscarinic agonist oxotremorine potentiates dopamine release evoked by high potassium concentrations, an effect that is lost in M4 knockout mice and likely mediated by inhibition of striatal GABA release (Zhang et al., 2002). These seemingly contradictory findings suggest complex modulatory mechanisms that are differentially engaged by different methods to drive dopamine release. Although earlier studies suggested that M4-mediated inhibition of striatal dopamine release is likely mediated by inhibition of ACh release from CINS (Shin et al., 2015; Threlfell et al., 2010), more recent studies in which M4 was conditionally deleted from D1-expressing SPNs demonstrated that activation of M4 in this population of neurons mobilized eCB release to inhibit dopamine release (Foster et al., 2016). Thus, M4 has the potential to regulate dopamine release driven by somatic firing and local acetylcholine-dependent release by distinct mechanisms.

Consistent with the inhibitory role of M4 observed under normal conditions, M4 PAMs reduce psychostimulant-induced dopamine release*in vivo* and inhibit the locomotor enhancing effects of psychostimulant drugs (Byun et al., 2014; Dall et al., 2017; Dencker et al., 2012; Foster et al., 2021). Likewise, M4 PAM administration reduces cocaine self-administration (Dencker et al., 2012). Consistent with the importance of M4 receptors expressed by D1-SPNs for inhibiting dopamine release, selective deletion of M4 from D1-SPNs impairs the ability of an M4 PAM to reduce cocaine self-administration (Dencker et al., 2012). However, M4 activation does not prevent all psychostimulant-induced rewarding effects; for example, mice treated with an M4 PAM still showed cocaine-conditioned place preference (Dall et al., 2017). M4 activation can constrain responses to non-stimulant drugs as well, as intrastriatal infusion of an M4 PAM reduces ethanol self-administration and cue-induced reinstatement (Walker et al., 2020). Based on these findings and others, M4 PAMs have been proposed for treatment of a variety of substance use disorders as well as other psychiatric disorders involving dopamine dysregulation (Foster et al., 2021; Walker et al., 2020).

### 5.3 M5 receptors

The highest levels of M5 receptor expression in the CNS are found in dopamine neurons in both the VTA and SNc (Vilaro et al., 1990; Weiner et al., 1990), where M5 regulates dopamine neuron physiology at both somatic and terminal sites. In the NAc shell, M5 activation potentiates dopamine release driven by optogenetic stimulation of dopamine neurons, and also potentiates glutamate co-release from a subset of VTA dopamine neurons (Shin et al., 2015). Activating M5 receptors also decreases dopamine clearance, likely by promoting PKC-dependent internalization of DAT (Shin et al., 2015; Underhill & Amara, 2021). In SNc neurons, M5 activation produces an inward current and increases firing rate (Foster et al., 2014). Contrary to observations in the NAc shell, M5 activation in the dorsal striatum reduced electrically-evoked dopamine release (Foster et al., 2014), suggesting that the direction of M5-mediated modulation of dopamine transmission could be region-specific.

Because M5 expression is relatively restricted to dopamine neurons, there has been significant interest in targeting M5 in disorders that involve dopamine dysregulation, including substance use disorders (Teal et al., 2019; Walker & Lawrence, 2020). For example, M5-selective negative allosteric modulators (NAMs) that block oxotremorine-induced firing of VTA neurons reduce opioid self-administration and opioid-associated cue reactivity in rats (Garrison et al., 2022; Gould et al., 2019). An M5 NAM also reduces cocaine self-administration in both fixed ratio and progressive ratio tasks (Gunter et al., 2018). In rats selectively bred for

high ethanol preference, systemic administration of an M5 NAM decreased ethanol self-administration and cue-induced ethanol seeking (Berizzi et al., 2018). Interestingly, intra-dorsolateral striatum (but not intra-dorsomedial striatum) injection of the M5 NAM reduced ethanol self-administration in rats with extensive prior ethanol experience (Berizzi et al., 2018). Based on the overall conclusion from *ex vivo* experiments that M5 activation facilitates dopamine neuron firing and release, M5 blockade could reduce drug taking by reducing the reinforcing properties of a variety of psychoactive drugs and inhibiting dopamine responses to drug-associated cues.

## 6. Modulation of dopamine transmission by cannabinoid receptors

### 6.1 CB1

CB1 receptors are $G\alpha_{i/o}$-coupled GPCRs that are widely expressed on presynaptic terminals in various regions of the CNS, including in the midbrain. Until recently, evidence for CB1 receptor expression in midbrain dopamine neurons had not been established; however, CB1 can regulate inputs to dopamine neurons and therefore indirectly control their activity (reviewed in Peters, Cheer, et al., 2021; Peters, Oleson, et al., 2021). Endocannabinoids (eCBs), the endogenous ligands for CB receptors, are synthesized on-demand in response to neuronal activity and/or intracellular calcium mobilization in many types of neurons including midbrain dopamine neurons (Wang & Lupica, 2014; Yanovsky et al., 2003). The newly synthesized eCBs (anandamide or 2-arachidonylglycerol [2-AG]) then undergo retrograde transport and activate presynaptic CB1 receptors to inhibit neurotransmitter release (Kano et al., 2009). CB1 receptor activation resulting from retrograde eCB signaling or agonist administration can disinhibit dopamine neurons by reducing GABAergic transmission (De Luca et al., 2015; Wang & Lupica, 2014). For example, in the VTA, eCB mobilization from dopamine neurons can be triggered by activation of $G\alpha_q$-coupled GPCRs including orexin 1 receptors, $\alpha$1 adrenergic receptors, and type I mGlu receptors, thus reducing GABA transmission to disinhibit dopamine neurons (Tung et al., 2016; Wang et al., 2015).

Although the majority of studies have focused on inhibition of GABA inputs to dopamine neurons in the midbrain as the primary mechanism of CB1 regulation of dopamine transmission, a recent study identified CB1 mRNA in a subset of VTA neurons that co-express the glutamate neuron marker Vglut2, suggesting that direct presynaptic inhibition of dopamine release is another possible mechanism (Han et al., 2023). Supporting the behavioral relevance of this finding, CB1 receptor activation reduces optogenetic intracranial self-stimulation of these neurons, and this effect is lost when CB1 is conditionally deleted from these neurons (Han et al., 2023). CB1 receptors expressed on glutamatergic terminals in striatal regions are also poised to regulate local ACh-mediated dopamine release. For example, eCB action on prefrontal cortex terminals inhibits dopamine release evoked by optogenetic stimulation of PFC inputs or CINs, and activation of this population of CB1 receptors reducing optogenetic intracranial self-stimulation of PFC terminals in the NAc (Mateo et al., 2017).

Psychoactive drugs that activate CB1 receptors, such as $\Delta$9-tetrahydrocannabinol (THC) and synthetic CB1 agonists, increase firing rates of VTA and SNc dopamine neurons (French et al., 1997; Gessa et al., 1998). Interestingly, CB1 receptors are also involved in dopamine release produced by several other classes of psychoactive drugs. For example, NAc dopamine transients evoked by systemic administration of nicotine, ethanol, cocaine, and amphetamine are reduced by CB1 blockade (Cheer et al., 2007; Covey et al., 2016). Activation of retrograde eCB signaling to reduce GABAergic transmission is likely to play a role, as fast-scan cyclic voltammetry experiments in midbrain slices demonstrate that cocaine application produces 2-AG synthesis and reduces inhibitory postsynaptic currents in VTA neurons (Wang et al., 2015). Findings from basic behavioral experiments suggest that engagement of the eCB system could contribute to many aspects of drug-associated reward, reinforcement, and addictive behaviors. For example, eCBs play a role in reward prediction, as disrupting VTA eCB signaling using antagonists attenuates cue-associated dopamine transients during a reward seeking task (Oleson et al., 2012). Activation of CB1 receptors modulates reward thresholds in intracranial self-stimulation task in a dose-dependent manner, as low doses of $\Delta$9-THC decrease intracranial self-stimulation thresholds, while higher doses increase reward thresholds (Katsidoni et al., 2013). These findings raise interesting questions about how simultaneous cannabis use affects physiological and

behavioral responses to other types of psychoactive drugs, including alcohol and psychostimulants.

### 6.2 CB2

Although there are relatively few reports of CB2 regulation of neurotransmission, there is recent evidence that CB2 is expressed in midbrain dopamine neurons and plays a role in regulation of dopamine transmission (Aracil-Fernandez et al., 2012; Zhang et al., 2014). As mentioned above (see section 5.2), M4 activation in D1-expressing SPNs in the dorsal striatum promotes eCB production to reduce dopamine release, and this effect is absent in mice lacking CB2 receptors and blocked by a CB2-selective antagonist (Foster et al., 2016). In midbrain slice preparations and *in vivo* , CB2 activation decreased VTA dopamine neuron firing rates (Ma et al., 2019; Zhang et al., 2014). This effect was maintained in the presence of glutamatergic and GABAergic transmission blockers, but disrupted by blocking G protein signaling in the recorded cell, suggesting a direct effect on dopamine neurons. Conditional deletion of CB2 from DAT-expressing neurons produced complex effects on responses to a variety of psychoactive drugs, providing additional evidence that CB2 receptors expressed by dopamine neurons can directly modulate dopamine transmission (Canseco-Alba et al., 2019). In addition, a CB2 agonist inhibited optogenetic intracranial self-stimulation for activation of VTA dopamine neurons (Han et al., 2023). The ability of CB2 to reduce dopamine transmission by reducing dopamine neuron firing and decreasing release at terminals suggests that CB2 activation could reduce responses to psychoactive drugs. Supporting this idea, direct injection of a CB2 agonist into the VTA inhibits cocaine self-administration (Zhang et al., 2014). Transgenic mice with CB2 overexpression show reduced locomotor responses to cocaine and attenuated cocaine self-administration, providing further evidence that CB2 receptors can constrain the primary reinforcing effects of some psychoactive drugs (Aracil-Fernandez et al., 2012).

## 7. Modulation of dopamine transmission by opioid receptors

Opioids regulate neurotransmission in many brain regions by acting on three types of receptors: delta opioid receptors (DOR), kappa opioid receptors (KOR), and mu opioid receptors (MOR) (Reeves et al., 2022; Stein, 2016). Opioid receptors in the CNS are activated by endogenous opioid peptides including enkephalin (MOR and DOR) and dynorphin (KOR). SPNs throughout the striatum produce opioid peptides, and opioid receptors are expressed on a variety of striatal neurons and afferents. The expression patterns of opioid peptides and their receptors facilitate substantial interaction between the opioidergic and dopaminergic systems (reviewed in Sgroi & Tonini, 2018). All three types of opioid receptors are $G\alpha_{i/o}$-coupled and when expressed at presynaptic sites, their activation can inhibit dopamine release via activation of GIRK channels and inhibition of voltage-gated $Ca^{2+}$ channels. Activation of presynaptic opioid receptors can induce both acute and long-term depression of synaptic transmission, depending on the synapse (Atwood et al., 2014; Atwood et al., 2014). Opioid receptors can modulate dopamine transmission by modulating several aspects of circuitry controlling dopamine release, including presynaptic inhibition of dopamine terminals, regulation of CIN excitability, presynaptic inhibition of glutamatergic inputs to the striatum, and inhibition of GABA transmission in the midbrain to disinhibit dopamine neurons (reviewed in Darcq & Kieffer, 2018).

### 7.1 Mu opioid receptors (MORs)

MORs are expressed by many neurons involved in regulation of nigrostriatal and mesolimbic dopamine transmission, including GABAergic neurons in the VTA, striatal SPNs that project to the midbrain, striatal CINs, and on glutamatergic afferents to the striatum (Darcq & Kieffer, 2018; Sgroi & Tonini, 2018). Regulation of dopamine transmission is complex and depends on the site of MOR activation. In the midbrain, activation of MOR on local and striatal GABAergic inputs results in disinhibition of dopamine neurons (Cui et al., 2014; Fields & Margolis, 2015; Johnson & North, 1992). In the striatum, MORs can be found in somatodendritic compartments of SPNs and CINs where they impact neuronal excitability (Ponterio et al., 2013). Decreasing CIN firing by activating MORs decreases spontaneous dopamine transients in the NAc (Yorgason et al., 2017). In addition, activation of MORs inhibits excitatory thalamostriatal transmission (Atwood et al., 2014), and this could in turn reduce synchronous activation of CINs and ACh-evoked dopamine release. Concordantly, dopamine transmission is sometimes reduced in the dorsal striatum and

NAc following MOR activation as measured by microdialysis or voltammetry, although the nature of MOR modulation of dopamine transmission can vary by striatal subregion (Campos-Jurado et al., 2017; Pentney & Gratton, 1991).

Evidence that MORs are the opioid receptor subtype that is responsible for the euphoric and addictive properties of opioid drugs comes from the finding that MOR knockout mice do not show behavioral signs of reward in response to opioid administration (Matthes et al., 1996). In addition to mediating the rewarding and reinforcing properties of opioid drugs, activation of MORs also contributes to the rewarding properties of non-opioid drugs including alcohol, Δ9-THC, and nicotine (Charbogne et al., 2014; Darcq & Kieffer, 2018). In the case of alcohol use disorder, the MOR antagonist naltrexone is effective for reducing alcohol craving, highlighting the translational importance of this mechanism (Hillemacher et al., 2011). Interestingly, restoring MOR expression in D1-expressing SPNs is sufficient to rescue opioid-induced dopamine release and partially rescues opioid self-administration, likely because MOR-mediated inhibition of striatonigral transmission increases activity of midbrain dopamine neurons (Cui et al., 2014). Because systemic MOR activation with opioid drugs could have differential effects on various drivers of dopamine release (i.e., somatic firing of midbrain dopamine neurons vs. ACh-dependent local mechanisms), it will be interesting to determine how inhibition of local release mechanisms and concurrent disinhibition of dopamine neuron firing contributes to both acute drug responses and transitions to maladaptive opioid-taking behaviors. It is also important to consider that exposure to exogenous opioid drugs can rapidly impair MOR signaling at some synapses (Atwood et al., 2014). Opioid-mediated desensitization could have profound effects on how MORs modulate dopamine transmission in the case of repeated exposures, particularly if different populations of MORs are subject to different degrees of desensitization.

### 7.2 Kappa opioid receptors (KORs)

KORs are $G\alpha_{i/o}$-coupled GPCRs that are expressed by midbrain dopamine neurons and SPNs and can exert complex control of dopamine transmission via both presynaptic and postsynaptic mechanisms (reviewed in Escobar et al., 2020). Pharmacological activation of KORs in the dorsal and ventral striatum decreases extracellular dopamine levels (Di Chiara & Imperato, 1988; Karkhanis et al., 2016; Spanagel et al., 1992), while KOR blockade or genetic deletion increases extracellular dopamine levels, suggesting tonic regulation of dopamine transmission by KORs (Chefer et al., 2005; Spanagel et al., 1992). KOR activation can decrease vesicular dopamine release by increasing $K^+$ conductance and inhibiting voltage-gated calcium channels (Margolis & Karkhanis, 2019). In the VTA, KORs inhibit dopamine neuron activity by activating GIRK and possibly by decreasing excitatory input, although the degree of inhibition varies by projection target (Ford et al., 2006; Margolis et al., 2003, 2005). In addition, KOR activation with the atypical hallucinogen Salvinorin A and other KOR agonists increase DAT activity, representing another mechanism by which KORs constrain dopaminergic transmission (Atigari et al., 2019; Kivell et al., 2014; but see Escobar et al., 2020).

In addition to reducing dopamine transmission under normal conditions, acute KOR activation can also reduce dopamine release and associated behaviors evoked by psychoactive drugs including amphetamine and cocaine (Gray et al., 1999). Similarly, dopamine release in response to cocaine injection is increased in KOR knockout mice (Chefer et al., 2005). KOR agonists reduce cocaine self-administration in non-human primates, although this effect could be partially explained by side effects such as sedation (Negus et al., 1997). However, the regulation of drug-induced dopamine release by KORs is complex, and other studies have shown that repeated KOR activation can actually facilitate dopamine release in response to psychostimulants (see Escobar et al., 2020). Moreover, history of psychoactive drug exposure can modulate KOR-mediated inhibition of dopamine release in the NAc (Karkhanis et al., 2016). For example, alcohol exposure during adolescence can facilitate or impair KOR-mediated inhibition of dopamine release depending on the age of rats during alcohol exposure (i.e., early vs. late adolescence) (Spodnick et al., 2020). The ability of KORs to reduce drug-induced dopamine transmission suggested that KOR agonists could be a treatment for substance use disorders by reducing the primary reinforcing value of psychoactive drugs. However, activation of KORs promotes a dysphoric state that could facilitate drug seeking. More recently, findings that KOR activity

contributes to negative affective states during drug withdrawal has led to interest in KOR antagonism as a pharmacological strategy to prevent reinstatement of drug use (Darcq & Kieffer, 2018).The ability of KOR antagonists to attenuate stress-induced drug seeking likely involves KOR effects in the VTA (Escobar et al., 2020; Graziane et al., 2013; Karkhanis et al., 2017; Polter et al., 2014).

## 8. Concluding remarks

A more thorough understanding of the implications of GPCR modulation of dopaminergic transmission will require further investigation into the distinct contributions of the various mechanisms driving dopamine release. The rapid increase in tools available to observe and manipulate circuit function with greater specificity regarding cell type and connectivity will no doubt accelerate elucidation of how somatic vs. local mechanisms that drive dopamine release contribute to motivated behaviors, and how these processes are fine-tuned by GPCRs (for review, see Lovinger et al., 2022). Conditional deletion of GPCRs from specific genetically and/or anatomically defined neurons has facilitated discovery of surprising mechanisms regulating dopaminergic transmission (e.g., Foster et al., 2016). The recent invention of genetically-encoded biosensors for dopamine has facilitated new progress in correlating behavior and psychoactive drug effects with dopamine release on a meaningful temporal scale (Labouesse & Patriarchi, 2021). Looking forward, there are many opportunities to expand our understanding of dopamine transmission and its involvement in various aspects of psychoactive drug use. For example, subsets of midbrain dopamine neurons co-release glutamate and GABA, yet there is relatively little known about how these co-released neurotransmitters impact behavior in the context of psychoactive drugs, or how GPCRs might differentially modulate GABA and glutamate co-release from dopamine neurons. How sex modulates GPCR regulation of dopamine transmission is another important consideration. Although some sex differences in regulation of dopamine transmission have been identified (see (Zachry et al., 2021), many previous studies were only performed in one sex (typically male animals) or do not report evaluation of sex differences, creating vast gaps in knowledge that could have important translational implications when using findings from preclinical studies to inform drug development (Shansky & Murphy, 2021). Because there are many neurological and psychiatric conditions that involve dysregulation of dopaminergic transmission, discovery of detailed GPCR-mediated regulatory mechanisms has the potential to broadly impact our understanding of the neurobiological basis of normal and disordered behavior far beyond the context of psychoactive drug use.

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## Figures and Figure Legends

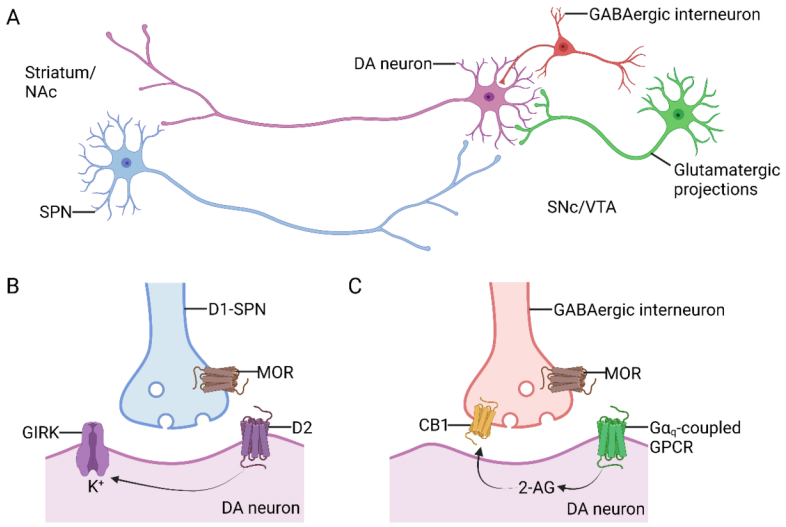


**Fig. 1. Examples of GPCR modulation of dopamine neuron activity in the midbrain.**

A) SNc and VTA neurons modulate striatal activity via projections to the dorsal striatum and NAc. Midbrain dopamine neurons receive both local and long-range GABA inputs, including GABAergic projections from the striatum, and glutamatergic inputs from a variety of brain regions (An et al., 2021). B) D2 autoreceptors expressed in somatodendritic compartments of dopamine neurons activate GIRK, causing hyperpolarization. Activation of presynaptic $G\alpha_{i/o}$-coupled GPCRs including MOR reduces GABAergic transmission in dopamine neurons, causing disinhibition. C) Activation of $G\alpha_q$-coupled GPCRs (e.g., orexin type 1 receptors, α1 adrenergic receptors) leads to eCB production and retrograde activation of CB1 receptors on GABAergic inputs including local GABAergic interneurons. Activation of $G\alpha_{i/o}$-coupled GPCRs causes presynaptic inhibition of GABA release and disinhibition of dopamine neurons. Abbreviations: 2-AG- 2-arachidonoylglycerol; DA- dopamine; eCB- endocannabinoid; GIRK- G protein-gated inwardly rectifying potassium channel; GPCR- G protein-coupled receptor; NAc- nucleus accumbens; SNc- substantia nigra pars compacta; SPN- striatal projection neuron; VTA- ventral tegmental area.

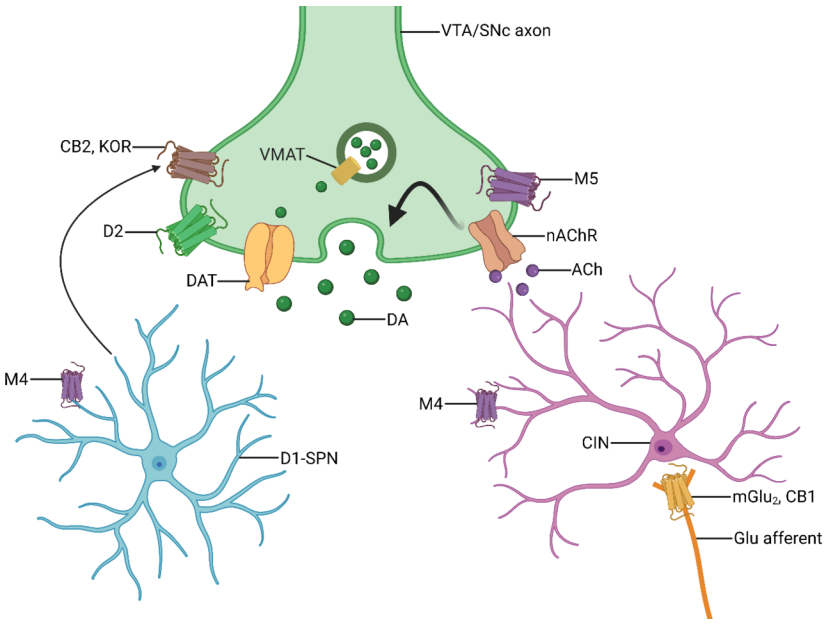


**Fig. 2. Examples of GPCR modulation of dopamine release in the striatum.** Dopamine release from VTA and SNc projections to the striatum is driven by both somatic action potential firing and local action potential generation produced by nAChR activation in dopamine neuron axons. D2 activation causes autoinhibitory feedback. Heteroreceptors expressed near dopamine release sites include CB2 and KOR (inhibitory) and M5 (typically excitatory). GPCRs expressed in dopamine neuron axons can also affect dopamine reuptake through DAT by modulating surface expression and transporter kinetics. M4 activation can inhibit dopamine release via several mechanisms, including inhibition of ACh release from CINs and mobilization of eCB signaling in D1-expressing SPNs. Retrogarde eCB signaling can then activate CB2 receptors on dopamine neurons to reduce dopamine release. The endogenous KOR agonist dynorphin is produced by D1-expressing SPNs, and can inhibit dopamine release by activating KORs. CIN activity and subsequent nAChR-dependent dopamine release can be driven by glutamatergic afferents from cortical and thalamic regions. Presynaptic GPCRs that inhibit glutamatergic inputs to CINs (e.g., $mGlu_2$, CB1) can indirectly inhibit acetylcholine-dependent dopamine release. Abbreviations: ACh- acetylcholine; CIN- cholinergic interneuron; DA- dopamine; DAT- dopamine transporter; Glu- glutamate; nAChR- nicotinic acetylcholine receptor; SNc- substantia nigra pars compacta; SPN- striatal projection neuron; VTA- ventral tegmental area.

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