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REVIEW

THE ROLE OF D2-AUTORECEPTORS IN REGULATING DOPAMINE NEURON ACTIVITY AND TRANSMISSION

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Abstract—Dopamine D2-autoreceptors play a key role in regulating the activity of dopamine neurons and control the synthesis, release and uptake of dopamine. These $G_{i/o}$-coupled inhibitory receptors play a major part in shaping dopamine transmission. Found at both somatodendritic and axonal sites, autoreceptors regulate the firing patterns of dopamine neurons and control the timing and amount of dopamine released from their terminals in target regions. Alterations in the expression and activity of autoreceptors are thought to contribute to Parkinson's disease as well as schizophrenia, drug addiction and attention-deficit hyperactivity disorder (ADHD), which emphasizes the importance of D2-autoreceptors in regulating the dopamine system. This review will summarize the cellular actions of dopamine autoreceptors and discuss recent advances that have furthered our understanding of the mechanisms by which D2-receptors control dopamine transmission.

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Key words: psychostimulants, cocaine, VTA, substantia nigra, GPCR.

Contents

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Abbreviations: AC, adenylyl cyclase; D2-IPSCs, D2-autoreceptor-mediated inhibitory post-synaptic currents; DAT, dopamine transporter; GIRK, G-protein-activated inwardly rectifying potassium channels; GPCRs, G-protein-coupled receptors; LTD, long-term depression; VMAT, vesicular monoamine transporter; VTA, ventral tegmental area.

INTRODUCTION

The dopamine system is comprised of three major divisions that include the mesocorticolimbic, striatonigral and tuberoinfundibular systems. These systems play critical roles in neuronal actions that range from cognition, locomotion, and reward processing to neuroendocrine function (Missale et al., 1998; Beaulieu and Gainetdinov, 2011). While the majority of dopamine receptors are located on non-dopamine neurons, dopamine receptors (autoreceptors) are also present on dopamine neurons themselves. These autoreceptors play a key role in regulating the dopamine system by providing feedback inhibition that controls cell firing and the synthesis, release, and uptake of dopamine. This review will focus on the cellular actions of dopamine autoreceptors in the mesocorticolimbic and striatonigral systems and discuss the role that these receptors play in regulating activity in the ventral tegmental area (VTA) and substantia nigra (SNc) and controlling the release of dopamine in projection areas.

Dopamine D2-autoreceptors – location and behavioral functions

Dopamine receptors (D1–D5) are members of the large, rhodopsin-like (Class A), seven transmembrane superfamily of G-protein-coupled receptors (GPCRs). The five mammalian receptor subtypes are divided into two major groups that form the D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors. Members of the D1-family are located on non-dopamine neurons and stimulate neuronal signaling via $G\alpha_{s/olf}$ to activate adenylyl cyclase (AC) and increase cAMP levels. In axon terminal regions, the activation of D1-receptors

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leads to increases in excitability and promotes transitions to the up-state via increases in NMDA receptor, L-type calcium channel and sodium channel currents (Surmeier et al., 2010).

Dopamine D2-like receptors are inhibitory. These receptors couple to $G_{i/o}$ to inhibit AC and calcium channels, and activate inhibitory G-protein-activated inwardly rectifying potassium channels (GIRK) (Neve et al., 2004; Beaulieu and Gainetdinov, 2011). The majority of D2-like receptors are found on non-dopamine neurons and mediate numerous brain functions, playing major roles in regulating locomotor activity, cognition and motivation (Missale et al., 1998; Beaulieu and Gainetdinov, 2011). As such, D2-receptors are important pharmacological targets for the treatment of a variety of psychiatric diseases (Missale et al., 1998; Beaulieu and Gainetdinov, 2011). D2-receptors are found in high density in the striatum, nucleus accumbens, and olfactory tubercle, and to a lower extent in the hippocampus, amygdala, hypothalamus and cortical regions (Missale et al., 1998; Schmitz et al., 2003; De Mei et al., 2009; Beaulieu and Gainetdinov, 2011).

Autoreceptors on dopamine neurons are comprised of the D2-subtype of dopamine receptors. These autoreceptors are located on the soma and dendrites of midbrain dopamine neurons in the VTA and substantia nigra pars compacta (SNc) as well as on their axon terminals in projection areas (Missale et al., 1998; Romanelli et al., 2010; Beaulieu and Gainetdinov, 2011). As feedback regulators, autoreceptors modulate activity directly through the activation of a potassium conductance and indirectly through downstream control of the expression of tyrosine hydroxylase and the plasma membrane dopamine transporter (DAT) to modulate dopamine dependent transmission. Activation of these receptors decreases both excitability of dopamine neurons and the release of dopamine. Thus, autoreceptors are key regulators of dopamine-dependent transmission. While both D2- and D3-receptors are present on dopamine neurons (Rivet et al., 1994; Levant, 1997; Koeltzow et al., 1998; Beaulieu and Gainetdinov, 2011), the D3-receptor likely plays only a minor functional role as an autoreceptor, and the vast majority of autofeedback inhibition is thought to be mediated through the D2-receptor.

Numerous studies have shown that activation of D2-autoreceptors leads to a reduction in locomotion and alters the motivating and reinforcing properties of drugs of abuse including psychostimulants like cocaine and amphetamine (Jackson and Westlind-Danielsson, 1994; Missale et al., 1998). As such, studies that have examined mice genetically lacking D2-receptors (D2-null) have found these animals to have altered extracellular levels of dopamine (Benoit-Marand et al., 2001; Rouge-Pont et al., 2002; Schmitz et al., 2002; Lindgren et al., 2003), and show reduced activity and decreased reinforcement to the rewarding effects of drugs of abuse including ethanol, cocaine and morphine (Baik et al., 1995; Maldonado et al., 1997; Phillips et al., 1998; Cunningham et al., 2000; Chausmer et al., 2002). Detailed reviews of the behavioral actions mediated by autoreceptors can be found in (Jackson and Westlind-Danielsson, 1994; Missale et al., 1998; Beaulieu and Gainetdinov, 2011).

As D2-receptors are found on both the terminals of dopamine neurons and post-synaptically on non-dopamine neurons (heteroreceptors), historically it has been difficult to separate the physiological and behavioral role of autoreceptors from that of heteroreceptors. To distinguish between these two populations, two groups have recently generated conditional knock out mice in which D2-receptors have been deleted only from dopamine neurons (autoreceptor-null) (Bello et al., 2011; Anzalone et al., 2012). These knock out mice exhibit normal levels of D2-heteroreceptors, yet lack D2-autoreceptor-mediated inhibition of dopamine release from dopamine terminals and hyperpolarizations measured in the cell body (Bello et al., 2011; Anzalone et al., 2012). Importantly, these animals are hyperactive and exhibit increased sensitivity to cocaine (Bello et al., 2011; Anzalone et al., 2012). This confirms the role of autoreceptors in regulating locomotor and reward-driven behaviors. As different genetic strategies were used to generate the two lines of autoreceptor null mice, there are several differences in the behavior and physiological actions between the two animals (Bello et al., 2011; Anzalone et al., 2012), however, both approaches confirm a key role of autoreceptors in regulating the dopamine system. This work largely supports past clinical observations that altered autoreceptor function correlates with changes in impulsivity and novelty-seeking behaviors (Zald et al., 2008; Buckholtz et al., 2010).

Short and long isoforms of the D2 receptor and the identity of the autoreceptor

Alternative splicing of the mRNA encoding the D2-receptor results in two isoforms of the receptor, short ($D2_S$) and long ($D2_L$), which differ by 29 amino acids within the third intracellular loop (Bunzow et al., 1988; Dal Toso et al., 1989; Giros et al., 1989; Grandy et al., 1989; Monsma et al., 1989). As the third intracellular loop is involved in G-protein coupling, $D2_S$ and $D2_L$ can couple to distinct G-proteins (Montmayeur et al., 1993; Senogles, 1994; Guiramand et al., 1995). However, attempts to assign specific signaling roles for each isoform have been difficult due to conflicting results depending on the assay and cell line used (Neve et al., 2004). The $D2_S$ receptor has a higher affinity for dopamine and several benzamides (Castro and Strange, 1993; Malmberg et al., 1993) and more effectively inhibits AC (Montmayeur and Borrelli, 1991). However, differences in the ability of $D2_S$ and $D2_L$ to activate subsequent downstream signaling cascades such as MAP kinases and Akt/GSK-3β have made it difficult to conclusively assign distinct signaling roles for the two isoforms (Neve et al., 2004), (Romanelli et al., 2010).

The physiological roles for the long and short forms of the D2-receptor have been predicted based on studies using selective $D2_L$ knockout mice (Usiello et al., 2000; Wang et al., 2000). In these animals, $D2_S$ receptor