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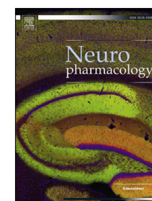

Differential dopaminergic regulation of inwardly rectifying potassium channel mediated subthreshold dynamics in striatal medium spiny neurons

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ABSTRACT

The dorsal striatum plays a key role in motor control and cognitive processes. Proper functioning of the striatum relies on the fine dynamic balance between the direct pathway projection medium spiny neurons (MSNs) that express D1 dopamine receptor (D1 MSNs) and indirect pathway projection MSNs that express D2 dopamine receptor (D2 MSNs). The inwardly rectifying K^+ channels (Kir), which express on both D1 and D2 MSNs, participate in the subthreshold dynamics including the membrane resonance and dendritic integration. However, it remains unclear whether dopamine differentially regulates Kir mediated subthreshold dynamics in two subtypes MSNs. Using transgenic mice that express either tdTomato in D1 MSNs or eGFP in D2 MSNs, we explored the Kir mediated subthreshold dynamics in D1 or D2 MSNs with whole cell patch clamp recording in acute brain slices. We found that D1 receptor agonist increased the Kir current while D2 receptor activation decreased the Kir conductance. The dopamine regulation of the Kir enhanced the resonant frequency and reduced the resonant impedance of D1 MSNs. The converse is ture for D2 MSNs. It also caused an opposing effect on dendritic integration between D1 and D2 MSNs, which can promote stability of the two pathways. The D1 receptor activation modulated Kir through cAMP-PKA signaling, whereas the D2 receptor modulated Kir through PLC-PKC signaling. Our findings demonstrated the differential dopaminergic regulation role of Kir, which mediates distinct subthreshold dynamics, and thus, contributes to the role of dopamine in fine tuning the balance of the striatal direct and indirect pathway activities.

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1. Introduction

The dorsal striatum, the main input nuclei of basal ganglion (BG), is thought to be involved in motor control, executive functions and learning (Balleine et al., 2007; DeLong, 1990; Yin and Knowlton, 2006). Its dysfunction has been implicated in many motion diseases and psychiatric disorders (Burguiere et al., 2013; Di Filippo et al., 2007; Gibb, 1997; Peça et al., 2011; Welch et al., 2007).

The principal neurons of striatum comprise GABAergic medium-sized spiny neurons (MSNs), which account for about 95% of neurons in the striatum. These neurons are divided into two types: the

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direct pathway projecting neurons that express D1 dopamine receptors (D1 MSNs), which project directly to BG output nuclei. The indirect pathway projecting neurons that express dopamine D2 receptors (D2 MSNs) and project to the globus pallidus pars externalis, which together with the subthalamic nucleus connecting to the BG output nuclei (Gerfen et al., 1990; Kawaguchi et al., 1990). Dopamine modulation is fundamental for maintaining the balance of D1 MSNs and D2 MSNs (Gerfen and Surmeier, 2011). An imbalance between these two pathways are also implicated in diseases (Andre et al., 2011; Kenny et al., 2013; Sciamanna et al., 2009; Shen et al., 2008). D1 dopamine receptors are Gs-coupled and have positive modulation to multiple downstream targets, such as AMPA receptors and L type Ca^{2+} channels (Gerfen and Surmeier, 2011). D2 dopamine receptors are Gi-coupled and are proposed to inhibit D2 MSNs output through several targets, such as L type Ca^{2+} channels, Nav1 channels, and AMPA receptors (Gerfen and Surmeier, 2011).

The inwardly rectifying K^+ channels (Kir) are large families of ion channels which generate big K^+ conductance at potentials negative to the equilibrium potential of K^+ (E_K) but show less conductance at potentials positive to E_k. Classical Kir (Kir2.x) is one of the subfamilies of Kir and exhibit strong inward rectification (Hibino et al., 2010). They are involved in the subthreshold dynamics of neurons and can be modulated by G protein-coupled receptor signaling (Carr and Surmeier, 2007; Hu et al., 2002; John and Manchanda, 2011; Wang et al., 2006). Kir2.x are expressed in both D1 MSNs and D2 MSNs (Karschin et al., 1996; Pruss et al., 2003; Shen et al., 2007). There are also evidence showing that either D1 receptors or D2 receptors can modulate the Kir2.x conductance and subthreshold dynamics of neurons in different brain area (Cazorla et al., 2012; John and Manchanda, 2011; Perez et al., 2006; Podda et al., 2010). However, it is still unclear how D1 and D2 dopamine receptors regulate the Kir activities differentially and how Kir mediated subthreshold dynamics of MSNs in dorsal striatum.

Membrane resonance is the ability of neurons to respond selectively to inputs at a preferred frequency (Hutcheon and Yarom, 2000). It is considered to be one of the cellular mechanisms of population oscillation (Castro-alamancos et al., 2007; Hutcheon and Yarom, 2000; Shtrahman and Zochowski, 2015; Tohidi and Nadim, 2009). A recent research claimed that the MSNs do not show the resonance at the resting potential and up state (Beatty et al., 2015). However, our previous results suggest that Kir is participated in the membrane resonance at hyperpolarized potentials in subiculum (Wang et al., 2006). It is thus necessary to check whether the MSNs show the membrane resonance at relative hyperpolarization level since the MSNs also receive multiple sources of inhibitions from several type GABAergic neurons in the striatum microcircuit (Kreitzer, 2009). It is also interesting to understand whether the dopamine can modulate the membrane resonance through the effect on Kir activities.

The MSNs receive excitatory inputs from the cortex, thalamus and amygdala, which are modified by dopamine afferents from substantia nigra, inhibitory afferents from the other MSNs, GABAergic striatal interneurons, and cholinergic inputs from cholinergic striatal interneurons. The outcome of various synaptic inputs highly rely on the dendritic integration properties through the distribution and modulation of ion channels expressed in the dendritic membrane (Sjostrom et al., 2008). Previous research suggested that the Kir was involved in dendritic integration which can be regulated by G-protein coupled receptors (Carr and Surmeier, 2007; Day et al., 2005; Shen et al., 2007). However, it is still unknown how dopamine potentially affects Kir mediated dendritic integration in D1 and D2 MSNs in dorsal striatum.

In our current work, we used the transgenic mice that express either tdTomato in D1 MSNs (Shuen et al., 2008) or eGFP in D2 MSNs (Gong et al., 2003) and analyzed Kir currents and related subthreshold dynamics in acute brain slices. We found that both D1 MSNs and D2 MSNs showed similar beta frequency (14–16 Hz) and comparable strength of membrane resonance, which was mediated by Kir. Activation of D1 dopamine receptors increased Kir currents through cAMP-PKA signaling pathway, which led to an increased membrane resonance frequency, but reduced membrane resonance impedance and dendritic integration in D1 MSNs. In contrast, D2 receptor agonists reduced the Kir conductance through reducing the phospholipase C (PLC) - protein kinase C (PKC) signaling pathway, which reduced the frequency but increased the impedance of membrane resonance and enhanced the dendritic integration in D2 MSNs. Together, these results demonstrated the differential dopamine regulation of Kir conductance in the two subtypes of MSNs via distinct signaling pathway, and as such, led to the opposing effect on the membrane resonance and dendritic integration in D1 and D2 MSNs to maintain a stable and balanced striatal output activity of the direct and indirect pathway.

2. Methods

2.1. Animals

The generation of D1-tdTomato transgenic mice, and D2-eGFP transgenic mice was described previously (Gong et al., 2003; Shuen et al., 2008). Experimental mice were the progeny of breeding in which only one of the parents expressed the D1-tdTomato or D2-eGFP transgenes. No experimental mice were homozygous for the transgenic fluorescent markers. We minimized the number of animals used and the extent of animal suffering during all experiments. All experiments were approved by the Institutional Animal Care and Use Committee of the Fourth Military Medical University, and carried out in accordance with the “Principles of Medical Laboratory Animal Care” issued by the National Ministry of Health. All experiments conformed to the guidelines of the ‘‘National Ordinance on Experiment Animals’’ for the ethical use of animals.

2.2. Slice preparation

Male or female mice at 5-8 week-old were used for all whole-cell electrophysiology procedures. Acute coronal striatal slices were prepared as follows: Briefly, mice were anesthetized with pentobarbital sodium (30–40 mg/kg body weight) and transcardially perfused with 20 ml of ice-cold carbogenated (95% O_2, 5% CO_2) cutting solution containing (in mM): 115 Choline-chloride, 2.5 KCl, 1.25 NaH_2PO_4, 0.5 $CaCl_2$, 8 $MgCl_2$, 26 $NaHCO_3$, 10 D-(+)-glucose 0.1 L-Ascorbic Acid, and 0.4 Sodium Pyruvate (with osmolarity of 300–305 mOsm). The brains were then rapidly removed and placed in ice-cold cutting solution for slice preparation. The coronal slices (300 μm) were prepared using a slicer (Vibrotome 1000 Plus, Ted Pella Inc., USA) and then incubated in a holding chamber at 32 °C with carbogenated cutting solution for 15–20 min. The slices were then transferred to artificial cerebral spinal fluid (ACSF) containing (mM): 119 NaCl, 2.3 KCl, 1.0 NaH_2PO_4, 26 $NaHCO_3$, 11 D-(+)-glucose, 1.3 $MgSO_4$, 2.5 $CaCl_2$ (pH 7.4, with osmolarity of 295–300 mOsm) at room temperature for at least 1 h.

2.3. Electrophysiological recording

The slices were placed in a recording chamber and constantly perfused with carbogenated ACSF at 24–28 °C (TC-324B, Warner Instruments). The perfusion rate was 2.0 ml/min. The flurorescently labeled D1 or D2 MSNs were visualized and identified with a

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