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ACTIVATION OF DOPAMINE D1 RECEPTORS ENHANCES THE TEMPORAL SUMMATION AND EXCITABILITY OF RAT RETINAL GANGLION CELLS

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Abstract—Dopamine (DA), an important neurotransmitter and neuromodulator, plays important roles in neuronal physiological functions by activating G-protein-coupled DA D1 and/or D2 receptors. Previous studies have demonstrated that D1 receptors are functionally expressed in retinal neurons and glial cells, including ganglion cells. In this study, we explored the effects of D1 receptor activation on retinal ganglion cell (RGC) temporal summation and excitability in rat retinal slices using electrophysiological techniques. Bath application of the selective D1 receptor agonist SKF81297 increased the ratio of excitatory postsynaptic potentials (EPSPs) (EPSP5/EPSP1) within an EPSP train evoked by a train stimulation (five current pulses at 40 Hz), which was blocked by co-application of SCH23390, a specific D1 receptor antagonist. Ba^{2+}, an inwardly rectifying K^+ channel (Kir) blocker, significantly suppressed the SKF81297-induced effect, whereas ZD7288, a specific hyperpolarization-activated cation current (I_h) blocker, showed a moderate inhibitory effect. The cAMP/protein kinase A (PKA) signaling pathway, but not phosphoinositide-specific phospholipase C (PI-PLC), mediated the SKF81297-induced modulation of EPSP temporal summation. Further experiments showed that SKF81297 suppressed Ba^{2+}-sensitive Kir currents in RGCs. Additionally, SKF81297 increased the spontaneous firing frequency of RGCs, and caused depolarization of the cells with or without the presence of synaptic receptor blockers. In contrast, SKF81297 did not significantly change the frequency of miniature excitatory postsynaptic currents (mEPSCs) recorded in RGCs. Our results indicate that D1 receptor activation enhances the temporal summation of RGCs mainly by suppressing Kir currents through the cAMP/PKA signaling pathway, thus increasing the excitability of rat RGCs.

Key words: dopamine, D1 receptors, retinal ganglion cell, temporal summation, excitability, inward rectifying K^+ channel.

INTRODUCTION

Dopamine (DA), an important neurotransmitter and neuromodulator, plays important roles in neuronal physiological functions by activating G-protein-coupled DA receptors (Gulledge and Jaffe, 1998; Missale et al., 1998; Barros et al., 2001; Gulledge and Jaffe, 2001; Bissière et al., 2003; Paspalas and Goldman-Rakic, 2005). There are two types of DA receptors: D1 receptors (including D1 and D5 subtypes) and D2 receptors (including D2, D3, and D4 subtypes), which couple to different G protein subunits (G_s and $G_{i/o}$ respectively) and have opposite effects on adenylate cyclase (AC) activity (Enjalbert and Bockaert, 1983; Sibley and Monsma, 1992; Missale et al., 1998). Numerous studies have shown that D1 receptors are widely distributed in different brain regions and that activation of these receptors modulates neuronal excitability and synaptic transmission, thus participating in regulation of locomotion, working memory, and behaviors related to reward (Gulledge and Jaffe, 1998; Bissière et al., 2003; Robinson and Siegelbaum, 2003; Paspalas and Goldman-Rakic, 2005; Kisilevsky et al., 2008). Modulation of voltage-gated ion channels is one of the mechanisms underlying D1 receptor-induced effects on neuronal excitability. These channels include hyperpolarization-activated cation currents (I_h) (Magee, 1998, 1999; Rosenkranz and Johnston, 2006; Chen and Yang, 2007), inward-rectifier K^+ (Kir) channels (Gorelova et al., 2002; Dong et al., 2004; Podda et al., 2010), voltage-gated K^+ channels (Dong and White, 2003; Kroner et al., 2005; Li et al., 2016), and fast voltage-gated Na^+ channels (Cantrell et al., 1999a,b; Maurice et al., 2001; Cooper et al., 2003).

DA, released mainly from amacrine cells (Gallego, 1971; Nguyen-Legros et al., 1999; Popova, 2014),

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Abbreviations: AC, adenylate cyclase; ACSF, artificial cerebral spinal fluid; DA, dopamine; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid; EPSP, excitatory postsynaptic potential; GCL, ganglion cell layer; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; I_h, hyperpolarization-activated cation currents; INL, inner nuclear layer; IPL, inner plexiform layer; Kir, inwardly rectifying K^+; mEPSCs, miniature excitatory postsynaptic currents; OPL, outer plexiform layer; PKC, protein kinase C; PLC, phospholipase C; RGCs, retinal ganglion cells; RM one-way ANOVA, repeated-measures one-way ANOVA; TTX, tetrodotoxin.

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modulates a variety of retinal functions by affecting retinal neuronal circuits (Witkovsky, 2004; Jackson et al., 2012; Lavoie et al., 2014; Beaulieu et al., 2015). For example, DA may indirectly influence spiking in retinal ganglion cells (RGCs) by regulating the balance of inhibitory and excitatory inputs to RGCs (Pourcho, 1982; Thier and Alder, 1984; Hokoc and Mariani, 1987; Gustincich et al., 1997). Additionally, DA may act directly on RGCs and regulate cell excitability by affecting voltage-gated Ca^{2+} or Na^{+} currents in turtles and goldfish (Liu and Lasater, 1994; Vaquero et al., 2001; Hayashida and Ishida, 2004; Hayashida et al., 2009; Ogata et al., 2012). In dissociated cell preparations, D1 receptor activation can modulate rat RGC excitability by suppressing outward K^{+} currents (Li et al., 2016). Chen and Yang (2007) reported that D1 receptor activation modulated RGC spikes in rat vertical retinal slices by affecting I_h.

Kir and I_h channels are widely distributed in neuronal dendrites (Shen et al., 2007; John and Manchanda, 2011), and modulation of these channels may influence the intrinsic excitability of the cells (Nichols and Lopatin, 1997; Nakamura et al., 1999; Reimann and Ashcroft, 1999; Tanaka et al., 2003; Biel et al., 2009; Shah et al., 2010; Kase and Imoto, 2012). Kir and I_h are also found in RGCs (Chen et al., 2004; Zhong et al., 2013), and these channels may be predominately distributed along RGC dendrites (Li et al., 2017). However, no data concerning the effects of D1 receptor activation on the integration of dendritic excitatory signals in RGCs are available. Therefore, we explored the effects of D1 receptor activation on the temporal summation of excitatory postsynaptic potentials (EPSPs) and the excitability of RGCs in rat retinal slices using patch-clamp electrophysiological techniques. We found that the activation of D1 receptors enhanced the EPSP5/EPSP1 ratio (Fig. 1) in RGCs by mainly suppressing Kir currents through the intracellular cAMP/protein kinase A (PKA) signaling pathway. Additionally, we found that D1 receptor activation increased RGC excitability by increasing fire frequency and inducing cell depolarization.

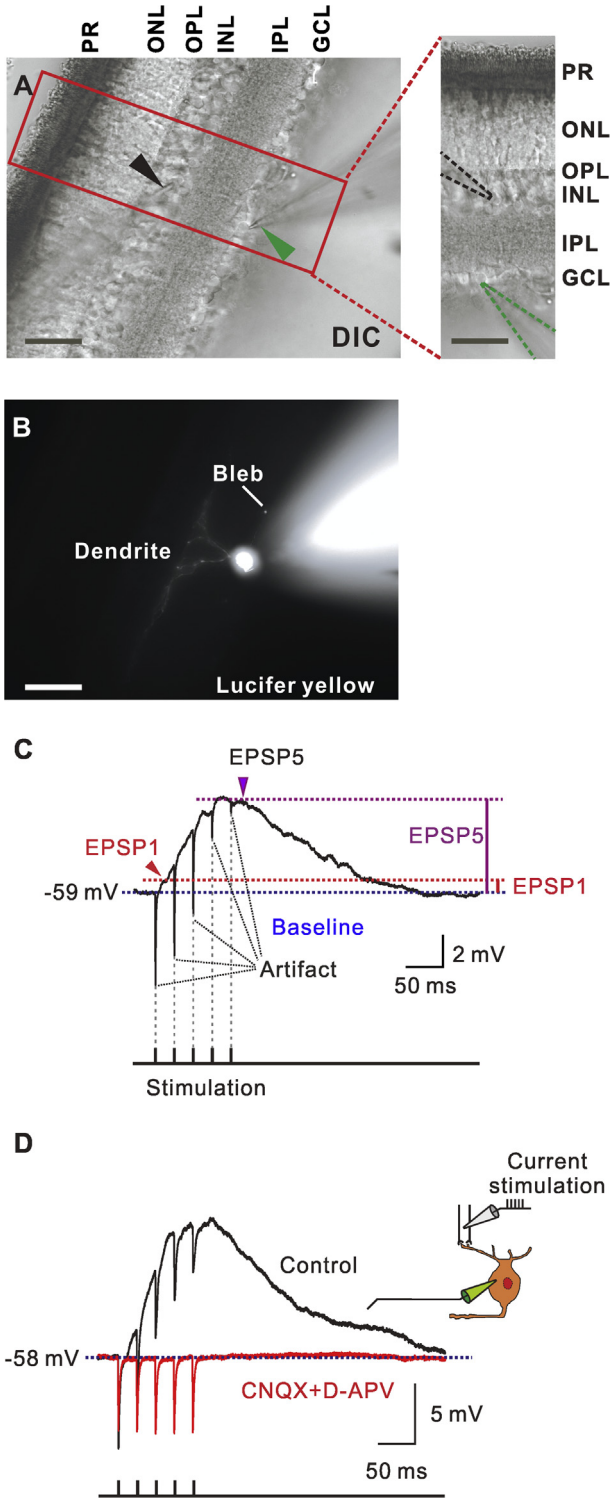

Fig. 1. Recording and measurement of EPSPs in rat RGCs. (A) Microphotograph image (DIC) showing the location of stimulation electrode (black arrowhead) and recording electrode (green arrowhead) in a rat retinal vertical slice. Scale bar = 50 μm. GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PR, photoreceptors. (B) Fluorescence microphotograph of a Lucifer Yellow-filled RGC, showing the dendrite arborizations in the IPL and the bleb of cut end of axon of the cell. Scale bar = 50 μm. (C) Representative trace showing a train stimulation-induced consecutive EPSPs in an RGC. The stimulation train consisted of five current pulses (200 μs duration, 40 Hz, 5–50 μA). The amplitude of individual EPSP (EPSP1–EPSP5) was determined from its peak or plateau (15 ms after the corresponding stimulation artifact) to baseline. (D) Glutamate receptors mediate the stimulation-evoked changes in membrane potential. Representative traces recorded form an RGC, showing that the stimulation-induced changes in membrane potential were eliminated by perfusion of non-NMDA receptor antagonist CNQX plus NMDA receptor antagonist D-APV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)