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Alpha-1 adrenoreceptors modulate GABA release onto ventral tegmental area dopamine neurons

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ABSTRACT

The ventral tegmental area (VTA) plays an important role in reward and motivational processes involved in drug addiction. Previous studies have shown that alpha1-adrenoreceptors (α1-AR) are primarily found pre-synaptically at this area. We hypothesized that GABA released onto VTA-dopamine (DA) cells is modulated by pre-synaptic α1-AR. Recordings were obtained from putative VTA-DA cells of male Sprague −Dawley rats (28–50 days postnatal) using whole-cell voltage clamp technique. Phenylephrine (10 μM; α1-AR agonist) decreased the amplitude of $GABA_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) evoked by electrical stimulation of afferent fibers ($n = 7$; $p < 0.05$). Prazosin (1 μM, α1-AR antagonist), blocked this effect. Paired-pulse ratios were increased by phenylephrine application ($n = 13$; $p < 0.05$) indicating a presynaptic site of action. Spontaneous IPSCs frequency but not amplitude, were decreased in the presence of phenylephrine ($n = 7$; $p < 0.05$). However, frequency or amplitude of miniature IPSCs were not changed ($n = 9$; $p > 0.05$). Phenylephrine in low Ca^{2+} (1 mM) medium decreased IPSC amplitude ($n = 7$; $p < 0.05$). Chelerythrine (a protein kinase C inhibitor) blocked the α1-AR action on IPSC amplitude ($n = 6$; $p < 0.05$). Phenylephrine failed to decrease IPSCs amplitude in the presence of paxilline, a BK channel blocker ($n = 7$; $p < 0.05$). Taken together, these results demonstrate that α1-ARs at presynaptic terminals can modulate GABA release onto VTA-DA cells. Drug-induced changes in α1-AR could contribute to the modifications occurring in the VTA during the addiction process.

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1. Introduction

The mesocorticolimbic system is composed of dopamine (DA) neurons projecting mainly from the ventral tegmental area (VTA) to cortical and ventral forebrain structures (Dahlstrom and Fuxe, 1964; Ungerstedt, 1971; Lammel et al., 2011). Activation of VTA DA neurons has been implicated in motivated behaviors as well as in mediating the reinforcing actions of drugs of abuse (Schultz, 2002; Kauer, 2004; Grace et al., 2007).

VTA DA neurons receive noradrenergic (NE) inputs from locus coeruleus and other pontine structures (Jones et al., 1977; Mejias-Aponte et al., 2009) and tracing studies have shown that NE afferents have extrasynaptic and synaptic connections on VTA DA neurons (Liprando et al., 2004). Moreover, the VTA contains alpha-1 adrenoreceptors (α1-ARs) (Greene et al., 2005) which are located primarily in pre-synaptic elements (Rommelfanger et al., 2009). Noradrenergic (NE) inputs have been shown to facilitate VTA DA neuronal transmission and induce changes in burst firing via α1 adrenergic receptors (α1-ARs) (Grenhoff et al., 1993; Grenhoff and Svensson, 1993; Grenhoff et al., 1995; Paladini and Williams, 2004). Also, α1-ARs participate in the development of stress and anxiety responses, and in addiction-related behaviors (Cecchi et al., 2002; Hague et al., 2003; Jimenez-Rivera et al., 2006; Greenwell et al., 2009).

The VTA receives considerable inhibitory inputs mainly in the form of GABAergic innervation from the mesopontine tegmentum, the lateral habenula via the rostromedial tegmentum (RMTg), nucleus accumbens (NAcc) and the periaqueductal gray (Jhou et al.,

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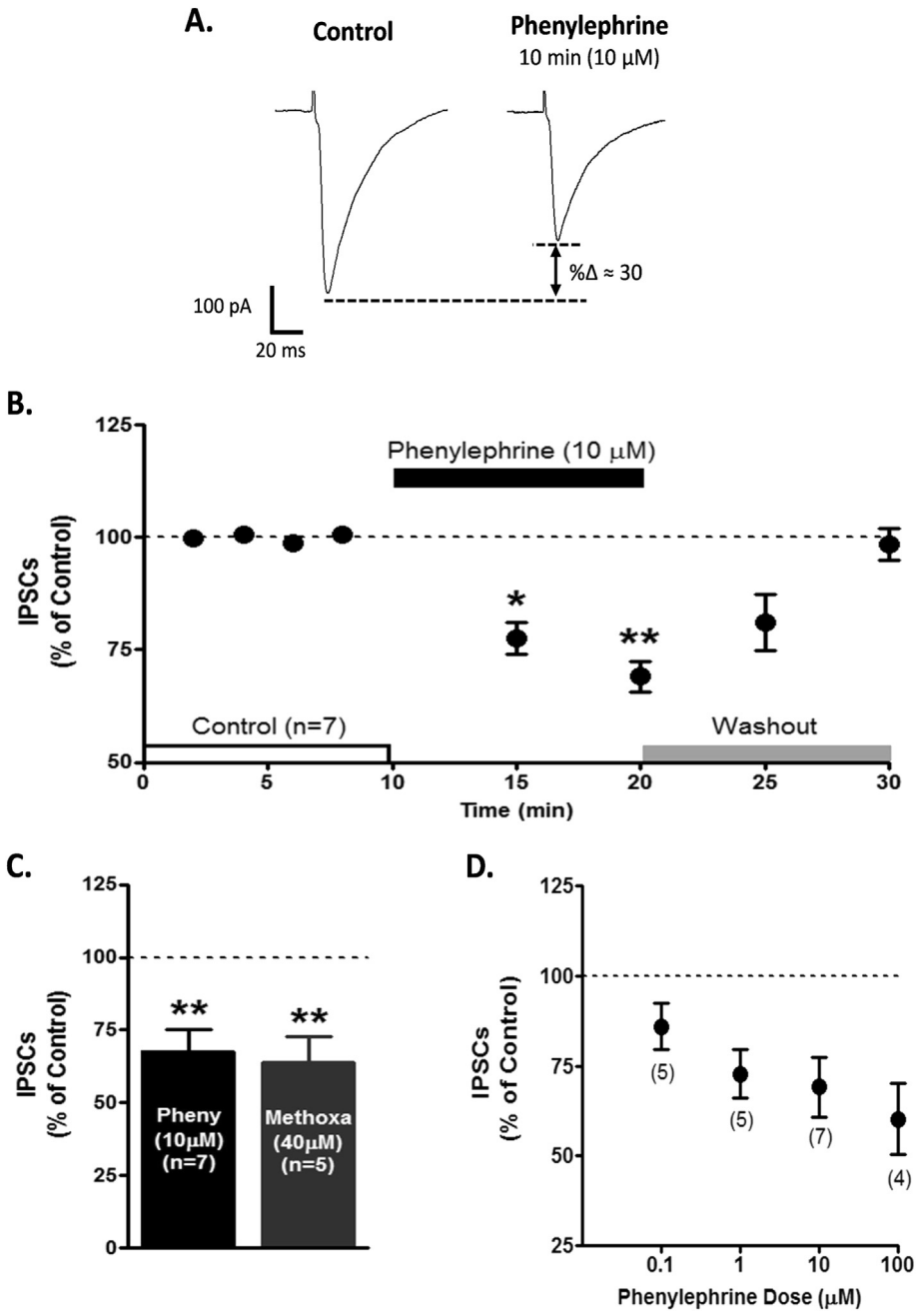

Fig. 1. Bath application of phenylephrine reduced $GABA_A$ IPSCs amplitude in putative VTA DA neurons. A. Representative recordings from the same cell, showing that phenylephrine's superfusion (10 μm) induced a significant reduction in $GABA_A$ IPSCs amplitude in a putative VTA DA cell voltage clamped at −70 mV. B. Summary time course of the effect of phenylephrine bath application on $GABA_A$ IPSCs amplitude recorded from 7 putative VTA DA neurons at 8 min of control (2 min intervals), 5 and 10 min phenylephrine (10 μM) and 5 and 10 min washout. A 5 and 10 min phenylephrine application caused amplitude reduction of $GABA_A$ IPSCs. There was a rapid return to control levels upon phenylephrine removal. C. Bar graph showing that, on average, phenylephrine ($n = 7$) and methoxamine ($n = 5$) application resulted in a ~30% decrease in $GABA_A$ IPSCs amplitude. D. Dose-response curve of phenylephrine's effect on $GABA_A$ IPSCs. Phenylephrine-induced decrease was dose-dependent over the concentration range of 0.1–100 μM $^{*}p < 0.05$, $^{**}p < 0.01$; One-way ANOVA, Newman–Keuls post hoc.

2009a, 2009b). Changes in GABAergic input on VTA DA neurons can control their firing patterns (Paladini and Tepper, 1999; Lobb et al., 2010). For example, decreased GABAergic inhibition contributes to the generation of bursts in DA neurons (Jhou et al., 2009a; Lobb et al., 2011; Morikawa and Paladini, 2011). Since bursting firing has been related to enhance neurotransmitter release (Floresco et al., 2003), modulation of DA neuronal bursting activity is one mechanisms that can modify DA release in VTA reward-related projections.

Pharmacological stimulation of α1-ARs induces changes in GABA-mediated synaptic transmission in different brain areas. This α1-ARs-mediated effect has been evidenced in different brain structures such as the hippocampus, frontal cortex, ventrolateral BNST, cerebellar, pyriform, and enthorhinal cortices, basolateral amygdala (BLA), septal and septohippocampal area (Mouradian et al., 1991; Alreja and Liu, 1996; Bergles et al., 1996; Marek and Aghajanian, 1996; Kawaguchi and Shindou, 1998; Braga et al., 2004; Dumont and Williams, 2004; Herold et al., 2005; Lei et al.,