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Research Report

Modulation of the striato-pallidal pathway by adenosine A2a receptors depends on dopaminergic striatal input

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ABSTRACT

The modulation of the striato-pallidal pathway by presynaptic adenosine A2a and dopamine D2 receptors has gained attention in the study of Parkinson's disease. Here, we analyzed the effect of presynaptic A2a receptors in the spiking activity of globus pallidus (GP) neurons recorded during electrical stimulation of the striato-pallidal pathway, in both sham and ipsilaterally dopamine-denervated rats. We found that intrapallidal blockade of A2a by 100 pMol KF-17383 in sham and lesioned rats did not modify the spiking rate of GP neurons. Local infusion of 100 pMol CGS-21680, an A2a agonist, did not change the spiking rate in sham rats, whereas the same concentration of NMDA strongly increased the firing frequency of all neurons tested. Moreover, in sham rats, local blockade of A2a receptors by 100 pMol KF-17383 suppressed the inhibition evoked by activation of the striato-pallidal pathway, while in dopamine-denervated rats the same dose of KF-17383 did not modify the inhibition. Our results show that the contribution of A2a receptors to the spiking control of GP by the striato-pallidal pathway depends on the state of the dopaminergic system.

1. Introduction

The GP, through GABAergic fibers, innervates the whole Basal Ganglia circuit and plays a key role in motor control (Bevan et al., 1998; Kita et al., 1999; Plenz and Kital, 1999), and lesions of GP evoke motor impairments (Byler et al., 2006). GABAergic release from the striatum through the striato-pallidal pathway contributes to the electrical activity of GP neurons (Kita et al., 2006; Nambu and Llinas, 1994): changes in the activity of striatal projection neurons are associated with modifications in the spontaneous firing rate of pallidal neurons in normal as well as in pathological conditions (Nakanishi et al., 1985; Tremblay et al., 1989).

The striato-pallidal pathway is modulated at the presynaptic level by dopamine, cannabinoid, adenosine and serotonine receptors (Cooper and Stanford, 2001; Herkenham et al., 1991; Mayfield et al., 1993; Querejeta et al., 2005). The interactions between dopamine D2-type and adenosine A2a receptors have gained much attention because of their potential therapeutic use in Parkinson's disease (Mally and Stone, 1998; Millan et al.,

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Abbreviation: 6-OHDA, 6-hydroxydopamine

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2007; Schwarzschild et al., 2006). Activation of D2 receptors diminishes GABA release from the striato-pallidal pathway while activation of A2a receptors augments GABA levels in the GP (Dayne Mayfield et al., 1996; Querejeta et al., 2001; Vortherms and Watts, 2004; Zahniser et al., 2000). The opposing effects of both receptor types significantly contribute to the basal firing rate of GP neurons (Shindou et al., 2001). Therefore, we hypothesized that suppression of the activation of one of either type of receptors would modify the effect of the activation of the other. Here, we analyzed the effect of the intrapallidal blockade of A2a receptors in the spiking of GP neurons under the activation of the striato-pallidal pathway, in both sham conditions and in the absence of dopamine in ipsilaterally 6-hydroxydopamine (6-OHDA)-lesioned rats using standard extracellular recording techniques.

2. Results

We recorded neurons in sham and in 6-OHDA-lesioned rats. The spontaneous firing rate of GP neurons was 18.7±0.7 spikes/sec for sham rats (n=36) and 16.2±1.3 spikes/sec for lesioned rats (n=15). There were no statistically significant differences between the GP baseline spiking rates of both groups of rats.

2.1. *Effect of intrapallidal blockade of A2a receptors*

The local infusion of 100 pMol KF-17383, an A2a antagonist, did not cause significant changes in GP neurons spontaneous spiking activity of either sham or lesioned rats (3.9±2.2% of baseline, n=15 and 3.4±3.3% of baseline, n=10; for sham and lesioned rats, respectively). Infusion of 10 pMol and 1 pMol KF-17383, did not cause changes in GP neurons of sham rats (2.7±3.1% of baseline, n=9 and 2.4±2.6% of baseline, n=9, respectively). Local application of 100 pMol CGS-21680, an A2a agonist, did not cause changes in the spontaneous firing rate of all neurons tested in sham rats (6.41±2.26% of baseline, n=6). To determine if the volume delivered into the GP reached the recording cell, an equal volume of 100 pMol NMDA was infused. All neurons significantly increased their spiking activity (361±14.14% of baseline, n=11). In some cases, the same neuron was infused with CGS-21680 and NMDA (Fig. 1).

2.2. *Effect of striatal electrical stimulation*

We analyzed the pallidal electrical activity under various electrical stimulus intensities applied to the striatum in sham rats. The spontaneous spiking rate of all neurons tested decreased in a stimulus intensity-dependent manner (n=5). Stimulus intensities of 10, 20, 30 and 40 μA diminished GP neurons firing frequency by 31.6±4.41%, 40.4±4.3 %, 64.25±12.8 and 89.26±2.7%, respectively. The pallidal response to striatal stimulation with 40 μA stimulus intensity was significantly different when compared to 10 and 20 and to 30 μA stimulus strengths (P<0.001 and P<0.01, respectively –data not shown). It is noteworthy that the striatal electrical stimulation did not cause a complete inhibition in any of the pallidal neurons recorded.

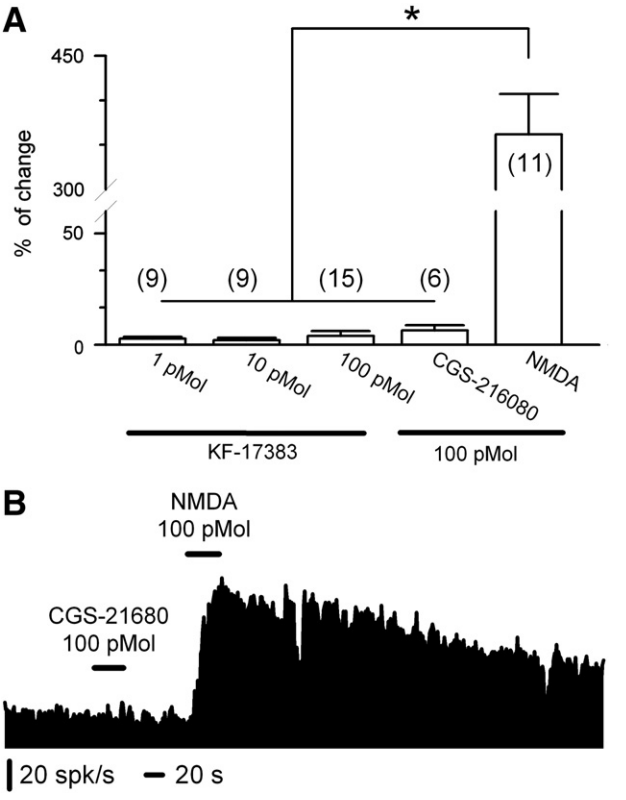

Fig. 1 – Intrapallidal blockade of A2a receptors has no effect on the spontaneous spiking rate of globus pallidus neurons on either sham or ipsilaterally dopamine-denervated rats. (A) Intrapallidal infusion of various doses of KF-17383, an A2a antagonist, does not cause significant changes on pallidal spiking activity; furthermore, activation of A2a receptors by CGS-21680 does not cause significant changes either. (B) To rule out if the lack of response to CGS-21680 was due to the infused volume not reaching the recording cell, in some neurons of sham rats the same volume of a 100 pMol NMDA solution was applied after CGS-21680 infusion. In all instances, the infusion volume was 100 nl. spks/s, spikes per second. In all Figures, numbers in parenthesis indicate number of cells tested, and the time scale bar applies to all procedures.

2.3. *Effect of intrapallidal blockade of A2a receptors during striato-pallidal pathway activation*

To understand how pallidal A2a receptors contribute to the modulation of the activation of the striato-pallidal pathway, we determined (using the stimulus intensity-response curve from point 2.3, above) that a stimulus intensity of 30 μA caused a ~half-maximal inhibition on GP neurons firing rate, this maneuver would allow us to observe either a negative or a positive modulation (Oviedo et al., 2008).

In sham rats, a striatal stimulus intensity of 30 μA decreased the spontaneous spiking rate by 64.25±12.8% (Fig. 2A), further, the same striatal stimulus caused a 5.8±11.38% pallidal spike rate reduction in the presence of intrapallidal 100 pMol KF-17383 (P<0.05; Figs. 2A, B). In all cases, the inhibition evoked by electrical stimulation only appeared during the stimulation