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Research Report

Presynaptic adenosine A_1 receptors modulate excitatory synaptic transmission in the posterior piriform cortex in rats

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ABSTRACT

The effect of adenosine on the fEPSP was examined in the lateral olfactory tract (Ia input) and associative tract (Ib input) of the rat piriform cortex. The fEPSP evoked in the Ia input showed paired-pulse facilitation, while that in the Ib input showed paired-pulse depression, suggesting a lower resting release probability in the Ia input. This was supported by results showing that MK801 blocked the NMDA receptor-induced fEPSP more rapidly in the Ib input than the Ia input. Adenosine caused dose-dependent inhibition of the fEPSP in both inputs, the sensitivity being higher in the Ib input. This effect was mimicked by the A_1 receptor agonist, CHA, and antagonized by co-application of the A_1 receptor antagonist, DPCPX, showing that adenosine was acting at A_1 receptors. Application of DPCPX alone caused an increase in the fEPSP, the increase being larger in the Ia input. DPCPX also caused paired-pulse depression in both inputs, and the paired-pulse ratio measured in its presence was very similar in both inputs. These results suggest there is a lower endogenous concentration of adenosine in the Ib sublayer than the Ia sublayer, which might account for the native difference in the resting release probability of the two inputs. The adenosine-induced inhibition of the fEPSP in both inputs was associated with a significant reduction in the rate at which MK801 blocked NMDA receptor-mediated fEPSP activity, suggesting a presynaptic location of the A_1 receptors. Blocking of N-, P/Q-type calcium channels occluded the inhibition by adenosine, indicating that they are downstream effectors of presynaptic A_1 receptor activation.

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Abbreviations: aCSF, artificial cerebrospinal fluid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AP5, DL-2-amino-5-phosphonopentanoic acid; CHA, N^6-cyclohexyladenosine; CNS, central nervous system; DNQX, 6,7-dinitroquinoxaline-2,3-dione; DPCPX, 1,3-dipropyl-8-cyclopentylxanthine; DPMA, N^6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)-ethyl]adenosine; fEPSP, field excitatory postsynaptic potential; GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartic acid; PPS, paired-pulse stimulation; VDCC, voltage-dependent calcium channel

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1. Introduction

Adenosine plays an important role as a modulator of synaptic transmission in the central nervous system (CNS) (Ribeiro, 1995; de Mendonca and Ribeiro, 1997). It exerts its neuromodulating effect by acting at type 1 purinergic receptors, namely A_1 and A_2 receptors (Van Calker et al., 1979), in many CNS regions (Fields and Burnstock, 2006). Adenosine enhances excitatory synaptic transmission by activating A_2 receptors (Nishimura et al., 1990; Sebastiao and Ribeiro, 1996). In contrast, it potently inhibits glutamate release from excitatory nerve terminals by activating presynaptic A_1 receptors, thereby strongly depressing excitatory synaptic transmission presynaptically (Prince and Stevens, 1992; Moore et al., 2003). Adenosine also acts on A_1 receptors to depress the release of other neurotransmitters, for example, acetylcholine and γ-amino-butyric acid (GABA) (Harms et al., 1979; Holins and Stone, 1980). The mechanism underlying the depressant effect of A_1 receptor activation on transmitter release has been shown to involve a reduction in calcium influx upon arrival of the action potential at presynaptic terminals (Manita et al., 2004). In agreement with the above physiological and pharmacological observations, autoradiographic experiments using tritiated A_1 ligands have shown a high density of A_1 receptors in many CNS regions, including the cerebellum, hippocampus, cerebral cortex, piriform cortex, caudate putamen, and nucleus accumbens (Goodman and Synder, 1982; Moore et al., 2000; Ribeiro et al., 2002). Because of its potent depressant effect on synaptic transmission by its action on A_1 receptors, adenosine is considered as an endogenous modulator regulating synaptic plasticity (Moore et al., 2003) and as an agent protecting neurons from metabolic insult caused by ischemia (Saransaari and Oja, 2003; Sugino et al., 2001) or hypoxia (Arlinghaus and Lee, 1996; Fowler et al., 2003; Schmidt et al., 1996) and from the development of seizure (Birnstiel et al., 1992; Bruno et al., 2003; Schubert, 1992). It has also been shown to have sedative, anticonvulsant, anxiolytic, and locomotor depressant effects (Jacobson and Gao, 2006).

The piriform cortex makes up the major part of the olfactory cortex, and consists of anterior, lateral, and posterior parts (Nevill and Haberly, 2004). Activity-dependent synaptic plasticity, e.g. long-term potentiation and depression, can be easily induced in the piriform cortex, making it an excellent candidate for a cellular substrate underlying sensory odor-related information storage in the piriform cortex (Hasselmo and Barkai, 1995; Saar et al., 1999). In addition, the piriform cortex is one of the brain regions in which epileptiform activity can be easily induced in animal models of epilepsy (Demir et al., 1999a,b). It is therefore of interest to examine the effect of adenosine on excitatory synaptic transmission in the piriform cortex. The principal neurons of the piriform cortex are pyramidal cells that receive two principal inputs from the olfactory bulb and from other cortical areas, including other parts of the piriform cortex (Nevill and Haberly, 2004). The fibers of these inputs are well organized in the most superficial part of the piriform cortex, layer I, in which the apical dendrites of the pyramidal cells are located and receive contacts from synaptic inputs. The fibers from the olfactory bulb, forming the lateral olfactory tract and carrying odor sensory information, project directly to the piriform cortex without thalamic intermediation and are located in the outer half of layer I; these are referred to as the Ia input in this study. The intrinsic associative fibers from other cortical areas are located in the inner half of layer I (Hasselmo and Bower, 1990; Nevill and Haberly, 2004) and are referred to as the Ib input in this study. In addition to this physical separation, previous studies have established certain criteria for distinguishing physiologically between the Ia and Ib inputs. For instance, paired-pulses delivered to the Ia input result in paired-pulse facilitation of the fEPSP, in which the synaptic response to the second stimulating pulse is larger than that to the first pulse. On the other hand, paired-pulse stimulation (PPS) of the Ib input causes paired-pulse depression of the fEPSP (Bower and Haberly, 1986; Franks and Isaacson, 2005). Moreover, it has been shown that the EPSP(C) evoked by stimulation of the Ib input is sensitive to the $GABA_B$ receptor agonist, baclofen, but that evoked by stimulation of the Ia input is not (Franks and Isaacson, 2005; Tang and Hasselmo, 1994). In the present study, we used these two criteria to confirm that the evoked fEPSP were in the Ia or the Ib input in the posterior piriform cortex and examined the effect of adenosine. Our aims were to examine whether adenosine had any differential effect on the Ia and Ib inputs and determine the underlying mechanism, to identify the receptor subtype involved in the effect of adenosine and its location, and to explore the molecular target affected by adenosine receptor activation.

2. Results

With the exception of the experiments shown in Fig. 5, all recordings were made at room temperature (25 °C). With the recording and stimulating electrodes placed in the outer half of layer I (hereafter referred to as the Ia sublayer) of the posterior piriform cortex (Figs. 1A, B1), the fEPSP evoked by two consecutive stimulation pulses showed paired-pulse facilitation when the inter-pulse interval (IPI) was between 20 and 500 ms (Fig. 1C1 upper trace), the maximal facilitation of 140% being obtained when the IPI was between 50 and 100 ms (Fig. 1C2, black circles, $n=8$ slices). The evoked fEPSP was insensitive to bath application of 10 μM baclofen, a $GABA_B$ receptor agonist, or to 100 μM CGP35348, a $GABA_B$ receptor antagonist, applied after the baclofen ($n=4$ slices) (Fig. 1D1). In contrast, with the recording and stimulating electrodes placed in the inner half of layer I (hereafter referred to as the Ib sublayer) (Figs. 1A, B2), the fEPSP showed paired-pulse depression when the IPI was less than 500 ms (Fig. 1C1 lower trace), with the maximal depression of 46% being obtained when the IPI was between 20 and 75 ms (Fig. 1C2, white circles, $n=6$ slices). Moreover, the fEPSP evoked in this condition was markedly attenuated by bath application of baclofen (56±10% of baseline; $n=4$, $p<0.005$, $t=5$, $df=3$, paired t-test), and this effect was antagonized by subsequent bath application of CGP35348 (84±9% of baseline; $n=4$, $p<0.005$, $t=8$, $df=3$, paired t-test) (Fig. 1D2). These results are consistent with previous reports (Franks and Isaacson, 2005; Tang and Hasselmo, 1994), which used the same criteria to verify the EPSPs activity of the Ia or Ib input, and also show that we were able to precisely evoke fEPSPs activity in the Ia or Ib input.