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Research Report

Repetitive stimulation of adenosine A1 receptors *in vivo*: Changes in receptor numbers, G-proteins and A1 receptor agonist-induced hypothermia

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ABSTRACT

Adenosine is an important neuromodulator and neuroprotective molecule, which is produced in the brain as a function of neuronal activity, coupling energy expenditure to energy supply. Under conditions of increased need and reduced availability of energy, including hypoxia and prolonged wakefulness, there is an increase in adenosine turnover and adenosine receptor stimulation. The aim of the present study was to examine how repetitive adenosine receptor stimulation affects receptor function and adenosinergic signaling in the brain. Adult male Wistar rats received daily intraperitoneal injections of the adenosine A1 receptor agonist N^6-cyclopentyladenosine (CPA; 0.25 mg/kg; once per day) and effects on adenosine signaling were established with receptor and G-protein autoradiography. Injections of CPA for 5 consecutive days caused a significant decrease in adenosine A1 receptor numbers in the hippocampus and somatosensory cortex. In contrast, while the amount of adenosine A1 receptor-activated G-proteins was not affected in most regions, a significant increase was found in the somatosensory cortex. On the level of physiological output, CPA-induced hypothermia was significantly attenuated, suggesting a functional desensitization of the A1 receptor system. Taken together, the present findings suggest that repetitive stimulation of the A1 receptors can affect elements of the adenosinergic signaling cascade in the rat brain in a region-specific manner.

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1. Introduction

The adenosine system is an important homeostatic neuromodulatory system that protects the brain against the harmful consequences of energy depletion (Rudolphi et al., 1992; Dunwiddie and Masino, 2001; Ribeiro et al., 2002). Adenosine is ideally suited for this role since it is a metabolite of ATP and its production is the immediate result of cellular energy use. Upon release into the extracellular space, adenosine provides an important feedback signal that has powerful modulatory effects on both neurons and glial cells via G-protein-coupled receptors (Fredholm et al., 2001; Klinger et al., 2002). The adenosine A1 receptor in particular is abundantly expressed throughout the brain, and its stimulation has a prominent neuroprotective effect by preventing energy depletion (Dunwiddie and Masino, 2001). When adenosine binds to A1 receptors, it directly inhibits neuronal activity and energy use by inducing hyperpolarization and by reducing neurotransmitter release. By these actions, adenosine protects neurons under conditions that threaten neuronal energy

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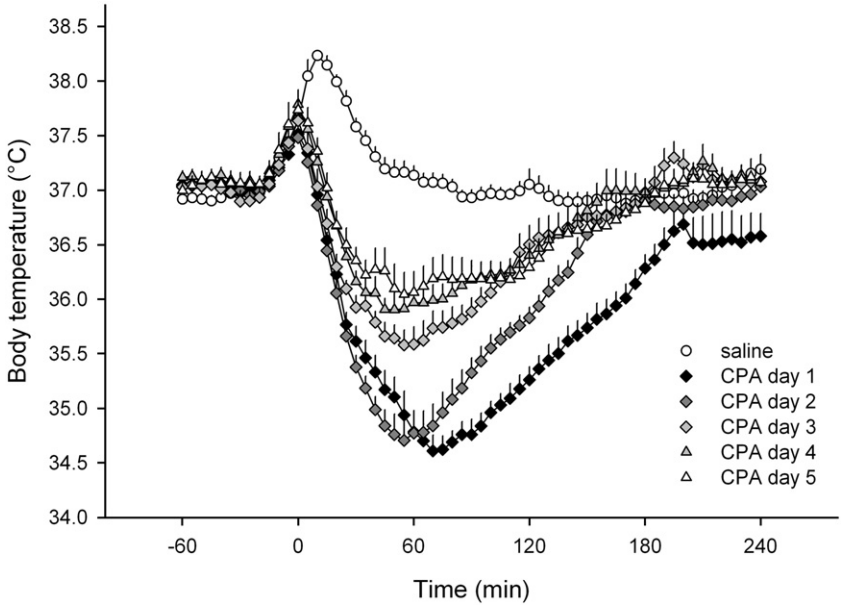

Fig. 1 – Repetitive CPA injections decrease the hypothermic response induced by CPA. Rats were injected with CPA ($n=9$) or saline ($n=9$) on 5 consecutive days. The repeated daily injections with CPA resulted in a gradually diminishing hypothermic response to the adenosine A1 receptor agonist. All the CPA-induced hypothermic responses were significantly different from the saline-induced hyperthermia. Between temperature responses on days 1 and 2, no significant difference was found. The hypothermic response on day 2 significantly differed from that one on day 3. The temperature responses on days 3, 4, and 5 were not significantly different from each other. Data are expressed as means ± SEM.

balance, which may occur as a consequence of, for example, hypoxia, hypoglycemia, excessive neuronal activity and prolonged wakefulness (Rudolphi et al., 1992; Porkka-Heiskanen et al., 2002; Ribeiro et al., 2002; Basheer et al., 2004).

Given the neuroprotective properties of adenosine and its A1 receptor-linked signaling pathway, adenosinergic compounds have been studied for their potential use as treatment in neurodegenerative conditions and diseases (Rudolphi et al., 1992; Jacobson et al., 1996; De Mendonca et al., 2000). However, a major complication is that chronic administration of adenosinergic drugs appears to have effects that are opposite to the effect of a single acute administration (Jacobson et al., 1996; De Mendonca et al., 2000). For example, in contrast to the neuroprotective effects of acute administration of adenosine A1 receptor agonists, exacerbation of neuronal damage after chronic treatment was found in models of ischemia (Von Lubitz et al., 1994).

The mechanism of this effect inversion with chronic treatment may be related to gradual decreases in receptor number and affinity. Yet, information on consequences of chronic treatment with adenosine analogues on adenosine receptors and signaling pathways is limited (Jacobson et al., 1996; De Mendonca et al., 2000). A number of studies have examined the effect of chronic adenosine receptor stimulation on adenosine receptor-linked signal transduction pathways (Abbracchio et al., 1992; Von Lubitz et al., 1994; Hettinger-Smith et al., 1996; Ciruela et al., 1997; Ruiz et al., 1996, 2005). The *in vitro* studies show that chronic exposure of neuronal or smooth muscle cell cultures and brain slice cultures to adenosine A1 receptor agonists result in a reduced density of A1 receptors (Abbracchio et al., 1992; Hettinger-Smith et al., 1996; Ciruela et al., 1997). Other reports show unchanged or reduced A1 receptor binding values after chronic *in vivo* treatment with A1 receptor agonists in whole brain preparations (Von Lubitz et al., 1994; Ruiz et al., 1996, 2005). Because of the limited and inconclusive information on the *in vivo* effects of chronic A1 receptor stimulation, the aim of the present study was to test whether repetitive application of the adenosine A1 receptor agonist N^6-cyclopentyladenosine (CPA) alters elements of adenosine signaling in various regions of the intact rat brain.

2. Results

2.1. *Adenosine A1 receptor-mediated physiological response*

In response to the first injection of CPA, body temperature of the rats decreased approximately 2.5 °C within 50–60 min and returned to baseline after about 180 min (Fig. 1). This hypothermic response was accompanied by an almost complete reduction of locomotor activity (data not shown). The consecutive daily injections of CPA were associated with a gradually diminished hypothermic response, suggesting a desensitization of the adenosine A1 receptor system (Fig. 1). An ANOVA with repeated measures revealed a significant treatment effect [$F_{(180,1224)}=8.787$; $p<0.001$]. After each individual CPA injection, the body temperature response was different from the temperature response to the saline injection (Tukey, $p<0.001$ in each case). Body temperature responses to CPA progressively diminished over the days, with the responses on days 3 to 5 being significantly smaller than the responses on the first 2 days.

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