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Brief Communication

Adenosine A_{2A} receptor blockade prevents memory dysfunction caused by β-amyloid peptides but not by scopolamine or MK-801

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Abstract

Adenosine A_{2A} receptor antagonists alleviate memory deficits caused by aging or by administration of β-amyloid peptides in rodents, which is in accordance with the beneficial effects of caffeine consumption (an adenosine receptor antagonist) on memory performance in aged individuals and in preventing Alzheimer's disease. We now tested if A_{2A} receptor blockade affords a general beneficial effect in different experimental paradigms disturbing memory performance in rodents. The β-amyloid fragment present in patients with Alzheimer's disease ($A\beta_{1-42}$, 2 nmol, icv) decreased spontaneous alternation in the Y-maze after 15 days (29%) to an extent similar to the decrease of memory performance caused by scopolamine (2 mg/kg, ip) or MK-801 (0.25 mg/kg, ip) after 30 min (28% and 39%, respectively). The selective A_{2A} receptor antagonist SCH58261 (0.05 mg/kg, ip every 24 h, starting 30 min before the noxious stimuli) prevented $A\beta_{1-42}$-induced amnesia, but failed to modify scopolamine- or MK-801-induced amnesia. Similar conclusions were reached when testing another A_{2A} receptor antagonist (KW6002, 3 mg/kg, ip). These results indicate that A_{2A} receptors do not affect general processes of memory impairment but instead play a crucial role restricted to neurodegenerative conditions involving an insidious synaptic deterioration leading to memory dysfunction.

Keywords: Adenosine; A_{2A} receptor; β-amyloid; Alzheimer's disease; Memory; Scopolamine; MK-801; NMDA; Locomotion

Introduction

Adenosine is a neuromodulator that can either inhibit or facilitate synaptic transmission through inhibitory A_1 or facilitatory A_{2A} receptors, respectively (Fredholm et al., 2005). These adenosine receptors also have the ability to control neuronal damage after different insults: A_1 receptors constitute a hurl that increases the threshold for brain damage, whereas the blockade of adenosine A_{2A} receptors affords neuroprotection against chronic noxious brain insults (Cunha, 2005). A_{2A} receptor antagonists have recently received particular attention as novel strategies to prevent or restrain the development of neurodegenerative diseases, namely in Parkinson's disease, where A_{2A} receptor antagonists are the leading non-dopaminergic therapy currently in phase IIb trials (Schwarzschild et al., 2006). It was also recently shown that A_{2A} receptor antagonists can prevent memory impairment in animal models of aging (Prediger et al., 2005) and Alzheimer's disease (Dall'Igna et al., 2007; Arendash et al., 2006), in accordance with the ability of chronic consumption of caffeine (an adenosine receptor antagonist) to enhance memory performance in the elderly (e.g. Johnson-Kozlow et al., 2002), to attenuate memory decline in the elderly (Ritchie et al., 2007) and to decrease the risk of Alzheimer's disease (Maia and de Mendonça, 2002).

Recent studies indicate that the genetic manipulation of A_{2A} receptors modifies memory performance in rodents (Gimenez-Llort et al., 2007; Wang et al., 2006) and can also modulate long term potentiation (d'Alcantara et al., 2001; Rebola et al., in press), a physiological correlate of learning and memory (Lynch,

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2004). Thus, it remains to be determined if A_{2A} receptors play a general role in controlling memory performance or if the impact of A_{2A} receptors on memory impairment is restricted to particular conditions where insidious neurodegenerative processes underlie memory dysfunction. To tackle this question, we compared the ability of A_{2A} receptor blockade to affect memory dysfunction caused by different experimental conditions, namely upon administration of a β-amyloid peptide (which triggers a slowly developing synaptic degeneration and memory dysfunction, see Coleman et al., 2004) and upon administration of either scopolamine (which triggers an acute memory impairment through a cholinergic block, see Hasselmo, 2006) or MK-801 (which triggers an acute memory impairment by blocking NMDA receptors, see Ellison, 1995).

Materials and methods

Animals

Male Wistar rats (Charles River, Barcelona, Spain) were used throughout this study and were handled according to the EU guidelines for use of experimental animals (86/609/EEC). The rats were maintained in our own animal facilities under controlled environment (23±2 °C, 12 h-light/dark cycle, free access to food and water) until 10–12 weeks old (*circa* 180 g). All behavioral experiments were conducted between 10:00 a.m. and 2:00 p.m.

Drugs and administration procedures

The β-amyloid (1–42) peptide fragment (Aβ) was dissolved in bidistilled water at a concentration of 1 mg/ml and stored at −20 °C until use. This led to the formation of soluble oligomers (Resende et al., 2007) and 2 nmol were intracerebroventricularly (icv) administered, as previously described (Dall'Igna et al., 2007). Control animals were icv injected with a similar volume of distilled water. The behavioral performance was evaluated 15 days after the administration of Aβ.

Scopolamine and MK-801 were dissolved in saline (0.9% NaCl) and were injected intra-peritoneally (ip) at doses of 2 mg/kg and 0.25 mg/kg, respectively. The animals were analyzed behaviorly 30 min after the administration of each drug. Control rats were injected ip with saline.

When rats were treated with the selective A_{2A} receptor antagonists SCH58261 (generously provided by Scott Weiss, Vernalis, UK) or KW6002 (or istradefylline, synthesized as described previously, see Hockemeyer et al., 2004), each of these drugs was injected ip (0.05 mg/kg of SCH58261 dissolved in 10% dimethylsulphoxide in saline; 3 mg/kg of KW6002 dissolved in 5% Tween 80 in saline) 30 min before the administration of memory-disturbing drugs (and once daily thereafter when testing Aβ). We chose to administer SCH58261 and KW6002 ip since this route of administration of these particular doses of SCH58261 and KW6002 afford effective brain

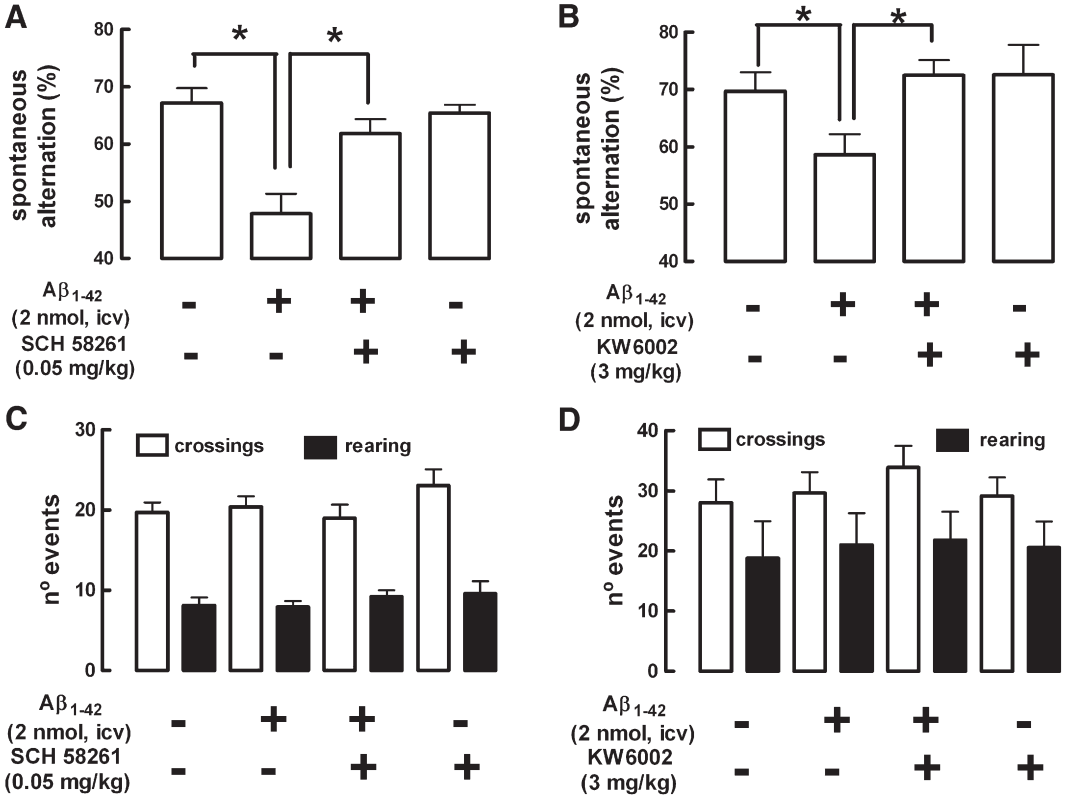

Fig. 1. Blockade of adenosine A_{2A} receptors prevents β-amyloid-induced decrease of spontaneous alternation. Rats were treated (2 nmol, icv) with β-amyloid peptide 1–42 fragment ($A\beta_{1-42}$) or distilled water. The A_{2A} receptor antagonists SCH58261 (0.05 mg/kg, ip) or KW6002 (3 mg/kg, ip) were administered daily starting 30 min before Aβ and rats were behaviorly analyzed after 15 days. (A, B) Spontaneous alternation in the Y-maze test and (C, D) spontaneous locomotion evaluated in an open field arena are expressed as mean±S.E.M. The data from panels A and C are from 10 rats in each experimental group (*$P<0.05$ between the indicated columns) and the data from panels B and D are from 6 rats in each experimental group (*$P<0.1$ between the indicated columns).