Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Low doses of the selective adenosine A_{2A} receptor agonist CGS21680 are protective in a rat model of transient cerebral ischemia

Alessia Melani[a,*], *Francesca Corti*[a], *Lucrezia Cellai*[a], *Maria Giuliana Vannucchi*[b], *Felicita Pedata*[a]

[a]*Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), Division of Pharmacology and Toxicology, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy*

[b]*Department of Experimental & Clinical Medicine, Section of Anatomy & Histology, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy*

ARTICLE INFO

Article history:
Accepted 14 January 2014
Available online 20 January 2014

Keywords:
A_{2A} adenosine receptor
CGS21680
Stroke
Neuroinflammation

ABSTRACT

Evidence indicate that adenosine A_{2A} receptor subtype is of critical importance in stroke. An overexpression of A_{2A} adenosine receptors occurs at central level on neurons and microglia of ischemic striatum and cortex after focal ischemia. Adenosine A_{2A} receptor subtype is localized not only at central level but also peripherally on blood cells, where it is known to exert antiinflammatory effect. Purpose of the present work was to investigate the putative neuroprotective effect of the adenosine A_{2A} receptor agonist CGS21680 in a rat model of transient medial cerebral artery occlusion (MCAo). Transient cerebral ischemia was induced by 1 h occlusion of MCA. CGS21680 (0.01 and 0.1 mg/kg, i.p.) was administered starting 4 h after ischemia according to a chronic protocol (twice/day for 7 days). CGS21680, at the dose of 0.1 mg/kg transiently increased heart frequency but did not modify blood pressure. At the dose of 0.01 mg/kg the drug did not modify either heart frequency or blood pressure. Following transient MCAo, CGS21680 at both doses protected from neurological deficit from the first day up to 7 days thereafter. At this time, it has reduced microgliosis, astrogliosis and improved myelin organization in the striatum and cytoarchitecture of the ischemic cortex and striatum. Two days after transient MCAo, CGS21680 has reduced the number of infiltrated granulocytes into the ischemic tissue. Data indicate that CGS21680 systemically administered is protective by immunosuppressive effects.

© 2014 Elsevier B.V. All rights reserved.

Abbreviations: BBB, blood brain barrier; BMDCs, bone marrow-derived cells; CGS21680, 2-[p-(2-carboxyethyl)-phenethylamino] -5'-Nethylcarboxamidoadenosine; DMSO, dimethyl sulfoxide; H&E, hematoxylin and eosin; MAG, myelin associated glycoprotein; MCAo, middle cerebral artery occlusion; mNSS, modified neurological Severity Score; PBS-TX, phosphate buffer saline-Triton X-100

*Corresponding author. Fax: +390554271280.

E-mail addresses: alessia.melani@unifi.it (A. Melani), francesca.corti@unifi.it (F. Corti), lucrezia.cellai@unifi.it (L. Cellai), mariagiuliana.vannucchi@unifi.it (M. Giuliana Vannucchi), felicita.pedata@unifi.it (F. Pedata).

0006-8993/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.brainres.2014.01.014

1. Introduction

Adenosine is a potent biological mediator whose concentration dramatically increases during brain ischemia (Melani et al., 1999; Phillis, 2004). During ischemia the extracellular adenosine reaches a concentration in a micromolar range able to stimulate all the four adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, A_3). In recent years, evidence indicated that adenosine A_{2A} receptor subtype is of critical importance in stroke (Chen et al., 2007). An overexpression of A_{2A} adenosine receptors occurs at central level on neurons and microglia of ischemic striatum and cortex after focal ischemia induced by permanent middle cerebral artery occlusion (pMCAo) (Trincavelli et al., 2008). Adenosine A_{2A} receptor subtype is localized not only at central level on neurons, astrocytes and microglia, but also peripherally on blood cells, platelets, vasculatures, where it is known to reduce adhesion cell factor production, platelet aggregation and neutrophil activation, exerting therefore an antithrombotic, antioxidant and anti-inflammatory effect (Sitkovsky et al., 2004).

Ischemia is a multifactorial pathology characterized by different events evolving in time: an acute injury characterized by a massive increase of extracellular glutamate is followed by activation of resident immune cells (i.e. microglia and astrocytes), and production or activation of inflammation mediators (Dirnagl et al., 1999). Proinflammatory cytokines, that up-regulate cell adhesion molecules, exert an important role in promoting blood cell infiltration and accumulation into ischemic tissue (Huang et al., 2006; Stoll et al., 1998). Although after ischemia, precocious activation of immune cells may be neuroprotective and supportive for regeneration, protracted neuroinflammation is now recognized as the predominant mechanism of secondary brain injury (Dirnagl et al., 1999). In agreement, A_{2A} agonists, systemically administered, protected from inflammation in various models of autoimmune disease such as rheumatoid arthritis (Mazzon et al., 2011; Szabo et al., 1998), colitis (Di Paola et al., 2010; Odashima et al., 2005), and hepatitis (Choukèr et al., 2008) and in models of spinal cord trauma (Li et al., 2006; Genovese et al., 2009; Paterniti et al., 2011) and of traumatic brain injury (Dai et al., 2010). To clarify the role of adenosine A_{2A} receptor in brain ischemia, purpose of the present work was to check the putative neuroprotective effects of the adenosine A_{2A} agonist, CGS21680 in a rat model of transient (1 h) focal cerebral ischemia. Since adenosine A_{2A} agonists are vasodilator drugs potentially hypotensive (Alberti et al., 1997), we verified that the doses administered systemically after ischemia do not alter cardiovascular parameters.

2. Results

2.1. Blood pressure and heart rate

The effect of the selective A_{2A} adenosine receptor agonist (CGS21680, 0.01 and 0.1 mg/kg i.p.) on blood pressure and heart rate was evaluated in a group of six rats (Table 1).

CGS21680 at the dose of 0.1 mg/kg, caused a transient, but not statistically significant reduction, of blood pressure 15 min after administration. In the first hour after administration it induced a small but significant increase of heart rate (Table 1; $p<0.0001$) that normalized after 1 h and 30 min. At the lower dose of 0.01 mg/kg CGS21680 did not modify either blood pressure or heart rate.

2.2. Effect of treatment with the adenosine A_{2A} receptor agonist on neurological deficit after tMCAo

After tMCAo (1 h), rats showed a clear neurological deficit that was evaluated by a sensory motor test (mNSS), according to Chen et al. (2001). Sham-operated rats did not show any neurological deficit.

Fig. 1A shows that in the mNSS test, sham-operated rats had a neurological score of 0.15–0.70 in the period from 1 to 7 days after tMCAo. Twenty-four hours after tMCAo, vehicle-treated rats showed a neurological score of 12.6±0.5 (mean±S.E.M.) that defines a severe injury. The neurological impairment spontaneously recovered over time, up to 7 days after tMCAo. Five days after tMCAo the neurological score was reduced to 8.2±0.7, 7 days after tMCAo, the neurological score was further reduced to 7.0±0.6 that represents a moderate injury. The chronic treatment with the A_{2A} receptor agonist, CGS21680, at both doses of 0.01 and 0.1 mg/kg,

Table 1 – Blood pressure and heart rate evaluation in rats treated with CGS21680 at the dose of 0.01 and 0.1 mg/kg (i.p.).

	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Mean pressure (mmHg)	Heart rate (bpm)
CGS21680 0.01 mg/kg (i.p.) ($n=3$)				
Pre-treatment	131.5±7.1	93.2±13.3	105.8±11	374.4±13.5
After 15 min	118.5±6.9	85.6±8.1	97.2±7.2	418.6±14.1
After 30 min	123.8±6.5	85.1±13.4	100.4±9.4	392.5±10.8
After 60 min	137.3±6.1	99.5±3.7	110.8±5.1	393.4±18.1
CGS21680 0.1 mg/kg (i.p.) ($n=3$)				
Pre-treatment	135.4±5.9	103.6±7.0	114.5±4.3	391.2±11.9
After 15 min	107.1±14.6	71.0±0.3	83.4±5.2	541.1±12.3*
After 30 min	113.2±9.4	93.3±5.3	103.9±8.4	517.7±9.5*
After 60 min	120.2±7.0	90.2±3.8	100.1±0.9	440.1±22.9*
After 90 min	129.1±6.1	91.8±3.1	105.9±3.8	403.8±12.0

Student's t test.
* $p<0.0001$ vs pre-treatment.

Download English Version:

https://daneshyari.com/en/article/4324363

Download Persian Version:

https://daneshyari.com/article/4324363

Daneshyari.com