The selective adenosine A_{2A} receptor agonist CGS21680 is neuroprotective in a rat model of focal cerebral ischemia

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In recent years, evidence indicated that adenosine A_{2A} receptor subtype is of critical importance in stroke (Chen and Pedata, 2008). An overexpression of A_{2A} adenosine receptors occurs at central level on neurons and microglia of ischemic striatum and cortex after focal cerebral ischemia (Trincavelli et al., 2008). Adenosine A_{2A} receptor subtype is localized not only at central level but also peripherally on leukocytes, where they are known to exert antinflammatory effect (Chen and Pedata, 2008). Our previous data demonstrate protection by A_{2A} agonists, systemically administered, in various models of peripheral (rheumatoid arthritis, colitis, acute lung inflammation) and central diseases such as spinal cord trauma (Paterniti et al., 2011), involving inflammation. Purpose of the present work was to investigate the putative neuroprotective effect of the adenosine A_{2A} receptor agonist, CGS21680, in the model of transient focal cerebral ischemia in the rat. Cerebral ischemia was induced by occlusion of middle cerebral artery (MCAo) for 1 h. CGS21680 (0.01 mg/kg, i.p.) was administered starting after 4 hours from ischemia according to a chronic protocol (twice/day for 7 days). Sensory motor deficit and body weight were evaluated 1, 5 and 7 days after transient MCAo. Seven days thereafter, infarct volume was histologically evaluated and astrogliosis and microgliosis were determinated by immunohistochemical studies (anti-GFAP and anti-IBA1 antibodies, respectively). After 2 and 7 days from transient MCAo, the number of infiltrated blood cells into cerebral ischemic tissue was evaluated by anti-HIS48 antibody (against granulocytes). CGS21680, administered at the low dose of 0.01 mg/kg intraperitoneous, modified neither blood pressure nor heart rate. Following transient MCAo, CGS21680 protected from neurological deficit from the first day up to seven days thereafter (at 7 day was: 7.00±0.64 n=9 in vehicle group and 4.37±0.90 n=4 in CGS2160 0.01 group; Student's t test: $p<0.001$). At this time, it reduced the volume of the ischemic cortical damage (75.15±5.13 n=9 in vehicle group and 51.88±10.37 n=4 in CGS2160 0.01 group; Student's t test: $p<0.02$) and improved the cytoarchitecture of ischemic areas (cortex and striatum) and the myelin organization in ischemic striatum. Seven days after transient MCAo, a strong microgliosis and astrogliosis was observed in ischemic areas, but none granulocyte infiltration was evident. On the contrary, 2 days after transient MCAo, a massive number of infiltrated granulocytes into cerebral ischemic tissue was observed (in cortex: 37.50±6.85 n=3; in striatum: 36.25±17.45 n=3). CGS21680 reduced infiltration in the ischemic areas (in cortex: 20.32±2.41 n=3, Student's t test: $p<0.02$; in striatum: 27.32±4.22 n=3, ns). This results indicate that adenosine A_{2A} receptor agonist CGS21680, systemically administered, improves ischemic tissue damage and neurological deficit by an immunosuppressive effect exerted in the first days after ischemia, bringing ultimately to a reduced inflammatory cascade in the ischemic brain area.

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Trincavelli et al. (2008). *J Neurochem*. 104: 479-490.
Paterniti et al. (2011). *J Neuroinflamm*. 8: 31.