Selective adenosine A_{2A} receptor agonists and antagonists protect at different times after brain focal ischemia in the rat

I. Dettori[1], A. Melani[1],L. Cellai[1], F. Pedata[1]

[1]Dept. of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Italy

In recent years, evidence indicated that adenosine A_{2A} receptor subtype is of critical importance in stroke (Chen and Pedata, 2008). Adenosine A_{2A} receptors located on neuronal and microglial cells of striatum and cortex are overexpressed 24 hours 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 it exerts an important anti-inflammatory effect.

The protective effect of the adenosine A_{2A} receptor agonist, CGS21680, administered starting 4 hours after ischemia (0.01 mg/kg, i.p., twice/day for 7 days) was investigated after transient (1 hour) focal ischemia induced in the rat by occlusion of the middle cerebral artery (tMCAo), by the monofilament technique. At this dose, CGS21680 modified neither blood pressure nor heart rate. CGS21680 protected from neurological deficit from the first day up to seven days thereafter (score at 7 day: 4.37±0.90, n=4 versus 7.00±0.64, n=9 in vehicle group; $p<0.001$). Seven days after the ischemic insult, it significantly reduced the volume of the ischemic cortical damage (51.88±10.37 mm^3, n=4 versus 75.15±5.13 mm^3, n=9 in vehicle group; $p<0.02$), improved the cytoarchitecture of ischemic cortex and striatum (evaluated by H&E), improved the myelin organization in ischemic striatum (evaluated by MAG staining) and reduced microgliosis (evaluated by Iba1 staining) and astrogliosis (evaluated by GFAP staining). Two days after tMCAo, a massive infiltration of granulocytes (evaluated by HIS-48 staining, specific for granulocytes) into cerebral ischemic tissue was observed. CGS21680 reduced granulocyte infiltration in the ischemic areas (in cortex: 20.32±2.41 cells/optical field, n=6 versus 37.5±6.8, n=3 in vehicle group; $p<0.02$) (Melani et al., 2014). Results indicate that the adenosine A_{2A} receptor agonist CGS21680, systemically administered, protected against ischemic damage by reducing blood cell infiltration and neuroinflammation along the days after ischemia.

The selective A_{2A} receptor antagonist SCH58261 administered starting from 5 min after ischemia at the dose of 0.01 mg/kg i.p. (twice/day for 7 days) significantly protected from the neurological deficit 1 day after tMCAo ($p<0.001$), but no more after 5 and 7 days. Seven days after tMCAo, SCH58261 has not protected ischemic areas from damage and has not ameliorated myelin organization into the ischemic striatum. Two days after tMCAo, SCH58261 has not reduced blood cell infiltration into ischemic striatal and cortical tissue. Protection by the A_{2A} receptor antagonist 24 hours after ischemia is attributable to reduced excitotoxicity (Melani et al. 2009). Seven days after ischemia the early protective effect of the A_{2A} receptor antagonist, likely has been overwhelmed by a secondary damage due to blood cell infiltration and neuroinflammation.

Melani et al. (2009*). Brain*, 132):1480-95.
Melani et al. (2014). *Brain Res*., 1551: 59-72.
Melani et al. (2015) *Neurol Sci., in press*
Trincavelli et al. (2008). *J Neurochem*., 104: 479-490.