THE SELECTIVE ANTAGONISM OF ADENOSINE A2B RECEPTORS PREVENTS SYNAPTIC AND NEURONAL DAMAGE INDUCED BY OXYGEN AND GLUCOSE DEPRIVATION IN CA1 RAT HIPPOCAMPUS.

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During hypoxia or ischemia, the extracellular concentrations of adenosine significantly increase reaching µmolar concentrations that activate all adenosine receptor subtypes so far identified: A1, A2A, A2B, and A3. The A2B receptor is the most enigmatic among all different adenosine receptor subtypes; no data about its involvement in cerebral ischemia are so far available.

In this work we investigated the role of A2B adenosine receptor during oxygen and glucose deprivation (OGD), a model of cerebral ischemia, in the CA1 region of rat hippocampus in vitro. For this purpose, two selective antagonists for this receptor subtype, MRS 1754 (N-(4-Cyanophenyl) -2-[4-(2,3,6,7-tetrahydro-2,6-dioxo- 1,3-dipropyl-1H-purin-8-yl) phenoxy] -acetamide) and PSB 603 (8-[4-[4-(4-Chlorophenzyl) piperazide-1-sulfonyl) phenyl]] -1-propylxanthine) were used. In order to better characterize the OGD-induced cell injury and pharmacological protection, if any, we conducted extracellular recordings of CA1 field excitatory post-synaptic potentials (fEPSPs); the extent of neuronal damage was assessed by immunohistochemical analysis.

Application of 7 or 30 min OGD induced the appearance of a marked depolarization, known as anoxic depolarization (AD), an unambiguous sign of neuronal damage, in all hippocampal slices (n = 38). Furthermore, 7 min OGD completely abolished fEPSPs that did not recover after return to normoxic condition. Seven or 30 min OGD were applied in the presence of MRS 1754 (500 nM, n = 10) or PSB 603 (50 nM, n = 9). The selective antagonism of the A2B receptors significantly delayed the appearance of AD and allowed the recovery of fEPSPs amplitude.

The extent of CA1 cell injury was assessed 1 hour after the end of 7 min OGD by immunofluorescence for NeuN. Substantial damage on CA1 pyramidal neurons occurred in untreated slices, determined by the decrease of immunofluorescence density of CA1 Neun+ neurons and by the increase in the number of pycnotic nuclei after fluorescent NeuN+ staining. These effects were completely blocked by the antagonist PSB 603 (50 nM, n = 5).

We showed for the first time that the selective adenosine A2B receptor antagonism delays the occurrence of AD and improves neuronal survival following severe OGD in the CA1 hippocampus, as demonstrated by the significant recovery of an otherwise disrupted neurotransmission and by the significant attenuation of neuronal damage induced by 7 min OGD.

The selective antagonists for the A2B adenosine receptor subtype may represent a new class of neuroprotective drugs.