PROTECTION BY ADENOSINE A_{2A} ANTAGONISM DURING ISCHEMIA

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An important role of adenosine A_{2A} receptors in ischemia is proved by observation that A_{2A} receptor knock-out mice show reduced cortical and striatal damage as well as associated neurological deficit following transient middle cerebral artery occlusion (MCAo)[1]. In the model of permanent MCAo, we have demonstrated that subchronic administration of the adenosine A_{2A} antagonist, SCH58261, protects against a controlateral turning behaviour, neurological deficit and cortical and striatal brain damage evaluated 24 hours after ischemia[2]. Phospho-p38 mitogen-activated protein kinase (MAPK) levels evaluated by Western Blot in vehicle-treated rats were increased by 500% in the ischemic striatum compared to the contralateral non ischemic striatum. In SCH58261-treated rats the phospho-p38 MAPK levels were significantly reduced by 70% in the ischemic striatum with respect to vehicle-treated rats. Phospho-p38 immunopositive cells showed swollen and hyper-trophic cell bodies, as well as processes, and exhibited morphological features of activated microglia. Colocalization of phospho-p38 and the microglial marker OX-42 confirmed the presence of the protein in microglial cells. Twenty-four hours after MCAo, no astrocytosis was present in the striatum and cortex. The aim of the present study was to evaluate the effect of subchronic treatment (5 min, 6 hours and 20 hours after MCAo) of SCH58261 on ERK1/2 and SAPK/JNK MAPK activation. Twenty four hours after ischemia, rats were sacrificed by transcardiac perfusion with 4% paraformaldehyde solution. In vehicle-treated rats, 24 h after MCAo, phospho-ERK1/2 immunopositive cells were localized in the cortex and striatum of the ischemic hemisphere and showed swollen and hyper-trophic cell bodies as well as processes. Double-immunostaining, with specified antibodies demonstrated that ERK1/2 was activated in microglial cells. Phospho-SAPK/JNK immunopositive cells were present only in the striatum of ischemic hemisphere. Double-immunostaining shows that presence of phospho-SAPK/JNK in few neurons and in association with oligodendrocytes. SCH58261 reduced phospho-SAPK/JNK immunoreactivity in the ischemic hemisphere while it had no effect on phospho-ERK1/2 immunoreactivity.

Results indicate that neuroprotective effect of A_{2A} antagonist, evaluated 24 hours after ischemia, involves inhibition of phospho-p38 and phospho-SAPK/JNK MAPK.

(Supported by MIUR (ex 40%) and Ente Cassa di Risparmio of Florence).

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