31° Congresso Nazionale della Società Italiana di Farmacologia
Trieste, 26-29 giugno 2003

THE ADENOSINE A_{2A} RECEPTOR ANTAGONIST ZM 241385 DIFFERENTIALLY INFLUENCES EXCITOTOXIC MECHANISMS AT PRE AND POST-SYNAPTIC SITE IN THE RAT STRIATUM

Tebano MT, Pintor A, Frank C, Domenici MR, Pepponi R., Potenza RL, Martire A, Grieco R, Nazzicone V, Popoli P.

Pharmacology Department, Istituto Superiore di Sanità, Viale Regina Elena, 299 Rome, Italy

In the brain adenosine A_{2A} receptors are highly expressed in the striatum and mainly mediate excitatory effects. Therefore they have been regarded as promising targets for the development of neuroprotective strategies. The aim of this study was to investigate the mechanism of possible neuroprotective action of the selective A_{2A} receptor antagonist ZM 241385 (ZM) in different models of pre and post-synaptic excitotoxicity.

"Pre-synaptic" models. Wistar rats were implanted with microdialysis probes in the dorsal striatum (N=5/group); the intrastriatal perfusion of ZM (5 nM) significantly reduced the raise in glutamate outflow induced by 5mM quinolinic acid (QA). Fifty nM ZM was less effective, as previously observed with another A_{2A} antagonist. In corticostriatal slices, extracellular field potentials (FPs) were recorded in the dorsal striatum using a protocol of Paired Pulse Stimulation (PPS). ZM (30-100 nM) reduced the effect of 100 mM 4-aminopyridine (4-AP) on the ratio between the second and the first FP amplitude (R2/R1=1.01±0.04 vs 0.78±0.06, $P<0.05$; N=5/group).

"Post-synaptic" models. In corticostriatal slices ZM (30-100 nM) did not prevent the reversible depression of FP amplitude elicited by NMDA (12.5-50 □M; N=6/group). In rat striatal neurons (primary cultures obtained from ED 17 embryos), ZM (50-100 nM) did not significantly influence NMDA induced toxicity (LDH release= 227.47±22.6% vs 204.3±14.2% of basal release, n.s.) and $[Ca^{2+}]_i$ increase (Fura-2AM ratio 340/380= 2.22±0.27.vs 2.7±0.36 n.s. N=4/group)

The ability of ZM to prevent QA-induced glutamate outflow and 4-AP effects in PPS, confirms that A_{2A} receptor antagonists have inhibitory effects on neurotransmitter release. The results obtained towards NMDA-induced effects suggest that A_{2A} receptor blockade may be unable to modulate excitotoxic mechanisms occurring at the post-synaptic site. This indicates that the neuroprotective potential of A_{2A} antagonists may be mainly evident in models of neurodegeneration in which pre-synaptic mechanisms play a major role.