THE SELECTIVE HISTAMINE H4 RECEPTOR ANTAGONIST JNJ7777120 PROTECTS FROM BEHAVIOURAL AND HISTOLOGICAL DAMAGE AFTER FOCAL TRANSIENT BRAIN ISCHEMIA IN THE RAT.

1)Gaviano L.. 2)Dettori I.. 3)Melani A.. 4)Lucarini L.. 5)Masini E.. 6)Pedata F..

Dept. NEUROFARBA, University of Florence

Histamine is a neurotransmitter or neuromodulator in the Central Nervous System (CNS). Recently, numerous studies have suggested that histamine and its receptors play important roles in cerebral ischemia. In the experimental model of focal cerebral ischemia induced by occlusion of the middle cerebral artery (MCAo) in rats, the levels of histamine evaluated by microdialysis increase in the ischemic areas. The human histamine H4 receptor is the most recently discovered member of the G protein-coupled receptor subfamily of histamine receptors. It is predominantly expressed in several cell types of immune system and in numerous areas of the CNS including cortex and striatum.

Characterization of the H4 receptor as the immune system histamine receptor with a pro-inflammatory role, directed growing attention towards its therapeutic exploitation in chronic inflammatory disorders.

The aim of our study was to assess the putative neuroprotective effects of the potent and selective histamine H4 receptor antagonist, JNJ7777120, chronically administered (1 mg/kg, i.p., twice/day for 7 days) on damage parameters in a model of focal ischemia induced in the rat by the transient (1 hour) occlusion of the MCAo (tMCAo) by the monofilament technique.

Chronic treatment with the histamine H4 receptor antagonist, JNJ7777120, significantly protected from the neurological deficit 1, 5 and 7 days after tMCAo (score at 7 day: 3.5 ± 0.5, n=10 versus 5.8 ± 0.4, n=13 in vehicle group; $p<0.001$) and significantly reduced the body weight loss at 5 and 7 days after tMCAo with respect to vehicle-treated rats (respectively $p<0.05$; $p<0.01$). Seven days after the ischemic insult, JNJ7777120 reduced the volume of the ischemic cortical damage (16.6±2.18 mm3, n=10 versus 28.7± 1.83 mm3, n=10 in vehicle group; $p<0.0005$) and the volume of the ischemic striatal damage (4.2±0.47 mm3, n=10 versus 10.1 ± 1.14 mm3, n=10 in vehicle group; $p<0.0001$). Moreover, seven days after ischemia, the chronic treatment with JNJ7777120, reduced gliosis evaluated by GFAP-staining (specific for astrocytes) and by IBA-1-staining (specific for microglia) both in ischemic cortex and striatum. JNJ7777120 decreased the plasma levels of the proinflammatory cytokines, IL-1β and TNF-α seven days after tMCAo.

Results indicate that the selective antagonist of histamine H4 receptor JNJ7777120, systemically and chronically administered after ischemia, reduces the ischemic brain damage and improves the neurological deficit. Results suggest that the H4 histamine receptor is a valuable pharmacological target after brain focal ischemia.

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