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YM872: A Selective, Potent and Highly Water-Soluble α-Amino-3-Hydroxy-5-Methylisoxazole-4-Propionic Acid Receptor Antagonist

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ABSTRACT

This review focuses on the *in vitro* and *in vivo* neuropharmacology of YM872, a potential neuroprotective agent currently undergoing clinical trials in the United States (trial name: AMPA Receptor Antagonist Treatment in Ischemic Stroke — ARTIST). Its neuroprotective properties in rats and cats with induced focal cerebral ischemia are described. YM872, [2,3-dioxo-7-(1*H*-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydroquinoxalin-1-yl]-acetic acid monohydrate, is a selective, potent and highly water-soluble competitive α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist. YM872 has a potent inhibitory effect on [^{3}H]AMPA binding with a K_i value of 0.096 μM. In contrast, YM872 has very low affinity for other ionotropic glutamate receptors. The solubility of YM872 is approximately 500 to 1000 times higher than that of the other competitive AMPA antagonists: YM90K, NBQX, or CNQX. The neuroprotective efficacy of YM872 was investigated in rats and cats subjected to permanent occlusion of the left middle cerebral artery. The animals were assessed either histologically or neurologically following ischemia. In rats with occluded middle cerebral artery (MCAO) YM872, by i.v. infusion, significantly reduced infarct volume measured at 24 h and 1 week after ischemia. Significant neuroprotection was maintained even when drug administration was delayed for up to 2 h after ischemia. In addition, YM872 significantly improved neurological deficit measured at 1 week after ischemia. In cats with MCAO YM872, by i.v. infusion, dose-dependently reduced infarct volume at 6 h after ischemia. YM872 produced no behavioral abnormalities and was not nephrotoxic. The evidence for the neuroprotective efficacy of YM872 suggests its therapeutic potential in the treatment of acute stroke in humans.