LSU Health Sciences Center NEW ORLEANS

School of Medicine

Neuroscience Center of Excellence

Chancellor's Award Lecture

in Neuroscience

Neuroprotective Effects of Guanosine Against Glutamatergic Excitotoxicity in Experimental Models of Brain Injury

Glutamate is the main excitatory neurotransmitter in mammalian CNS, essential for brain activities, as those involved in brain ontogeny and ageing, memory, and adaptation to the environment. However, high glutamate levels in synaptic cleft may be potentially neurotoxic, involved in the pathogenesis of various acute and chronic brain injuries (excitotoxicity). The main process responsible by maintaining the extracellular glutamate concentration below toxic levels, thus favoring the physiological glutamatergic tonus, is the glutamate uptake exerted by transporters located in neural cell membranes, mainly in astrocytes.

Our group has given strong evidence that the guanine-based purinergic system is effectively neuroprotective against glutamate toxicity, in acute and chronic animal models, both in vitro and in vivo studies. Although the administration of guanine derivatives (GD) exerts neuroprotection, our results strongly indicate that the active compound is the nucleoside guanosine (Guo). In vivo experimental studies, Guo administration protects against seizures induced glutamatergic agents, brain ischemia and glutamatergic pain. In vitro studies, Guo protects cell death in brain slices caused by in vitro ischemia.

Our group investigated the mechanisms implicated in this neuroprotection. We demonstrated that: i) Guo stimulates the astrocytic glutamate uptake (in astrocyte cultures and brain slices), the main process involved in endogenous neuronal protection; ii) QA induced-seizures decrease glutamate uptake by brain slices (ex-vivo) and this decrease is reversed by systemic Guo administration only when it acts as anticonvulsant; iii) Brain ischemia decreases glutamate uptake by hippocampal slices and systemic Guo administration prevents this decrease. Thus we propose that the stimulatory effect on glutamate uptake is involved in the neuroprotective actions of Guo. These results encourage further studies aiming to understand the involvement, in humans, of Guo in acute (hypoxia, ischemia, brain traumatism) and chronic (neurodegenerative diseases) brain diseases involving glutamate excitotoxicity.

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12:00 p.m.
Friday
April 27, 2012

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Neuroscience Center of Excellence Conference Room

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