LSU Health Sciences Center

Neuroscience Center of Excellence

FACULTY CANDIDATE

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Presenting

Cell Death Signals in Glutamate Receptor Degeneration

Glutamate is the major excitatory transmitter in the mammalian central nervous system (CNS) and plays an essential role in neural development, excitatory synaptic transmission, and plasticity. Immediately following ischemia, however, glutamate accumulates at synapses, resulting in extensive stimulation of its receptors that can eventually be toxic to neurons. Although excess stimulation of glutamate receptors contributes to neuronal degeneration, blocking them totally could be deleterious to animals and humans because targeting these receptors would block the receptor physiological action as well. Recently, we have explored an idea approach for treatment of neurological disorders by targeting at the specific glutamate receptor "cell death signals" whereby the pathological effects of glutamate receptors is selectively blocked, leaving the physiological action unaffected. In our earlier work, we have identified that transient global ischemia impairs the ADAR2-dependent RNA editing of synaptic AMPA receptor subunit GluR2 at Q/R site. Combined with gene targeting with electrophysiological studies, we have shown that impairment of the GluR2 Q/R site editing induces injurious Ca^{2+} entry into vulnerable neurons through AMPA receptor channels. Significantly, engineering vulnerable neurons with expression of Ca^{2+}-impermeable AMPA receptor channels prevents neurons from forebrain ischemic insults (Liu et al, Neuron, 43: 43-55, 2004; Peng et al., Neuron, 49: 719-733, 2006). In addition to these synaptic AMPA receptor signals, we have also explored the cell death signals that link to the synaptic NMDA receptors. Specifically, we have found that transient global ischemia induces prolonged activation of cycline-dependent kinase 5 (CdK5), which in turn phosphorylates synaptic NMDA receptor NR2A subunit at Ser-1232 and enhances NMDA receptor channel activity. Genetic inactivation of Cdk5 blocks ischemic enhancement of synaptic NMDA receptor and protects against ischemic injury. Thus, we conclude that covalent modulation of synaptic NMDA receptors by Cdk5 is the primary intracellular event underlying the selective degeneration of neurons (Wang et al., Nature neuroscience, 6: 1039-1047, 2003).

Monday May 26, 2008 11:30am,
8th Floor Neuroscience Center Conference Room,
LSU Lion's Building, 2020 Gravier Street, New Orleans