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Ashpole, Nicole M.

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Abstract:

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a critical modulator of synaptic function, plasticity, and learning and memory. In neurons and astrocytes, CaMKII regulates cellular excitability, cytoskeletal structure, and cell metabolism. A rapid increase in CaMKII activity is observed within the first few minutes of ischemic stroke in vivo; this calcium-dependent process is also observed following glutamate stimulation in vitro. Activation of CaMKII during pathological conditions is immediately followed by inactivation and aggregation of the kinase. The extent of CaMKII inactivation is directly correlated with the extent of neuronal damage. The studies presented here show that these fluctuations in CaMKII activity are not correlated with neuronal death; rather, they play a causal role in neuronal death. Pharmacological inhibition of CaMKII in the time immediately surrounding glutamate insult protects cultured cortical neurons from excitotoxicity. Interestingly, pharmacological inhibition of CaMKII during excitotoxic insult also prevents the

aggregation and prolonged inactivation of the kinase, suggesting that CaMKII activity during excitotoxic glutamate signaling is detrimental to neuronal viability because it leads to a prolonged loss of CaMKII activity, culminating in neuronal death. In support of this, CaMKII inhibition in the absence of excitotoxic insult induces cortical neuron apoptosis by dysregulating intracellular calcium homeostasis and increasing excitatory glutamate signaling. Blockade of the NMDA-receptors and enzymatic degradation of the extracellular glutamate signal affords neuroprotection from CaMKII inhibition-induced toxicity. Co-cultures of neurons and glutamate-buffering astrocytes also exhibit this slow-induced excitotoxicity, as CaMKII inhibitors reduce glutamate uptake within the astrocytes. CaMKII inhibition also dysregulates calcium homeostasis in astrocytes and leads to increased ATP release, which was neurotoxic when applied to naïve cortical neurons. Together, these findings indicate that during aberrant calcium signaling, the activation of CaMKII is toxic because it supports aggregation and prolonged inactivation of the kinase. Without CaMKII activity, neurons and astrocytes release stores of transmitters that further exacerbate neuronal toxicity.

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