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Zinc-induced Neurotoxicity and Its Role in Brain Diseases

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Mammalian brian contains substantial amounts of chelatable zinc in presynaptic vesicles of certain glutamatergic terminals. The synaptic zinc is released with intense neuronal activity, suggesting its role in synaptic transmission. However, in pathological conditions, zinc may get released too excessively, which may contribute to neuronal death as shown in cortical cultures. Recently, we reported that translocation of zinc indeed may play a key role in selective neuronal death following transient global ischemia in rats. First, there is one-to-one correlation between zinc accumulation in neurons and their death in hippocampus and other vulnerable brain areas. Second, zinc translocation precedes neuronal death. Third, blockade of zinc translocation with an extracellular chelator, CaEDTA, markedly reduces selective neuronal death in all the brain areas. These results clearly demonstrate that zinc translocation is one of the key mechanisms of ischemic neuronal death. In addition to global ischemia, we recently found that similar zinc translocation occurs in seizures and focal ischemia, extending the potential role of zinc as a neurotoxin to several important brain diseases. As to its toxic mechanism, we found that zinc induces neuronal death mainly by atypical necrosis, which is largely mediated by oxidative stress. Our preliminary data suggest that activation of PKC may link zinc influx to free radical generation and cell death.

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