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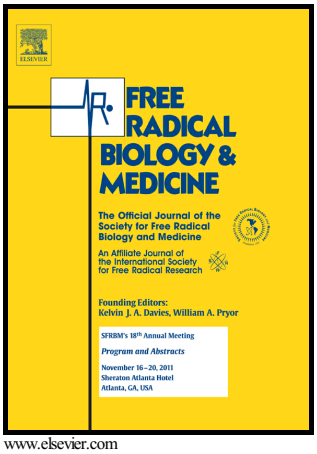

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Potentiation of Glutathione Loss and Nerve Cell Death by the Transition Metals Iron and Copper: Implications for Age-Related Neurodegenerative Diseases

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Abstract

There is growing evidence for alterations in iron and copper homeostasis during aging that are exacerbated in neurodegenerative diseases such as Alzheimer's disease (AD). However, how iron and copper accumulation leads to nerve cell damage in AD is not clear. In order to better understand how iron and copper can contribute to nerve cell death, a simple, well-defined *in vitro* model of cell death, the oyxtosis assay, was used. This assay uses glutamate to induce glutathione (GSH) depletion which initiates a form of oxidative stress-induced programmed cell death. A reduction in GSH is seen in the aging brain, is associated with cognitive dysfunction and is accelerated in many CNS diseases including AD. It is shown that both iron and copper potentiate both GSH loss and cell death in this model. Iron and copper also potentiate cell death induced by other GSH depleters but not by compounds that induce oxidative stress via other pathways. At least part of the effects of copper on GSH are related to its ability to reduce the activity of glutamate cysteine ligase, the rate limiting enzyme in GSH synthesis. Both metals also