Why iron and copper may be harmful to the aging brain

Similar to other organs, brain function declines with age. Furthermore, age is the single greatest risk factor for Alzheimer's disease as well as other neurodegenerative diseases. Both iron and copper increase in the brain with aging and are further elevated in Alzheimer's disease and other neurodegenerative diseases suggesting that they could contribute to the decrease in cognitive function that is the hallmark of the disease. How iron and copper accumulation lead to nerve cell damage in aging and Alzheimer's disease is not clear at this time. Both iron and copper are metals that are able to undergo reversible oxidation/reduction reactions. While this property is critical to many of their important biological functions, it also means that they can readily generate reactive oxygen species thereby leading to increases in oxidative stress. In addition, there is evidence for other activities of these metals that could contribute to the development and progression of Alzheimer's disease. In order to better understand how iron and copper can contribute to nerve cell death we turned to a simple, well-defined cell culture model of cell death, the oxytosis assay. This assay uses glutathione (GSH) depletion to initiate a form of oxidative stress-induced cell death. GSH is the major, endogenous intracellular antioxidant. A reduction in GSH is seen in the aging brain and is accelerated in many CNS diseases including Alzheimer's disease. Importantly, GSH loss in the brain is associated with impairments in cognitive function. Because of the generality of the toxicity pathway in oxytosis and its mechanistic association with aging and age-associated neurodegenerative diseases such as Alzheimer's disease, it is an excellent model for studying pathways involved in nerve cell death.

In this study, I found that low, physiological concentrations of both iron and copper potentiated both GSH loss and cell death in the oxytosis model. In contrast, iron and copper did not potentiate cell death induced by compounds that directly cause oxidative stress such as potent oxidants like hydrogen peroxide. Both metals appeared to act at multiple steps in the oxytosis cell death pathway to enhance cell death but their effects were not identical. For example, although both iron and copper potentiated the loss of GSH in the oxytosis assay, at least some of the effects of copper on GSH levels were related to its ability to reduce the activity of the rate limiting enzyme in GSH synthesis. In contrast, iron had no effect on the activity of this enzyme. Both metals also altered several signaling pathways involved in modulating nerve cell death. Importantly, an inhibitor of one of these pathways was able to prevent the potentiation of nerve cell death by both iron and copper, independent of effects on GSH levels. Together, these results suggest that *in vivo* iron and copper may specifically enhance nerve cell death under conditions where GSH levels are reduced. This could have significant implications for the aging brain where the lower levels of GSH could put nerve cells at significantly greater risk to the harmful effects of iron or copper. Whether similar effects are seen with other types of brain cells remains to be determined but is an important question for further studies.

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