Changes in Brain Iron and Iron Handling Proteins after Excitotoxicity

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Abstract

Insights into iron transport and trafficking in the normal and diseased brain could lead to better understanding of the mechanisms of iron overload and free radical damage in neuropsychiatric disorders. An increasing amount of iron is found in the degenerating hippocampus with time, after injection of the excitotoxin, kainic acid in rats. Iron is originally present in the ferric (Fe3+) form, but with the passage of time, it is found more and more in the ferrous (Fe2+) form. An increase in the iron-storage protein, ferritin, is initially seen in the hippocampus, but ferritin levels decreased at long time intervals, e.g. 2 months after kainate injury. There is thus a widening mismatch between increasing iron levels and decreasing ferritin levels. Ferrous iron that is not bound or stored in ferritin is particularly effective in catalyzing free radical damage via the Fenton reaction. The increase in iron in the degenerating hippocampus at long time intervals after kainate induced excitotoxicity is not accompanied by an increase in heme oxygenase-1 (HO-1) expression. This indicates that the increased iron did not arise as a result of breakdown of heme proteins. Rather, an increase in iron influx proteins, duodenal cytochrome b (DCYTB1) and divalent metal transporter 1 (DMT1), are found in astrocytic end-feet around blood vessels, suggesting that iron could be transported into the brain tissue. Such an increased influx of divalent cations into the brain after kainate excitotoxicity is shown in rats that were fed with lead and cadmium in the drinking water (with the Pb2+ and Cd2+ ions acting as tracers for divalent metal ions). On the other hand, knockdown of a protein that removes iron from the brain, ceruloplasmin, increased iron levels and free radical damage in the degenerating hippocampus. This suggests a protective role of ceruloplasmin. Interestingly, intravenous infusion of recombinant ceruloplasmin reduced iron levels and oxidative stress in lesioned areas of the brain. An increase in the iron-siderophore binding protein, lipocalin 2 (LCN2) is also found the degenerating hippocampus. This may be important in ferrying iron ions that have crossed the blood-brain barrier, to neurons, which normally express the LCN2 receptor (LCN2R).

Keywords: *Iron, Neuropsychiatruc disorders, Influx protein, Excitotoxicity, Astrocytic, Ceruloplasmin*