An oxidative stress-mediated positive-feedback iron uptake loop in neuronal cells

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Intracellular reactive iron is a source of free radicals and a possible cause of cell damage. In this study, we analyzed the changes in iron homeostasis generated by iron accumulation in neuroblastoma (N2A) cells and hippocampal neurons. Increasing concentrations of iron in the culture medium elicited increasing amounts of intracellular iron and of the reactive iron pool. The cells had both IRP1 and IRP2 activities, being IRP1 activity quantitatively predominant. When iron in the culture medium increased from 1 to 40 ?M, IRP2 activity decreased to nil. In contrast, IRP1 activity decreased when iron increased up to 20 ?M, and then, unexpectedly, increased. IRP1 activity at iron concentrations above 20 ?M was functional as it correlated with increased 55Fe uptake. The increase in IRP1 activity was mediated by oxidative-stress as it was largely abolished by N-acetyl-L-cysteine. Culturing cells with iron resulted in proteins and DNA modifications. In summary, iron uptake by N2A cells and h