Regulation of iron homeostasis through beta-amyloid precursor processing in neuronal health and disease.

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Research Abstract

The life essential element iron is required as a cofactor in central nervous system metabolic processes, but unbound iron catalyzes the production of toxic reactive oxygen species. Neuronal iron accumulation is a common pathological feature in the cortex in Alzheimer’s disease (AD), the substantia nigra (SN) in Parkinson’s disease (PD), and the tauopathies. Since too much or too little iron can compromise cell viability, cellular iron homeostasis is tightly regulated. Ferroxidases, oxidize Fe2+ to Fe3+, and are essential for maintaining intracellular iron homeostasis. A deficiency in the surface presented ferroxidase leads to toxic iron accumulation and degeneration. Ferroxidase activities in the brain may fail with aging and a range of neurodegenerative disorders (ND), possibly contributing to disease pathogenesis.

My group has discovered that the ferroxidase activity of ?-amyloid precursor protein (APP) is essential for neuronal iron efflux and inhibited APP ferroxidase activity parallels iron accumulation in some ND. Disruption in the correct localization of a ferroxidase may be fundamental in the disease process. Of relevance, neuronal anterograde transport of APP requires tau and we have recently shown decreased tau expression impairs the presence of cell surface APP leading to inefficient efflux of iron and intensifying the risk of excitotoxicty within the region via intraneuronal iron accumulation.

Primary aims will elucidate the role of APP trafficking and processing on iron efflux regulation within general neurobiology and investigate this mechanism in iron accumulating age- and pathologically- affected neurons already known to have problems with APP, tau and excitotoxicity.

Some current therapeutic compounds for ND are proposed to work via restoring metal homeostasis. A final aim will determine if these compounds, as well as a number of novel derivatives, work through a pathway that restores APP to its correct function in neuronal iron efflux.

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