SUPPRESSION OF B-AMYLOID PRECURSOR PROTEIN BY NITRIC OXIDE MAY LEAD TO TOXIC NIGRAL IRON ACCUMULATION IN PARKINSON'S DISEASE

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Introduction: Parkinson's disease (PD) is typified by Substantia Nigra (SN) neuron degeneration, toxic iron elevation and protein nitration. We recently demonstrated that the Amyloid Precursor Protein (APP) has ferroxidase activity that facilitates iron export. APP possesses an iron responsive element (IRE) on 5' untranslated mRNA; binding of iron responsive binding proteins (IRP) inhibits translation of APP. IRP binding is dictated by iron and nitric oxide (NO) concentrations. APP activity is reduced in Alzheimer's disease which may contribute to the iron accumulation pathology.

Aim: Investigate if iron accumulation in PD is contributed by APP failure in human PD tissue and in an MPTP PD animal model.

Methods: Iron and APP were measured in SN from human control and PD post mortem brains and at timed intervals after administration of MPTP to mice. To determine if restoration of APP protected against MPTP toxicity:

(1) mice over-expressing APP (Tg2576) and

(2) mice treated with neuronal nitric oxide synthase inhibitor, 7-nitroindazole, were intoxicated with MPTP.

Nigral iron content and nigral cell number were measured.

Results: Iron was elevated in PD SN with a coincidental decrease in APP levels and activity. MPTP intoxication caused iron accumulation correlating with APP depression over the timecourse. APP overexpression (Tg2576) protected against iron elevation and toxicity. 7-nitroindazole inhibited MPTP induced NO elevation which restored APP levels, prevented iron accumulation and protected against toxicity.

Conclusions: NO elevation in PD is likely upstream in a pathway that causes APP failure, iron elevation and eventual neuronal degeneration.