L-DOPA INDUCES CHANGES IN METHYLATION METABOLITES, PP2A DEMETHYLATION AND HYPER-PHOSPHORYLATION OF TAU PROTEIN IN MOUSE BRAIN

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Introduction: L-dopa is metabolized by catechol-O-methyltransferase to 3-O-methyl-dopa, a reaction which requires S-adenosylmethionine (SAM), and produces S-adenosylhomocysteine (SAH). In preclinical and clinical studies, the administration of L-dopa is associated with decreased SAM and increased SAH concentrations in tissues, CSF and blood. We have previously shown that a reduced SAM/SAH ratio is associated with the down-regulation of Ser/Thr protein phosphatase 2A (PP2A) methylation and concomitant increase in the phosphorylation of Tau, a major brain PP2A substrate.

Aims: To study the effect of L-dopa on the methylation of PP2A and phosphorylation of Tau protein.

Methods: Groups of male C57BL/6 mice received acute intraperitoneal injections of either saline or L-dopa in combination with a peripheral amino acid decarboxylase inhibitor. Brain tissue was obtained for HPLC analysis of methylation metabolites and PP2A and phosphorylated Tau by western blot analysis.

Results: SAM levels were significantly decreased in the striatum and other brain regions; whereas SAH levels were significantly increased in all regions, except the striatum. L-dopa treatment significantly decreased PP2A methylation, and markedly increased Tau phosphorylation in all brain regions.

Conclusions: Methylation of PP2A is regulated by the tissue concentration of SAM and SAH. Alterations in PP2A methylation status, is associated with enhanced phosphorylation of Tau in brain tissue. Our results suggest that L-dopa therapy may promote the accumulation of phosphorylated Tau in the CNS. Since phospho-Tau is toxic to the CNS, and is associated with Alzheimer's disease pathology, the long term use of L-dopa in Parkinson's disease may promote a decrease in cognitive function.