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Parkinson's disease-like effects of S-adenosyl-L-methionine: effects of L-dopa.

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5-HT = serotonin

The major symptoms of Parkinson's disease (PD) are due to degeneration of the nigrostriatal pathway and depletion of dopamine (DA). Tyrosine hydroxylase (TH), norepinephrine (NE), serotonin (5-HT), and melanin pigments are also decreased and acetylcholinergic activity increased. Biochemically, increased methylation can cause the depletion of DA, NE, 5-HT, and melanin pigments and also an increase of acetylcholine; thus, increased methylation can present a biochemical picture that resembles the biochemical changes that occur in PD. During the therapy of PD with L-dopa, it is well known that L-dopa reacts avidly with S-adenosyl-L-methionine (SAM), the biologic methyl donor, to produce 3-O-methyl-dopa. Correspondingly, L-dopa has been shown to deplete the concentration of SAM, and SAM has been found to induce PD-like motor impairments in rodents; therefore, an excess of SAM-dependent methylation may be associated with Parkinsonism. To further study the effects of methylation, SAM was injected into the lateral ventricle of rats. SAM caused tremors, rigidity, abnormal posture, and dose-related hypokinesia. Doses of 9.38, 50, and 400 nM/rat caused 61.9, 73.4, and 94.8% reduction, respectively, of motor activity. A 200-mg/kg IP dose of L-dopa, given before 50 nM SAM, blocked the SAM-induced hypokinesia. SAM also caused a decrease in TH immunoreactivity, apparent degeneration of TH-containing fibers, loss of neurons, and the accumulation of phagocytic cells in the substantia nigra. These results showed that excess SAM in the brain, probably due to its ability to increase methylation, can induce symptoms that resemble some of the changes that occur in PD.

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