

## Long-Term L-DOPA Treatment Causes Indiscriminate Increase in Dopamine Levels at the Cost of Serotonin Synthesis in Discrete Brain Regions of Rats

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**Abstract** (1) The treatment of choice for Parkinson's disease (PD) is 3,4-dihydroxyphenylalanine (L-DOPA) with peripheral decarboxylase inhibitor, but long-term therapy leads to motor and psychiatric complications. In the present study we investigated 5-hydroxytryptamine (5-HT) and dopamine concentrations in serotonergic and dopaminergic nuclei following chronic administration of L-DOPA to find whether the neurotransmitter synthesis in these brain areas are compensated. (2) Rats were administered L-DOPA (250 mg/kg) and carbidopa (25 mg/kg) daily for 59 and 60 days, and killed on the 60th day, respectively at 24 h and 30 min after the last dose. L-DOPA, norepinephrine, 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), dopamine, homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DOPAC) were measured in striatum, nucleus raphe dorsalis (NRD), nucleus accumbens (NAc), substantia nigra, cerebellum, and cortex employing HPLC-electrochemical procedure. (3) Prolonged treatment of L-DOPA caused depression in the animals as revealed in a forced swim test. Serotonin content was significantly decreased in all brain regions studied 30 min after long-term L-DOPA, except in NAc. The cortex and striatum showed lowered levels of this indoleamine 24 h after 59 doses of L-DOPA. Dopamine, HVA, and DOPAC concentrations were significantly higher in all the regions studied after 30 min, and in the cerebellum after 24 h of L-DOPA. The levels of DOPAC were elevated in all the brain areas studied 24 h after prolonged L-DOPA treatment. (4) The present results suggest that long-term L-DOPA treatment results in significant loss of 5-HT in serotonergic and dopaminergic regions of the brain. Furthermore, while L-DOPA metabolism per se was uninfluenced, dopamine synthesis was severely impaired in all the regions. The imbalance of serotonin and dopamine formation may be the cause of overt cognitive, motor, and psychological functional aberrations seen in parkinsonian patients following prolonged L-DOPA treatment.

**Keywords** Parkinson's disease · Forced swim test · Dopamine and serotonin synthesis · Motor behavior · Nucleus raphe

5-HT = serotonin

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