Medical Applications of Fullerene Nanostructures. Systemic Treatment by C_3 Carboxyfullerene Rescues Dopaminergic Synapses and Decreases Parkinsonian Symptoms in 6-Hydroxydopamine Lesioned Rats

[1]Dugan, L, [1]Quick, K [4]Kang, UJ, [4]Nakamura, K, [1,2]Lovett, EG, and [3]O'Malley, K.

[1]Department of Neurology and Center for the Study of Nervous System Disease, [2]Department of Chemistry, and [3]Department of Cell Biology, Washington University School of Medicine, St. Louis, MO, and [4]Department of Neurology, University of Chicago Medical School, Chicago, IL.

Parkinson's disease (PD) is an important cause of disability in both young and older individuals. Although advances have been made in the symptomatic treatment of PD, no treatment has yet been shown to stop the progressive loss of dopaminergic neurons and nerve terminals that underlie the disease. Because the C_3 malonic acid C_{60} isomer has been shown to be neuroprotective in other model systems, we tested this compound in a rat model of PD. Fisher 344 rats had Alzet mini-osmotic pumps placed intraperitoneally either just before intrastriatal injection of 6-hydroxydopamine (6-OHDA) (Group 1), or 24 h prior to lesioning (Group 2). Group 1 received 10 mg/kg/day, and group 2 received 15 mg/kg/day C_3. Control rats received color-matched solutions of food coloring. Group 1 had a single injection of 6-OHDA, resulting in loss of dopaminergic nerve terminals, but minor drop-out of dopaminergic neurons, so group 2 was lesioned with 2 sequential intrastriatal injections of 6-OHDA at 30 min. intervals to increase the level of injury. Rats were then tested at weekly intervals for hemi-Parkinsonism (spontaneous paw stepping), and were sacrificed at 3 weeks for tyrosine hydroxylase (TH) immunocytochemistry of the striatum and substantia nigra. Preservation of TH-positive dopaminergic nerve terminals in the striatum was determined using densitometry. C_3-treated rats in both groups showed a significant preservation of striatal nerve terminals (15% for Group 1, 24% for Group 2) by t-test ($p<0.05$). C_3 also rescued TH positive (dopaminergic neurons) in the substantia nigra, as assessed by unbiased stereology cell counts. Spontaneous paw stepping was improved by 29% in C_3-treated animals in Group 1, and was nearly 80% of the unlesioned ("normal") side. Behavioral data for Group 2 are not yet available. These data suggest that C_3 can protect the dopaminergic system, and preserve behavior in this rat model of PD. Because a pilot study testing C_3 at 3 mg/kg/day indicated that this dose might also be neuroprotective in this PD model, future studies are planned to evaluate lower doses of C_3.

Supported by NIH NS 37688 (LLD) and MH 45330 (KOM).