Buckminsterfullerene C60 derivatives as neuroprotective catalytic antioxidants

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Development of small molecules capable of eliminating reactive oxygen species, such as superoxide and H2O2, has been an important recent focus of biomedical research. We previously reported that malonic acid derivatives of buckminsterfullerene (C60) exhibit superoxide scavenging properties, as determined by electron paramagnetic resonance (EPR) spectroscopy. We have subsequently determined that one such C60 derivatives, the e,e,e tris malonic acid isomer (C3) is a catalytic scavenger of both superoxide and hydrogen peroxide, with a ki for superoxide of 3 x 106. We found that treatment of SOD2 -/- mice, which develop progressive mitochondrial dysfunction and die soon after birth, with C3 extended survival of the pups by 300% ($p<0.05$). In addition, FALS (familial ALS G93A G1) mice treated with C3 not only show a modest increase in survival, as previously reported, but have lower ambient levels of superoxide in spinal motor neurons, as assayed by cell-specific dihydroethidium oxidation and confocal fluorescence imaging. This is consistent with pharmacokinetic studies using 14C - C3 which show that C3 can cross the blood-brain barrier. Trials of C3 are ongoing in both rat and primate models of Parkinson's disease, with pilot data from rats lesioned with intrastriatal 6-hydroxydopamine suggesting significant protection of dopaminergic nerve terminals and neurons. Water-soluble derivatives of C60 molecule may represent an alternative class of biologically attractive antioxidants with promising neuroprotective properties.

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