Central Nervous System Effects of Celastrol, a Potent Antioxidant and Antiinflammatory Agent

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ABSTRACT

Evidence is accumulating that neuronal degeneration in the brains of patients with Alzheimer’s disease (AD) is accompanied by markers of chronic inflammation. These markers include the activation of microglia and the production of the proinflammatory cytokines TNF-α and IL-1β. Activated microglia release superoxide, which generate reactive oxygen species in the presence of redox-active metals. These, in turn, oxidize lipids to produce 4-hydroxynonenenal and other reactive products. Lipid peroxidation adducts as well as other oxidative modifications, including advanced glycation end products and free carbonyls, are observed in the brains of people with AD. In macrophage-lineage cells and in endothelial cells, proinflammatory cytokines induce the expression of an inducible isoform of nitric oxide synthase, which releases relatively high levels of nitric oxide over a long period of time. Nitric oxide and superoxide combine to form peroxynitrite, which damages neurons and other cell types. A marker of peroxynitrite generation is nitrotyrosine, which has been used to demonstrate widespread peroxynitrite-mediated damage in AD brains.

If each of the processes described above contributes to the pathogenesis of AD, an effective treatment should: (1) suppress microglial activation; (2) inhibit the production of proinflammatory cytokines; (3) display antioxidant activity; and (4) selectively inhibit the production of NO by the inducible form of NO synthase. The compound should not inhibit constitutive NO synthases in neuronal or endothelial cells, which are required to maintain neuronal function and vascular perfusion.

This review describes a plant-derived small molecule, celastrol, which in low concentrations displays all the required activities. Furthermore, when administered to rats in low doses, celastrol significantly improves their performance in memory, learning and psychomotor activity tests. The potent antioxidant and antiinflammatory activities of celastrol and its effects on cognitive functions suggest that the drug may be useful to treat neurodegenerative diseases accompanied by inflammation and oxidation, such as AD and Parkinson’s disease.