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Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease.

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Abstract: The neurohormone melatonin has been reported to exert anti-beta-amyloid aggregation, antioxidant, and anti-inflammatory actions in various in vitro and animal models. To comprehensively determine the potential for long-term melatonin treatment to protect Alzheimer's transgenic mice against cognitive impairment and development of beta-amyloid (A beta) neuropathology, we administered melatonin (100 mg/L drinking water) to APP + PS1 double transgenic (Tg) mice from 2-2.5 months of age to their killing at age 7.5 months. A comprehensive behavioral battery administered during the final 6 weeks of treatment revealed that Tg mice given melatonin were **protected from cognitive impairment in a variety of tasks of working memory, spatial reference learning/memory, and basic mnemonic function**; Tg control mice remained impaired in all of these cognitive tasks/domains. Immunoreactive Abeta deposition was significantly reduced in hippocampus (43%) and entorhinal cortex (37%) of melatonin-treated Tg mice. Although soluble and oligomeric forms of Abeta1-40 and 1-42 were unchanged in the hippocampus and cortex of the same melatonin-treated Tg mice, their plasma Abeta levels were elevated. These Abeta results, together with our concurrent demonstration that melatonin suppresses Abeta aggregation in brain homogenates, are consistent with a melatonin-facilitated removal of Abeta from the brain. Inflammatory cytokines such as tumor necrosis factor (TNF)-alpha were decreased in hippocampus (but not plasma) of Tg+ melatonin mice. Finally, the cortical mRNA expression of three antioxidant enzymes (SOD-1, glutathione peroxidase, and catalase) was significantly reduced to non-Tg levels by long-term melatonin treatment in Tg mice. Thus, **melatonin's cognitive benefits could involve its anti-A beta aggregation, anti-inflammatory, and/or antioxidant properties.** Our findings provide support for long-term melatonin therapy as a primary or complementary strategy for abating the progression of Alzheimer disease.

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