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Team finds melatonin delays ALS symptom onset and death in mice

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Melatonin injections delayed symptom onset and reduced mortality in a mouse model of the neurodegenerative condition amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, according to a new study by researchers at the University of Pittsburgh School of Medicine. In a report published online ahead of print in the journal *Neurobiology of Disease*, the team revealed that receptors for melatonin are found in the nerve cells, a finding that could launch novel therapeutic approaches.

Annually about 5,000 people are diagnosed with ALS, which is characterized by progressive muscle weakness and eventual death due to the failure of respiratory muscles, said senior investigator Robert Friedlander, M.D., UPMC Endowed Professor of neurosurgery and neurobiology and chair, Department of Neurological Surgery, Pitt School of Medicine. But the causes of the condition are not well understood, thwarting development of a cure or even effective treatments.

Melatonin is a naturally occurring hormone that is best known for its role in sleep regulation. After screening more than a thousand FDA-approved drugs several years ago, the research team determined that melatonin is a powerful antioxidant that blocks the release of enzymes that activate apoptosis, or programmed cell death.

"Our experiments show for the first time that a lack of melatonin and melatonin receptor 1, or MT1, is associated with the progression of ALS," Dr. Friedlander said. "We saw similar results in a Huntington's

disease model in an earlier project, suggesting similar biochemical pathways are disrupted in these challenging neurologic diseases."

Hoping to stop neuron death in ALS just as they did in Huntington's, the research team treated mice bred to have an ALS-like disease with injections of melatonin or with a placebo. Compared to untreated animals, the melatonin group developed symptoms later, survived longer, and had less degeneration of motor neurons in the spinal cord.

"Much more work has to be done to unravel these mechanisms before human trials of melatonin or a drug akin to it can be conducted to determine its usefulness as an ALS treatment," Dr. Friedlander said. "I suspect that a combination of agents that act on these pathways will be needed to make headway with this devastating disease."

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