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Melatonin delays onset, reduces deaths in mouse model of Huntington's disease

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Melatonin, best known for its role in sleep regulation, delayed the onset of symptoms and reduced mortality in a mouse model of Huntington's disease, say researchers at the University of Pittsburgh School of Medicine and Harvard Medical School. Their findings, published today in the *Journal of Neuroscience*, show for the first time that certain receptors for the hormone reside in the mitochondria, and that there are fewer of them both in affected mice and human brains.

Huntington's disease (HD) is an inherited, lethal disorder of involuntary movement, progressive loss of intellectual function and emotional problems, explained senior investigator Robert M. Friedlander, M.D., chair, Department of Neurological Surgery and UPMC Endowed Professor of neurosurgery and neurobiology. A mutant protein, called huntingtin, kills neurons in the brain's striatum and then the cortex.

"In earlier work, we screened more than 1,000 FDA-approved drugs to see which ones could block the release of a small protein called cytochrome c from the mitochondria to interrupt a key step in a chain reaction known as apoptosis, or programmed cell death," he said. "Melatonin, which we know to be a potent antioxidant, was one of the agents that could do this in the test tube, but we needed to determine if it would also be neuroprotective in a transgenic animal model of HD."

For the study, the researchers injected HD mice daily with either melatonin or a placebo, evaluated them weekly for signs of the disease, and examined their brain tissue after death. They found that melatonin

treatment delayed the onset of disease by 19 percent, slowed disease progression and prolonged life span by 18 percent.

The researchers determined also that type 1 melatonin (MT1) receptors are found on mitochondria, which supplies energy for the cell, and that they were depleted in both HD-affected human and mice brain tissue samples. In lab experiments, administration of an agent that prevents melatonin from binding to the MT1 receptor encouraged cell death, while gene-engineering to increase the number of receptors led to greater neuroprotection, even when melatonin levels were normal.

"Extra melatonin might help fill all the available MT1 receptors, allowing the hormone to counter the programmed cell death cascade and thus protect neurons," Dr. Friedlander said. "This suggests that melatonin or similar agents that influence the MT1 receptor have potential as an HD treatment, which we've never had before."

Low levels of circulating melatonin have been seen in other neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. The research team is continuing to explore what might cause the loss of MT1 receptors and to assess other drugs that block cytochrome c and cell death.

"Perhaps the best approach will be to develop a cocktail of drugs that target different molecular pathways that are responsible for creating HD," Dr. Friedlander said. "We plan to see if combining different agents leads to a greater impact on disease progression and mortality."

Provided by University of Pittsburgh

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