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PD-like sleep and motor problems observed in alpha-synuclein mutant mice

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The presence of Lewy bodies in nerve cells, formed by intracellular deposits of the protein α-synuclein, is a characteristic pathologic feature of Parkinson's Disease (PD). In the quest for an animal model of PD that mimics motor and non-motor symptoms of human PD, scientists have developed strains of mice that overexpress α-synuclein. By studying a strain of mice bred to overexpress α-synuclein via the Thy-1 promoter, scientists have found these mice develop many of the age-related progressive motor symptoms of PD and demonstrate changes in sleep and anxiety. Their results are published in the latest issue of *Journal of Parkinson's Disease*.

PD is the second most common neurodegenerative disorder in the United States, affecting approximately one million Americans and five million people worldwide. Its prevalence is projected to double by 2030. The most obvious symptoms are movement-related, such as involuntary shaking and muscle stiffness; non-motor symptoms, such as increases in anxiety and sleep disturbances, can appear prior to the onset of motor symptoms. Although the drug levodopa can relieve some symptoms, there is no cure – intensifying the pressure to find an animal model that can help clarify the pathological processes underlying human PD and find new medications to treat the pathology and/or relieve symptoms.

Investigators at the National Institute on Aging compared wild type mice with specially bred mice that were transgenic for the A53T mutation of the human α-synuclein (SNCA) gene under the control of a human thymus cell antigen 1, theta (THY-1) promoter. As the mice aged, their

motor performance on a rotarod test (which measures how long the mouse can remain on a rotating rod) became impaired and the length of their strides were significantly shorter than the wild type control mice.

The study also found that SNCA mice displayed fragmented nighttime activity patterns compared to wild type controls and appeared to have a reduced overall sleep time. "Despite the prevalence of abnormal sleep patterns in PD, very few studies to date have outlined sleep disturbances in animal models of PD," says Sarah M. Rothman, PhD, a researcher with the National Institute on Aging, in Baltimore, MD.

Many PD patients typically show an increase in anxiety and depression, and in this respect the SNCA mouse model did not replicate the human condition. SNCA mice displayed an early and significant decrease in anxiety-like behavior that persisted throughout their lifespan, as shown by both open field and elevated plus maze tests (in which mice have the choice of spending time in open or closed arms of a maze). Other rodent models that utilize changes in expression of α-synuclein have also reported lower anxiety levels. The authors suggest that higher levels of serotonin found in the hypothalamus of the SNCA mice may be associated with the reduced anxiety observed.

The authors say it is important to remember that the SNCA "model utilizes the presence of a mutation that only occurs very rarely in PD. While all PD patients display α-synuclein pathology, they do not all express the mutated form of the protein," says Dr. Rothman.

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