Mouse model of Parkinson's reproduces nonmotor symptoms

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The classic symptoms of Parkinson's disease involve tremor, stiffness and slow movements. Over the last decade, neurologists have been paying greater attention to non-motor symptoms, such as digestive and sleep problems, loss of sense of smell and depression.

A genetically engineered mouse reproduces many of the non-motor symptoms associated with Parkinson's disease seen in humans and sheds light on their possible causes, Emory scientists report in the June 24 issue of the *Journal of Neuroscience*.

"These mice are very useful for studying the major non-motor symptoms of Parkinson's because they have them together as a package," says Gary Miller, PhD, professor of environmental and occupational health in the Rollins School of Public Health and neurology and pharmacology in the School of Medicine at Emory University.

The mice were engineered to be deficient in VMAT2 (vesicular monoamine transporter 2), a protein that helps to store the brain chemicals Parkinson's patients gradually lose the ability to produce.

Miller and his colleagues previously published a description of the neurodegeneration of the VMAT2-deficient mice, but focusing on the part of the brain associated with Parkinson's motor symptoms. Graduate student Tonya Taylor is first author of the 2009 paper on non-motor symptoms.

The VMAT2-deficient mice could become research tools in the search for medications to treat non-motor symptoms, Miller says. Most non-motor symptoms do not respond to L-dopa, the medication most commonly given to people with Parkinson's, he notes.

L-dopa can be converted by the body into the neurotransmitter dopamine, the lack of which is responsible for the main motor difficulties in Parkinson's.

Within brain cells, VMAT2 packages neurotransmitters such as dopamine, norepinephrine, and serotonin into vesicles, containers that deliver chemical messages to other cells. In the VMAT2-deficient mice, the improperly stored neurotransmitters are thought to damage brain cells.

In other mouse models of Parkinson's, scientists use chemicals such as the pesticide rotenone or the neurotoxin MPTP to kill the brain cells analogous to those that patients gradually lose, or they have the mice overproduce proteins that aggregate into toxic clumps.

The VMAT2-deficient mice have aggregated proteins in their brains, which appears to be a byproduct of improper neurotransmitter storage, Miller says.

The Emory scientists showed that the mice have delayed emptying of the stomach, they fall asleep more quickly and they have a loss of the sense of smell.

In tests scientists use to model depression, aged VMAT2-deficient mice display signs of depression and respond to classical antidepressants. They also showed greater reluctance to explore elevated, lighted places, a measure of anxiety.

The mice have normal vision, sense of touch and muscle strength, qualities Miller says are important to show that the mice are not generally sick - a difference from some toxin models.

More information: Non-motor symptoms of Parkinson's disease revealed in an animal model with reduced monoamine storage capacity. T. Taylor, W. Caudle, K. Shepherd, A. Noorian, C. Jackson, P.M. Iuvone, D. Weinshenker, J. Greene,

and G. Miller. *J. Neurosci.* 29, xx-yy (2009).

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