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Protein build-up leads to neurons misfiring

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Using a two-photon microscope capable of peering deep within living tissue, researchers at the University of California, San Diego School of Medicine have found new evidence that alpha-synuclein protein build-up inside neurons causes them to not only become "leaky," but also to misfire due to calcium fluxes.

The findings – the first recorded in vivo using a transgenic mouse model of Parkinson's disease – are published in the July 18 issue of The *Journal of Neuroscience* and provide new insights into how Parkinson's disease and other neurodegenerative disorders known as synucleinopathies work and progress at the cellular level.

Previous in vitro studies using cell cultures had suggested abnormal accumulation of alpha-synuclein dysregulated intracellular handling and movement of calcium, which is used as a signaling molecule and neurotransmitter. It was unclear, however, whether calcium alterations occurred in more complex, living animals.

"This is the first time we've been able to verify the role of alpha-synuclein aggregates in vivo," said senior author Eliezer Masliah, MD, professor of neurosciences and pathology.

"The aggregates affect the cell membrane of neurons, making them more porous. They also affect the membranes of organelles inside neurons, such as the mitochondria that are part of the cell's machinery for generating energy. Energy is necessary to pump calcium in and out of the cell. If mitochondria membranes are compromised, calcium

accumulates, further damaging the neuron and causing it to misfire."

Masliah said the new revelations, made using imaging technologies developed by first author Anna Devor, PhD, associate adjunct professor of neuroscience, may help scientists and doctors quantify and repair neuronal damage caused by alpha-synuclein accumulation.

"We have already started to utilize this discovery as a bio-marker and reporter of neuronal damage," said Masliah. "We have compounds developed in collaboration with others to 'plug' the holes in the neurons and mitochondria and prevent the abnormal calcium currents. We can monitor in real-time in live animals how our drugs revert the toxic effects of alpha-synuclein. This represents a unique and fast strategy to evaluate novel compounds."

Provided by University of California - San Diego