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Tau disrupts neural communication prior to neurodegeneration

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A new study is unraveling the earliest events associated with neurodegenerative diseases characterized by abnormal accumulation of tau protein. The research, published by Cell Press in the December 22 issue of the journal *Neuron,* reveals how tau disrupts neuronal communication at synapses and may help to guide development of therapeutic strategies that precede irreversible neuronal degeneration.

Tau normally contributes to the supportive framework of proteins in the cell. It is well established that abnormal tau sometimes clumps into neuron-damaging filamentous deposits and that aggregates of tau with multiple phosphate groups attached are a defining feature of neurodegenerative disorders called "tauopathies", which include Alzheimer's disease and other dementias.

"Research has shown that healthy neurons have more tau in the axon and less in the cell body and dendrites, and that this gradient is reversed in neurodegenerative disorders like Alzheimer's," explains study author, Dr. Karen H. Ashe from the University of Minnesota. "Although studies have shown that accumulation of tau in dendrites induced neurodegeneration, they do not address how tau diminished brain function at preclinical disease stages preceding neurodegeneration."

Dr. Ashe, co-author Dr. Dezhi Liao, and their colleagues investigated how tau induces early memory deficits and disrupts neuronal communication, prior to obvious neuron damage. The researchers found that early accumulation of hyperphosphorylated tau in dendrites and

dendritic spines disrupted communication coming in from other neurons. Dendritic spines are sites where there is a synapse between two neurons. The phosphorylation state of tau played a critical role in mediating tau mislocalization and subsequent impairment of synaptic communication.

"These findings capture what is likely the earliest synaptic dysfunction that precedes synapse loss in tauopathies and provide an important mechanistic link between tau phosphorylation and the mislocalization of tau to dendritic spines," concludes Dr. Liao. "Understanding the key interactions that occur prior to neuronal loss will become increasingly important as preventative strategies shift the timing of interventions to pre-degenerative phases of disease," adds Dr. Ashe. "The aberrant mislocalization of tau proteins in dendritic spines might be a novel target in these strategies."

Provided by Cell Press