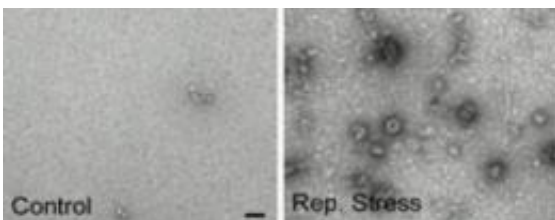


Chronic stress spawns protein aggregates linked to Alzheimer's

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Exposing mice to 14 days of repeated stress resulted in an accumulation of insoluble phosphorylated tau protein aggregates in brain cells, visualized in this electron micrograph. Credit: Image courtesy of Robert Rissman, UC San Diego

Repeated stress triggers the production and accumulation of insoluble tau protein aggregates inside the brain cells of mice, say researchers at the University of California, San Diego School of Medicine in a new study published in the March 26 Online Early Edition of the *Proceedings of the National Academy of Sciences*.

The aggregates are similar to neurofibrillary tangles or NFTs, modified protein structures that are one of the physiological hallmarks of Alzheimer's disease. Lead author Robert A. Rissman, PhD, assistant professor of neurosciences, said the findings may at least partly explain why clinical studies have found a strong link between people prone to stress and development of sporadic Alzheimer's disease (AD), which accounts for up to 95 percent of all AD cases in humans.

"In the mouse models, we found that repeated episodes of [emotional stress](#), which has been demonstrated to be comparable to what humans might experience in ordinary life, resulted in the phosphorylation and altered solubility of tau proteins in neurons," Rissman said. "These events are critical in the development of NFT pathology in Alzheimer's disease."

The effect was most notable in the hippocampus, said Rissman, a region of the brain linked to the formation, organization and storage of memories. In AD patients, the hippocampus is typically the first region of the brain affected by tau pathology and the hardest-hit, with substantial cell death and shrinkage.

Not all forms of stress are equally threatening. In earlier research, Rissman and colleagues reported that [acute stress](#) – a single, passing episode – does not result in lasting, debilitating long lasting changes in accumulation of phosphorylated tau. Acute stress-induced modifications in the cell are transient, he said, and on the whole, probably beneficial.

"Acute stress may be useful for brain plasticity and helping to facilitate learning. Chronic stress and continuous activation of stress pathways may lead to pathological changes in stress circuitry. It may be too much of a good thing." As people age, perhaps their neuronal circuits do too, he said, becoming less robust and perhaps less capable of completely rebounding from the effects of stress.

"Age is the primary, known risk factor for Alzheimer's disease. It may be that as we age, our neurons just aren't as plastic as they once were and some succumb."

The researchers observed that stress cues impacted two key corticotropin-releasing factor receptors, suggesting a target for potential therapies. Rissman noted drugs already exist and are in human trials (for other

conditions) that modulate the activity of these receptors.

"You can't eliminate stress. We all need to be able to respond at some level to stressful stimuli. The idea is to use an antagonist molecule to reduce the effects of stress upon neurons. The stress system can still respond, but the response in the brain and hippocampus would be toned down so that it doesn't result in harmful, permanent damage."

Provided by University of California - San Diego

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