Disrupted biological clock linked to Alzheimer's disease

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Fruit fly

New research has identified some of the processes by which molecules associated with neurological diseases can disrupt the biological clock, interfere with sleep and activity patterns, and set the stage for a spiral of health concerns that can include a decreased lifespan and Alzheimer's disease.

The research was published in *Neurobiology of Disease* by scientists from Oregon State University and the Oregon Health & Science University, in work supported by the National Institutes of Health.

Previous studies have shown that disruption of the biological clock – the natural pattern of day-night activity that's genetically controlled in many animals – can cause neurodegeneration, loss of motor function and early death.

The newest results help outline the molecular mechanisms involved, and show how proteins associated with neurological disease can diminish the biological clock function and ultimately lead to very serious health problems, including severe cognitive deterioration. It also confirms that these risks increase significantly with age.

"The molecular basis underlying biological clock deficits in Alzheimer's disease has been difficult to tease out," said Matthew Blake, an OSU faculty research assistant and author of the study. "Only recently have we been able to utilize our model system to accurately dissect this mechanism."

This research was done with fruit flies, which have many genes and biological processes that are similar or identical to those of humans, retained through millions of years of evolution. Circadian clocks are so essential to health that they are found throughout the nervous system and peripheral organs.

Proper function of circadian rhythms has been shown to affect everything from sleep to stress reaction, feeding patterns, DNA repair, fertility and even the effectiveness of medications.

"Alzheimer's disease has always been of interest in this research, because sleep disruption is one of its earliest symptoms, and almost everyone with Alzheimer's has some sleep problems," said Jadwiga Giebultowicz, corresponding author of this study, a professor in the Department of Integrative Biology in the OSU College of Science, and expert on the biological and genetic underpinnings of the biological clock.

"This research adds more support to the hypothesis that neurological damage is a circular process that, in turn, causes more disruption of the biological clock," Giebultowicz said. "We've identified a new player in this process, a fragment of the amyloid precursor protein called AICD, that is able to enter the nucleus of cells and interfere with central clock function."

One known cause of Alzheimer's disease is cleavage of an amyloid precursor protein, which creates a peptide that's toxic to neurons. An enzyme involved is elevated in Alzheimer's patients. This study took that process further and showed that increased production of the enzyme, which in flies is called dBACE, reduced the expression of a core clock protein.

The results suggest that dBACE acts via dAICD to cause the disruption of the biological clock and loss of daily sleep and activity cycles. This disruptive process was much more severe in older flies.

"A general message from this is that normal day-night, sleep and activity cycles are important," Giebultowicz said.

"There's evidence that proper sleep allows neuronal repair activity and the maintenance of neuronal health," she said. "Since neuronal damage is a destructive process that can build on itself once it begins, it's important that sleep issues should be taken seriously by people and their doctors, especially as they age."

Molecular clock oscillations decline with age, Giebultowicz said, and finding ways to help maintain or restore them might form the basis for a possible therapy to reduce or prevent the associated health problems.

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