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Investigating mechanisms that connect Alzheimer's disease with circadian disruptions

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Keywords

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Abstract

Recent research suggests that disruptions in circadian rhythms, including sleep-wake cycles, are early signs of Alzheimer's disease (AD) and may contribute to the pathological processes. The Amyloid Precursor Protein (APP) plays a key role in AD because when cleaved by β- and γ-secretase, it generates the toxic β-amyloid fragments. However, when α-secretase activity is followed by γ-secretase cleavage of APP, no β-amyloid is produced. Interestingly both APP processing pathways produce the same C-terminal APP intracellular domain (AICD), which has been linked to transcription regulation. Previous studies in Drosophila have shown that overexpression of α-secretase, β-secretase, or AICD in circadian pacemaker neurons disrupted locomotor activity rhythms. These studies suggest that the misregulation of APP processing and the consequent changes in AICD localization may contribute to the pathological processes in AD. To investigate how changes in the AICD function may contribute to AD, we used transgenic flies with induced AICD expression in circadian pacemaker neurons or mushroom body neurons. We determined that AICD overexpression caused a shortened lifespan, a decline in locomotor performance, and disrupted rhythmic activity in addition to increased sleep fragmentation (shorter but more sleep bouts). To study the subcellular localization of the AICD, transgenic flies expressing the fly or human APP tagged with GFP at the N-terminus and RFP at the C-terminus were used to follow cleavage products in pacemaker neurons in vivo. We found that the levels of nuclear AICD change during the day, with little AICD detectable in nuclei during the daytime while it accumulated in the nucleus in the night. Furthermore, the pattern of AICD nuclear localization is disrupted in aged flies and flies overexpressing secretases. Together, these data suggest the AICD as a functional link between AD and circadian rhythms, providing the basis to investigate whether similar mechanisms contribute to AD pathology in humans.