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NEURODEGENERATIVE DISEASE

Sleeping away amyloid plaques?

Aggregation of extracellular amyloid-β (Aβ) is thought to play a major part in the pathogenesis of Alzheimer's disease. Amyloid plaques form when levels of the monomeric, soluble Aβ peptide build up in the interstitial fluid (ISF) in the brain. Holtzman and colleagues now show that orexin influences ISF Aβ levels by regulating the sleep–wake cycle.

The authors used microdialysis to measure ISF Aβ levels in the hippocampus of wild-type mice and transgenic mice that are used as a model of Alzheimer's disease. A diurnal fluctuation in ISF Aβ levels, with higher levels during waking and lower levels during sleep, was detected in both sets of mice and in healthy humans, indicating that it results from a normal regulatory process. In the transgenic mice the levels correlated with the amount of time spent awake.

Housing mice under constant light did not abolish the sleep–wake cycle or the fluctuations in Aβ levels. By contrast, subjecting mice to sleep deprivation increased ISF Aβ levels relative to the normal concentration during the light period, and Aβ levels decreased as soon as the animals fell asleep. These findings indicate that the regulation of ISF Aβ levels is coupled to the sleep–wake cycle rather than to light or dark exposure.

As orexin is a major regulator of sleep and wakefulness, the authors examined whether this neuropeptide also mediates the diurnal fluctuations in ISF Aβ. Intracerebroventricular infusion of orexin for 6 h at the beginning of the light period (when Aβ concentrations are normally low and mice asleep) increased both ISF Aβ levels and wakefulness. Conversely, continuous administration of an orexin receptor antagonist for 24 h by microdialysis reduced wakefulness and overall ISF Aβ levels and abolished the diurnal Aβ fluctuations. The diurnal rhythm was restored immediately upon removal of the antagonist. Together, these findings suggest that orexin signalling regulates ISF Aβ levels.

The finding that the sleep–wake cycle regulates Aβ levels raises the question of whether chronic sleep deprivation can cause Aβ accumulation in the brain. The authors showed that, in transgenic mice, sleep deprivation resulted in greater Aβ plaque deposition than in non-sleep-deprived controls. Importantly, systemic administration of the orexin receptor antagonist decreased plaque formation in several brain regions.

This study shows that orexin signalling and sleep–wake behaviour regulate the level of soluble Aβ in the ISF, and that manipulating either of them can influence Aβ plaque formation in a mouse model of Alzheimer's disease. Interestingly, sleep disturbances are common in people with neurodegenerative disorders. Future studies may therefore investigate whether improving sleep patterns or manipulating orexin levels in individuals at risk for Alzheimer's disease could slow the formation of amyloid plaques and ultimately dementia.

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ORIGINAL RESEARCH PAPER Kang, J.-E. *et al.* Amyloid-β dynamics are regulated by orexin and the sleep-wake cycle. *Science* 24 Sep 2009 (doi:10.1126/science.1180962)