Potential Role of Sleep in Alzheimer’s Disease Pathogenesis

Ashish Heda

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Recommended Citation
http://openscholarship.wustl.edu/vol8_iss1/61

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Accumulation and aggregation of amyloid-beta (Aβ) peptide in the extracellular space of the brain is a major pathological hallmark of Alzheimer’s disease (AD) and is known to occur years before clinical symptoms develop. Sleep quality degrades with aging but is more severely impaired in AD. Previous research indicates that decreased signaling of orexin, a hormone which regulates wakefulness, in a mouse model of AD results in decreased accumulation of Aβ plaques in the brain. It is unknown whether the changes in orexin or secondary changes in sleep by orexin causes the decreased Aβ plaques in the brains of mice. We hypothesized that focal overexpression of orexin will lead to increased wakefulness as well as increased Aβ plaques in the brain. Mutations in the genes of amyloid precursor protein (APP) and presenelin 1 (PS1) are known to increase AD pathology in the brain by increasing aggregation and accumulation of Aβ. A lentiviral vector containing orexin cDNA or a control vector was injected in the bilateral hippocampi of APP/PS1 mice. Sleep-wake cycle was monitored by electroencephalography (EEG) and electromyography (EMG) along with measurements of interstitial fluid lactate, a measure of brain activity, using microdialysis. Both results are compared. Overexpression of orexin did not increase gross wakefulness in comparison to the control mice. Lactate levels fluctuate according to the sleep-wake cycle, but did not show differences between the two groups. There was no difference in the amount of Aβ pathology between groups. Current results suggest that focal overexpression of orexin in the hippocampus does not affect the sleep-wake cycle as well as Aβ pathology in the brain. Overexpression of orexin in different brain areas which govern the sleep-wake cycle or knocking out of orexin in the mouse models of AD may further demonstrate the relationship between the sleep/orexin and AD pathology.