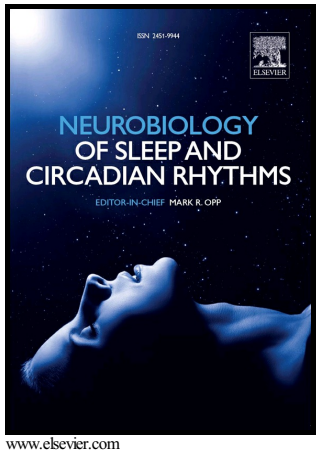

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Enhanced sleep reverses memory deficits and underlying pathology in Drosophila models of Alzheimer's disease

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Abstract

To test the hypothesis that sleep can reverse cognitive impairment during Alzheimer's disease, we enhanced sleep in flies either co-expressing human amyloid precursor protein and Beta-secretase (APP:BACE), or in flies expressing human tau. The ubiquitous expression of APP:BACE or human tau disrupted sleep. The sleep deficits could be reversed and sleep could be enhanced when flies were administered the GABA-A agonist 4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3-ol (THIP). Expressing APP:BACE disrupted both Short-term memory (STM) and Long-term memory (LTM) as assessed using Aversive Phototaxic Suppression (APS) and courtship conditioning. Flies expressing APP:BACE also showed reduced levels of the synaptic protein discs large (DLG). Enhancing sleep in memory-impaired APP:BACE flies fully restored both STM and LTM and restored DLG levels. Sleep also restored STM to flies expressing human tau. Using live-brain imaging of individual clock neurons expressing both tau and the cAMP sensor Epac1-camps, we found that tau disrupted cAMP signaling. Importantly, enhancing sleep in flies expressing human tau restored proper cAMP signaling. Thus, we demonstrate that sleep can be used as a therapeutic to reverse deficits that accrue during the expression of toxic peptides associated with Alzheimer's disease.

Introduction

Alzheimer's disease is a complex disorder that has been linked with altered β-amyloid (Aβ) peptide processing, tau protein hyper-phosphorylation, inflammation, oxidative damage, reduced neurotrophins, an alteration in the balance between excitatory and inhibitory synapses and cognitive impairment leading to dementia (JOHN and BERG 2015; LI et al. 2016). It has become increasingly clear that abnormal phosphorylation of tau also plays a prominent role in the pathogenesis of Alzheimer's disease (FERNANDEZ-FUNEZ et al. 2015). A crosstalk between Aβ and tau has been demonstrated such that each may not only exert their toxic effects independently but also interact synergistically (NISBET et al. 2015). As a consequence, therapeutic interventions that target either Aβ or tau separately may not be adequate to fully treat the disorder (FERNANDEZ-FUNEZ et al. 2015;