(J20) that express human amyloid precursor protein (APP) carrying AD-linked mutations exhibit similar symptoms. We previously described corticothalamic network dysfunction in APP mice, highlighted by reduced activity in the thalamic reticular nucleus (TRN). The TRN is a critical inhibitory control nucleus whose activity underlies the slow wave activity characteristic of SWS, the phase of sleep during which metabolites such as Aβ are cleared from the brain. The reduction in TRN activity in APP mice was associated with sleep fragmentation. Therefore, the TRN may be a master regulator of AD pathophysiology, and restoration of its activity might be a therapeutic strategy to improve sleep and clearance of Aβ from the brain.

Methods: Selective activation of TRN in APP mice was achieved by stereotactically targeting the TRN with an AAV driving expression of CRE-dependent excitatory DREADDs. We used APP mice and nontransgenic controls that had been crossed with mice expressing CRE in GABAergic neurons. In vivo activation of DREADDs using intraperitoneal (IP) injection of CNO was confirmed by staining of brain sections with a marker of activity.

Results: A single IP injection of CNO led to acute activation of DREADD-expressing TRN neurons in APP mice, reduced sleep fragmentation and improved SWS. Chronic, daily CNO treatment (30 days) led to stable reductions of sleep fragmentation and enhanced SWS throughout the treatment period. We found robust reductions in Aβ plaque load relative to vehicle-treated APP mice.

Conclusion: These results demonstrate that selective activation of TRN is sufficient to normalize sleep architecture and reduce Aβ accumulation in APP mice. Therefore, the TRN may be a master regulator of pathology and function in several cognitive and behavioral domains in AD.

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0299

EFFECT OF GLYCEMIC EXTREMES ON SLEEP/WAKE AND ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

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Introduction: Type 2 diabetes increases the risk of developing Alzheimer's disease by 2-4-fold. Further, sleep disruption is characteristic of both Alzheimer's disease and metabolic dysfunction. It remains unclear, however, how alterations in peripheral and brain metabolism alter pathology and, ultimately, impact the sleep/wake cycle. The goal of this study, therefore, was to elucidate how the brain regulates metabolism in euglycemic conditions, as well as when challenged with hyper- and hypoglycemic conditions, with the hypothesis that altered glucose homeostasis and sleep dysregulation may be leading to accelerated disease progression.

Methods: Biosensors were implanted bilaterally into the hippocampus of APP/PS1 mice, a model of amyloid-beta (Aβ) overexpression, to measure ISF fluctuations in glucose, glutamate, and lactate. These were paired with cortical EEG and EMG recordings for simultaneous sleep/wake analysis. To examine the effect of glycemic extremes on the brain's metabolic profile and arousal state, the mice were challenged with a 2g/kg IP injection of glucose, a 1mg/kg IP injection of glibenclamide, a K_{ATP} channel antagonist, as well as a .5U/kg injection of insulin.

Results: Both hyper- and hypoglycemic challenges result in significant increases in arousal in 3-month old, wildtype mice. This increased arousal matched the increases in ISF lactate, indicating an increase in overall neuronal activity. However, in an aged APP/PS1 model mouse, the metabolic response to glycemic challenges was muted and there was seemingly no impact on arousal state, which is likely due to an increase in the overall amount of time spent awake. This finding is consistent with previous data demonstrating progressive age and pathology-dependent increases in arousal time.

Conclusion: This study represents a novel approach to understanding the interactions between sleep, cerebral metabolism, and Alzheimer's Disease progression. The results show both glycemic extremes and Alzheimer's Disease pathophysiology can cause increased arousal, which is known to further contribute to metabolic dysregulation, accelerate amyloid-beta and tau deposition and neurodegeneration, suggesting a cyclic relationship between sleep and disease pathology.

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0300

LINKING SLEEP DISTURBANCES WITH AMYLOID AND TAU IMAGING. PRELIMINARY FINDINGS FROM THE HARVARD AGING BRAIN STUDY

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Introduction: Growing evidence suggests that sleep disturbances can modulate the aging process and increase the risk of developing cognitive impairment and dementia. Given that sleep and cognition share biological regulatory mechanisms, the aim of this study was to characterize the association between sleep disturbances and imaging markers of Alzheimer's disease (amyloid and Tau) in participants of the Harvard Aging Brain Study in relation to their cognitive status.

Methods: We carried out home level 2 polysomnography studies on 24 participants of the prospective Harvard Aging Brain Study. As part of this longitudinal study, individuals, who were recruited when cognitively intact, undergo longitudinal multi-modality imaging including Pittsburgh Compound B PET scans to detect amyloid deposition and Tau imaging using the F18-labeled ligand (T807) as well as sensitive yearly cognitive assessments, including the Preclinical Alzheimer's Cognitive Composite (PACC), to define predictive factors of preclinical Alzheimer's disease.

Results: Among the participants, 14 were female and the average age was 74.1 (±1.97). A positive correlation was found between inferior temporal Tau and percent time in N1 sleep (p=0.006), whereas percent time in N3 (slow-wave) sleep (p=0.016) and REM sleep (p = 0.05) were inversely and independently correlated with inferior temporal Tau. Cortical amyloid burden correlated positively with percent time in N1 (p=0.01). All these associations remained after controlling for age and total sleep time. PACC score correlated positively with percent time in N1 (p= 0.04) and negatively with REM sleep (p = 0.001) although this association diminished after correction for age and total sleep time. We did not find