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SLEEPINESS IN COGNITIVELY UNIMPAIRED OLDER ADULTS IS ASSOCIATED WITH CSF BIOMARKERS OF INFLAMMATION AND AXONAL INTEGRITY.

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Introduction: We have previously shown that older adults with excessive daytime sleepiness (EDS) appear to be more vulnerable to longitudinal amyloid PET accumulation before the onset of the dementia. It remains unclear whether this vulnerability is specific to amyloid or extends to other biomarkers of Alzheimer's disease pathology, or axonal integrity and inflammation, which can also contribute to neurodegeneration and cognitive changes.
Methods: For this cross-sectional analysis, we identified 260 cognitively unimpaired adults (>60 years old) without neurologic disorder who underwent CSF quantification of AD biomarkers (CSF Aβ-42, p-tau181, p-tau217) along with at least one other biomarker of interest (neurofilament light chain [NfL], IL-6, IL-10, and TNF-α) from the Mayo Clinic Study of Aging – a longitudinal population-based cohort in Olmsted County, Minnesota. CSF biomarkers were available in 251-260 individuals, depending on the biomarker. We fit linear regression models to assess whether the CSF biomarkers were associated with sleepiness as measured by the Epworth Sleepiness Scale (ESS), after controlling for age, sex, APOE4 genotype, BMI, hypertension, dyslipidemia, and OSA diagnosis (by chart review).
Results: Higher ESS scores were independently associated with higher CSF IL-6 and NfL, but not with the other biomarkers in the whole sample. For every single-point increase in the ESS score, there was a .008 ([95% CI .001-.016], p=0.033) increase in the log of IL-6 and .01 ([95% CI .002-.018], p=0.016) increase in the log of NfL. A sensitivity analysis showed a correlation between ESS scores and log of p-tau/Aβ-42 ratio only in participants with abnormal ratio (>0.023), after controlling for APOE4 (partial r=.27, p=039).
Conclusion: Our results corroborate previous literature suggesting that higher inflammatory milieu reflected by increased CSF IL-6 is associated with sleepiness. The association between NfL and sleepiness suggests that sleepiness may be related to disturbed connectivity due to axonal damage. Alternatively, NfL may be a surrogate of active axonal injury associated with more disrupted sleep. A correlation between sleepiness and CSF p-tau/ab-42 ratio was only seen in patients with abnormal ratio, suggesting a stronger association between sleepiness and AD pathology as the disease progresses, possibly because AD pathology worsens sleep quality and/or vice-versa.
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SAMELISANT (SUVN-G3031), A HISTAMINE H3 RECEPTOR INVERSE AGONIST IN ANIMAL MODELS OF NARCOLEPSY

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Introduction: Samelisant (SUVN-G3031) is a potent and selective H3 receptor (H3R) inverse agonist with hKi of 8.7 nM. It lacks measurable affinity against 70 other targets which includes GPCRs, ion channels, transporters, enzymes, peptides, steroids, second messengers, growth factors and prostaglandins. Samelisant exhibited desired pharmacokinetic properties and favorable brain penetration in preclinical species. Samelisant blocked R-α-methylhistamine induced dipsogenia in rats and increased tele-methylhistamine levels in brain and cerebrospinal fluid as well. Samelisant is currently being evaluated in a Phase-2 study as monotherapy for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy with and without cataplexy (ClinicalTrials.gov Identifier: NCT04072380).
Methods: In brain microdialysis, samelisant was evaluated for its effects on modulation of neurotransmitters like histamine and norepinephrine in prefrontal cortex. In male orexin knockout mice, electroencephalography (EEG), electromyography and activity were monitored using telemetric device. Effects of samelisant on sleep/ wake profile and cataplexy episodes were evaluated during active period of animals. Animals were allowed three weeks of recovery from surgery prior to EEG recording.
Results: Samelisant significantly increased histamine, dopamine and norepinephrine levels in the prefrontal cortex. Samelisant did not change dopamine levels in the striatal and accumbal. These suggest that samelisant may not have propensity to induce abuse liability. Samelisant produced a significant increase in wakefulness with concomitant decrease in non-rapid eye movement sleep in orexin knockout mice. It also significantly decreased number of cataplectic episodes in orexin knockout mice.
Conclusion: The results from non-clinical studies presented here provide a strong evidence for the potential utility of samelisant for the treatment of EDS and cataplexy in patients with narcolepsy.
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