Journal Club

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Chronic Sleep Disruption Potentiates Locus Ceruleus Tauopathy in a Mouse Model of Alzheimer's Disease

Jereme G. Spiers¹ and Hsiao-Jou Cortina Chen²

¹Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Victoria, 3083, Australia, and ²School of Biomedical Sciences, The University of Queensland, St Lucia, Queensland 4072, Australia

Review of Zhu et al.

Alzheimer's disease (AD), the most prevalent cause of dementia, is a fatal neurodegenerative disorder characterized by progressive cognitive impairment and memory loss. Two major pathological hallmarks of AD are accumulation of toxic amyloid- β protein aggregates and formation of neurofibrillary tangles composed primarily of the cytosolic microtubule-associated protein, tau, in a hyperphosphorylated form. Tau is normally enriched in axons of mature and growing neurons where it promotes formation and stabilization of axonal microtubules and drives neurite outgrowth (Kadavath et al., 2015; Sayas et al., 2015). Phosphorylation reduces the ability of tau to interact with microtubules by promoting disulfide bonding of cysteine residues, and it leads to aggregation of soluble tau oligomers, which can further expand and precipitate as granular tau oligomers.

Some of the earliest tau pathology is found in the locus ceruleus (LC), which, as the main source of noradrenaline in the brain, is a critical mediator of the central "fight or flight" stress response (Joëls and Baram, 2009). Hyperphosphorylated tau appears in the LC decades before any sign

of cognitive impairment (Braak et al., 2011). This tau pathology then progresses along LC axons to other memory-related areas (usually the transentorhinal region first) and extends through much of the neocortex by the later stages of AD (Braak et al., 2011).

Several pieces of evidence suggest that the formation and spread of tau pathology within and beyond the LC is regulated by neuronal activity. The LC modulates a wide range of behavior including wakefulness, attention, learning, and memory (Sara and Bouret, 2012), and its activity is highest during wakefulness (Bellesi et al., 2016). A recent study showed that reduced sleep was associated with increased tau pathology measured in predominantly cognitively normal people (Lucey et al., 2019). Consistent with this, sleep disturbances are an early component of AD, with sleep disruption being markedly exaggerated in patients with mild cognitive impairment and AD relative to age-matched cognitively normal subjects (Musiek et al., 2015). Furthermore, in a well characterized mouse model of AD, sleep deprivation accelerated tau pathology in whole-brain homogenates by potentiating misfolding, which significantly decreased tau protein solubility (Di Meco et al., 2014).

In a recent article published in *The Journal of Neuroscience*, Zhu et al. (2018) further examined the effects of chronic

sleep disruption on the behavioral, biochemical, and neuroanatomical aspects of tauopathy in the LC and hippocampus of mice expressing a human tau protein containing an AD-linked mutation (Pro301Ser). This study demonstrated that chronic short sleep in early adulthood accelerated the deterioration of motor performance, increased loss of LC neurons, and elevated levels of pathogenic tau oligomers in AD-model mice. The increased levels of tau oligomers were observable after a 6 month recovery from sleep deprivation, indicating pathogenic alterations in the LC were sustained. Zhu et al. (2018) showed that the chronic sleep disruption procedure induced immediate tau misfolding in the LC of P301S mice. Moreover, the presence of tau disulfide cross-linked oligomers, typically associated with increases in oxidation, was sustained in the LC up to 6 months after sleep deprivation.

Because glial activation has been shown to precede neurofibrillary tangle formation, and microglia can effectively propagate tau pathology, Zhu et al. (2018) examined the effects of sleep deprivation on glial activation. Immediately after the chronic sleep disruption procedures, Zhu et al. (2018) observed a subtle but significant increase in astrocytic activation within the hippocampus, a region where pronounced degeneration is thought to

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Correspondence should be addressed to Jereme G. Spiers at j.spiers@latrobe.edu.au or Hsiao-Jou Cortina Chen at h.chen@uq.edu.au.

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underlie many of the cognitive symptoms of AD. Next, Zhu et al. (2018) demonstrated profound glial activation was sustained in the CA1 region of the hippocampus. Using different markers, the authors detected robust activation of both microglia and astrocytes alongside increased tau hyperphosphorylation and oligomerization, all of which persisted after recovery from sleep disturbance in early adulthood. Collectively, these data show that both astrocyte and microglial reactivity is sustained within regions exhibiting tau pathology in the P301S mice after sleep disruption in early adulthood.

One factor that might link sleep deprivation to tau oligomerization and accumulation is oxidative stress, where increased free radicals cause oxidative modifications to proteins, lipids, and nucleic acids resulting in altered protein function, lipid membrane peroxidation, and DNA damage, respectively. Previous work has indicated that neuronal activation induces mitochondrial oxidative stress in LC neurons, an effect driven by nitric oxide synthase (Sanchez-Padilla et al., 2014). Mitochondrial ATP synthesis results in superoxide radical production as a byproduct of oxidative phosphorylation and these reactive oxygen species (ROS) are removed by normal antioxidant activity. However, the additional mitochondrial nitric oxide production occurring in the LC because of prolonged wakefulness might exceed the detoxifying capacity of antioxidants, resulting in accumulation of ROS. Furthermore, increases in oxidative products that form dityrosine cross-bridges between proteins have been found in neural tissue from Alzheimer's patients (Zheng et al., 2002; Green et al., 2004). As mentioned, dityrosine cross-bridging is a critical oxidative process in the formation of tau aggregates and tau proteins lacking tyrosine residues resist radical-induced oligomerization (Reynolds et al., 2005).

Another possible contributor to tau accumulation following sleep deprivation is an increase in glucocorticoid stress hormones. Zhu et al. (2018) asserted that there was no difference in circulating glucocorticoid concentrations based on a previous study in which glucocorticoids were measured once after exposure to the sleep disruption procedure (Zhang et al., 2014). During a stress response, peak glucocorticoid concentrations reach the brain 60 min after stress exposure and begin exerting negative feedback on the hypothalamic–pituitary–adrenal axis to curtail glucocorticoid production (Qian

et al., 2011). However, the sleep disruption procedures used by Zhu et al. (2018) extend over a significant period of time, which might mask changes in peak glucocorticoid concentrations by activating these negative feedback mechanisms (Gjerstad et al., 2018). Chronic activation of corticosteroid receptors has previously been shown to induce gliosis and exacerbate tauopathy in mouse models of AD (Jauregui-Huerta et al., 2010; Sierra-Fonseca and Gosselink, 2018). Although this is most notably documented in the hippocampus, the LC is also extremely susceptible to stress-induced glucocorticoid signaling, with a single stress event causing the downregulation of mineralocorticoid receptors for up to 4 weeks (Li et al., 2011). Furthermore, sleep disruption caused by administration of glucocorticoids has been shown to act specifically via glucocorticoid receptors in the LC, indicating the importance and sensitivity of glucocorticoid signaling in this region (Wang et al., 2015).

Understanding the importance of sleep disruption patterns and how they induce molecular changes leading to the progression of AD is critical for determining potential early intervention strategies. Zhu et al. (2018) provided strong evidence that chronic sleep disruption in early adulthood produces sustained alterations in LC tau pathology, contributing to the pathological progression of tauopathy in the P301S mouse model of AD. These alterations in tau pathology were observed alongside increased gliosis, which preceded tau pathology in the hippocampus, indicating that chronic sleep disruption may exacerbate the role of glia in potentiation of tauopathy. However, the mechanisms underlying these significant and lasting changes require much further elucidation and future studies should explore molecular targets susceptible to chronic LC activation following chronic sleep disruption.

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