

Accepted Manuscript

Title: Tau Pathology of Alzheimer's disease: A Possible Role of Sleep Deprivation

Authors:

Nahid Ahmadian

Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;
Department of Molecular Medicine, Faculty of Advanced Biomedical Sciences, Tabriz
University of Medical Sciences, Tabriz, Iran; ahmadiannahid@gmail.com

Sajjad Hejazi

Department of Anatomy, Tabriz Branch, Islamic Azad University, Tabriz, Iran;
sajjadhejazi1@gmail.com

Javad Mahmoudi

Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;
mahmoudi2044@yahoo.com

Mahnaz Talebi (Corresponding Author)

Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;
talebi511@yahoo.com

Number of text pages: 12

Number of figures: 1

Number of tables: 0

To appear in: Basic and Clinical Neuroscience

Received date: 05 Oct. 2017

Revised date: 26 Dec. 2017

Accepted date: 26 Dec. 2017

This is a “Just Accepted” manuscript, which has been examined by the peer-review process and has been accepted for publication. A “Just Accepted” manuscript is published online shortly after its acceptance, which is prior to technical editing and formatting and author proofing. Basic and Clinical Neuroscience Journal provides “Just Accepted” as an optional and free service which allows authors to make their results available to the research community as soon as possible after acceptance. After a manuscript has been technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Please note that technical editing may introduce minor changes to the manuscript text and/or graphics which may affect the content, and all legal disclaimers that apply to the journal pertain.

Please cite this article as:

Ahmadian, N., Hejazi, S., Mahmoudi, J., Talebi, M. (In Press). Tau pathology of Alzheimer’s disease: a possible role of sleep deprivation. *Basic and Clinical Neuroscience*. Just Accepted publication Dec. 26, 2017.

Abstract

Sleep deprivation (SD) has become a common phenomenon in the modern societies. Reduced amounts of sleep has elevated the risk for neurodegenerative conditions such as Alzheimer's disease. Several studies have indicated that restricted sleep increases the level of deposition of beta-amyloid and the formation of neurofibrillary tangles, the major brain microstructural hallmarks for Alzheimer's disease. The mechanisms by which sleep deprivation affects the pathology of Alzheimer's disease has not yet been fully and definitively identified. However, so far, risk factors like apolipoprotein E risk alleles, kinases and phosphatases dysregulation, reactive oxygen species, endoplasmic reticulum damages, glymphatic system dysfunctions and orexinergic system inefficacy have been identified as the most important factors which mediates between the two conditions. In this review, these factors are discussed briefly.

Keywords: Alzheimer's disease; Sleep deprivation; Beta-amyloid; Neurofibrillary tangles

Accepted Manuscript

Introduction

The biological and behavioral roles of sleep have not been entirely elucidated. Studies have shown that sleep plays a crucial role in the continuity of cognitive sequences and executive functions (Cirelli, Shaw, Rechtschaffen, & Tononi, 1999; Wilckens, Woo, Kirk, Erickson, & Wheeler, 2014). Sleep deprivation (SD) as a common phenomenon in the modern societies, endangers individual health both in acute and chronic states. Reduced amount of sleep hours is related to alterations in living style, increase in night work hours and late-night activities (Navara & Nelson, 2007). Studies have shown that people with insomnia or sleep disorders are at elevated risk for neurodegenerative disorders such as Alzheimer's disease (AD) (Cedernaes et al., 2016). Moreover sleep disorders are seen across moderate to severe AD and are worsen with progression of the disease (Anderson & Bradley, 2013).

Tau is one of the most important microtubule associated proteins (MAP) in the neurons. The balanced tau phosphorylation makes it binding to the microtubules and the assembly of microtubules and maintaining the structure and stability of the neurons (Kadavath et al., 2015). However, hyperphosphorylation of tau causes its aggregation and the formation of paired helical filamentous structures known as neurofibrillary tangles (NFTs) (Harrison & Owen, 2016). NFTs are among the main neurological hallmarks of AD (Cox, Davis, Mash, Metcalf, & Banack, 2016). Evidence from animal models has illustrated that changes in the sleep-wake cycle may elevate hyperphosphorylated tau protein in the brain (Di Meco, Joshi, & Praticò, 2014; Sharon Ooms et al., 2014; Rothman, Herdener, Frankola, Mughal, & Mattson, 2013). It is reported that two months of SD causes more than 50% elevation of the insoluble tau in the brain (Nunomura et al., 2001).

In addition, chronic SD has been suggested to increase extracellular amyloid, the main component of the amyloid plaques found in the brains of Alzheimer patients (Sadigh-Eteghad et al., 2015) and sleep extension decreases plaques in animal models (M. M. Lim, Gerstner, & Holtzman, 2014). It has been indicated that CSF A β levels predict amyloid plaque deposition and sleep deprivation is associated with fluctuations in the level of beta-amyloid in the cerebrospinal fluid and its deposition in the brain (Roh et al., 2012); So that, even one night of sleep deprivation is proposed to be associated with a 6% decrease in CSF A β 42 levels (S. Ooms, S. Overeem, K. Besse, M. O. Rikkert, et al., 2014). Therefore, in general, it seems that sleep deprivation can affect Alzheimer's pathology through intermediate mechanisms.

In this article we're going to briefly review the most significant factors mediating between sleep deprivation and Alzheimer's disease, including Apolipoprotein E risk alleles, kinases and phosphatases dysregulation, reactive oxygen species, endoplasmic reticulum damages, glymphatic system dysfunctions and orexinergic system inefficacy. Obviously, studying these factors in an integrated and concise way can be useful for researchers in the field of sleep and Alzheimer's pathology.

Apolipoprotein E risk alleles

Apolipoprotein E (ApoE), as the main component of chylomicrons and intermediate-density lipoproteins (IDLs), plays an essential role in the normal catabolism of lipoproteins (Huang & Mahley, 2014). ApoE transfers lipoproteins, fat-soluble vitamins, and cholesterol to the lymph vessels and then to the bloodstream. It is originally synthesized in the liver, but it is also abundant in the central nervous system (Mahley, 2016). There are at least three variants (alleles) of the APOE gene, ϵ 2, ϵ 3, and ϵ 4 (Ryu, Atzmon, Barzilai, Raghavachari, & Suh, 2016).

APOE ϵ 4 genetic variant is known as the main genetic risk determinant of Alzheimer's disease. The ϵ 4 allele also increases the risk for cerebral amyloid aggregation and age-related cognitive impairments (Liu, Kanekiyo, Xu, & Bu, 2013). APOE risk variants are believed to be able to activate specific intracellular pathways by binding to surface receptors and peptides of the neurons, which ultimately leads to neurodegeneration and synaptic dysfunction (Giau, Bagyinszky, An, & Kim, 2015).

Furthermore, pathological influence of ApoE on increasing cerebral A β deposition has been demonstrated in several studies (Morris et al., 2010). ApoE-lipoproteins, by removing the soluble A β from the extracellular matrix, can facilitate its uptake through LRP1, LDLR, and HSPG receptors (29). Additionally, the

association between ApoE, 24S-hydroxycholesterol and tau shows its direct involvement in generation of NFTs (Leoni, Solomon, & Kivipelto, 2010).

On the other hand, the association of APOE with sleep disorders has also been proven. For example, Kadotani et al. (2001) has reported significant relationship between sleep-disordered breathing and APOE $\epsilon 4$ variant in the general population (Kadotani et al., 2001) and Tisko et al. (2014) reported that obstructive sleep apnea (OSA) is associated with $\epsilon 4$ allele (Tisko et al., 2014). Also, Lim et al. (2013) has proposed that specific APOE $\epsilon 4$ genotypes may predispose to sleep disruption and sleeping adequately inhibits the effect of ApoE on the formation of NFTs and progression of AD (A. S. P. Lim et al., 2013).

Kinases and phosphatases dysregulation

Protein kinases and phosphatases are two groups of enzymes that transfer phosphate to and from substrates such as tau protein (Cheng, Qi, Paudel, & Zhu, 2011; Nichol, Parachikova, & Cotman, 2007). Several protein kinases such as cyclic AMP-dependent protein kinase A (PKA), Calcium/calmodulin-dependent protein kinase II (CaMKII), glycogen synthase kinase-3 β (GSK-3 β) and protein phosphatases 2A (PP2A) have role in tau phosphorylation and de-phosphorylation (Shanavas & Pappasozomenos, 2000).

PKA is one of the enzymes involved in sleep/wake regulation (Avila et al., 2012; Hellman, Hernandez, Park, & Abel, 2010). There is evidence that sleep deprivation causes PKA activation in the brain (Datta & Desarnaud, 2010; Graves et al., 2003) and its activation increases phosphorylation in multiple sites of tau (Ittner et al., 2016). CaMKII is a complex protein kinase and have an important role in synaptic plasticity and memory formation (Giese & Mizuno, 2013). Animal studies have showed that sleep deprivation remarkably dysregulates CaMKII-related phosphorylation (Cui et al., 2016). Furthermore CaMKII also is a tau kinase and its dysregulation is associated with Alzheimer's progression (Ghosh & Giese, 2015) and that CaMKII inhibits tau- microtubule interaction by tau phosphorylation (Singh et al., 1996). Evidence shows that GSK-3 β is another enzyme which influences sleep-wake organization (Ahnaou & Drinkenburg, 2011; Albrecht, 2012; Hickie, Naismith, Robillard, Scott, & Hermens, 2013). This enzyme phosphorylates at least 36 residues of tau protein (Hanger et al., 2007). As a matter of fact, GSK-3 activation is a critical step in brain aging and AD which triggers cascade of detrimental events such as NFT formation and neuronal death pathways (Takashima, 2006).

On the other hand, an extracellular signal-regulated kinase (ERK) is centrally involved in memory consolidation process (Kelly, Laroche, & Davis, 2003). Phosphorylation of ERK is a key step in initiation of its activity in response to synaptic stimuli (Grewal, York, & Stork, 1999). In 2004, Guan et al. demonstrated that sleep deprivation impairs ERK phosphorylation process in the hippocampus and this leads to spatial memory impairments in rats (Guan, Peng, & Fang, 2004). Future studies may clarify the role of this protein in the relationship between sleep disorders and Alzheimer's in humans.

Reactive oxygen species

Reactive Oxygen Species (ROS) are a number of molecular oxygen-derived reactive molecules and free radicals, which are produced as byproducts during the mitochondrial electron transport or through oxidoreductase enzymatic activities (Ray, Huang, & Tsuji, 2012). Recent works have demonstrated that ROS have a role in cellular signaling cascades, including apoptosis, cell cycle regulation, phagocytosis, enzyme activation and gene expression. The imbalance ROS and antioxidant capacity of cells leads to oxidative stress (Dixon & Stockwell, 2014). Generally, due to the higher metabolic rate and the low rate of regeneration, nerve cells are more susceptible to oxidative damage (Manoharan et al., 2016).

Studies have shown that inefficient antioxidant system and the excess of free radicals such as superoxide anion, hydrogen peroxide and nitric oxide may be one of the causes of the emergence of Alzheimer's disease (Xie et al., 2002). Positive association between the amyloid plaque and 4-hydroxynonenal and malondialdehyde as the main lipid peroxidation markers proves this hypothesis to some extent (Massaad, 2011). Furthermore, it has been demonstrated that iron accumulation in the brain of AD patients is responsible for generating free radicals through the Fenton reaction (Zhao & Zhao, 2013).

On the other hand, it has been shown that sleep deprivation can reduce the function of the antioxidant system of the cells. Ramanathan et al. (2002) have showed that prolonged sleep deprivation profoundly decreases superoxide dismutase antioxidative activity in the hippocampus and brainstem of rats (Ramanathan, Gulyani, Nienhuis, & Siegel, 2002). Mathangi et al. (2012) have reported that paradoxical sleep deprivation is a potent oxidative stressor which is likely to play a role in the behavioral changes of animal models (Mathangi, Shyamala, & Subhashini, 2012). It has also been shown in humans that sleep deprivation can increase malondialdehyde (El-Helaly & Abu-Hashem, 2010). Therefore, it can be concluded that sleep deprivation increases the oxidative stress and may thus contribute to the etiology of Alzheimer's disease.

Endoplasmic reticulum damages

The endoplasmic reticulum (ER) is involved in folding and trafficking of proteins, redox homeostasis, energy production and apoptosis (Cao & Kaufman, 2014). Malfunctions of the ER may lead to a cell stress response, which can eventually trigger programmed cell death. Increasing evidence has emphasized on the role of ER in the development and progression of neurodegenerative diseases (Scheper & Hoozemans, 2015). Studies have indicated that apoptosis generally occurs through two main pathways: the death receptor (extrinsic) and the mitochondrial (intrinsic) pathways (Elmore, 2007).

It has been showed that, ER stress has a main role in the pathogenesis of AD. Inositol-requiring kinase 1 (IRE1) initiate the ER stress pathway by triggering apoptosis signal-regulating kinase 1 (ASK1), which in turn activated c-Jun N-terminal kinase (JNK) signaling route (Okazawa & Estus, 2002). This cascade has the potential to trigger AD pathogenesis through dysregulation of amyloid precursor protein (APP) processing and intracellular amyloid beta (A β) accumulation; activation of activator protein 1 (AP-1), a transcription factor that regulates inflammatory genes expression; and hyperphosphorylation of tau protein and aggregation of neurofibrillary tangles (Viana, Nunes, & Rodrigues, 2012).

Also, ER stress causes deposition of unfolded or misfolded proteins such as tau (Kanemoto & Wang, 2012; Naidoo, 2009). Prolonged presence of these toxic unfolded proteins triggers intrinsic apoptosis pathways (Fribley, Zhang, & Kaufman, 2009). Degradation of tau was decreased by 20% in ER stress due to decrease in the binding of tau to CHIP (carboxyl terminus of Hsc70-interacting protein), which delays the degradation of tau through the ubiquitin-proteasome pathway (Sakagami et al., 2013).

Sleep deprivation increases ER stress in brain tissue (Sakagami et al., 2013). REM sleep deprivation has been proposed to elevate the level of noradrenaline in the brain (Ranjan, Biswas, & Mallick, 2010). Animal studies have indicated that REM sleep deprivation changes BAX and Bcl2 functions and initiate mitochondrial apoptosis pathway (Ranjan et al., 2010). Somarajan et al. (2016) suggested that elevated noradrenaline acting on α 1-adrenergic receptor causes mitochondrial damage and release of cytochrome c and induction of apoptosis intrinsic pathway (Somarajan, Khanday, & Mallick, 2016). Therefore, it can be resulted that sleep deprivation can be related to the Alzheimer's pathology through induction of neuronal apoptosis.

Glymphatic system dysfunctions

In 2012, Iliff et al. discovered the dynamic characteristics of the glymphatic system in mice, using in vivo two-photon microscopy (Iliff et al., 2012). By fluorescent labeling of CSF, they showed the rapid entry of the CSF into the brain along the cortical pial arteries, following by influx into the Virchow-Robin spaces through penetrating arterioles. In fact, the CSF enters the parenchyma through a definite periarterial pathway surrounding by perivascular astrocytic endfeet (Iliff et al., 2012). It can be concluded that glymphatic system plays a key role in feeding the neurons and purgation of the brain's environment.

Glymphatic system works differently during sleep and awakening. It is hypothesized that during the sleep, the CSF flows more profusely and the elimination of toxic substances from neurons and intercellular spaces is greatly increased. When sleep is restricted, glymphatic system does not have enough time to fulfill its function, so, toxins and misfolded protein will be accumulated, and the effects will be appeared in cognitive capabilities and executive functions (Eugene & Masiak, 2015).

On the other hand, Weller and colleagues (2008) demonstrated that macroscopic glymphatic system-based clearance of interstitial metabolites may be of particular significance for neurodegenerative diseases like Alzheimer's, in which, the accumulation of protein aggregates is observed (Iliff et al., 2012). In this regard, Iliff et al. found that β -amyloid ($A\beta$) is rapidly broken down and eliminated in the glymphatic system route (Iliff et al., 2012). In other words, imbalance between $A\beta$ production and clearance can cause the accumulation of $A\beta$ and the emergence of Alzheimer's. As a result, it may be hypothesized that sleep deprivation is associated with a decrease in the ability of the glymphatic system and an increase in the accumulation of $A\beta$ and Alzheimer's etiology.

Orexinergic system inefficacy

The orexins (hypocretins), as hypothalamic neuropeptides, play an important role in sleep-wake cycle regulation (Sakurai, Pandi-Perumal, & Monti, 2015). Abnormal levels of these neuropeptides in people with sleep disorders led to research into its role in sleep regulation (Ebrahim, Howard, Kopelman, Sharief, & Williams, 2002). In humans, orexinergic neurons are restricted to the dorso-lateral hypothalamus and project densely to various regions like the locus coeruleus (LC), amygdala, suprachiasmatic nucleus, dorsal raphe nuclei and cholinergic brainstem (Mieda & Sakurai, 2016).

Although the role of the orexinergic system in sleep regulation is not certainly known, however, it is believed that orexinergic projections modulate cholinergic and monoaminergic activities during the sleep cycle. Indeed, inputs from suprachiasmatic nucleus to the orexinergic system exhibit the dependence of this system function on the dark-light cycle (Hungs & Mignot, 2001). Studies have shown a significant reduction in the number of orexinergic neurons in human narcolepsy (Mieda & Sakurai, 2016).

Mehta et al. (2015) measured orexin-A level in LC, cortex, posterior hypothalamus, hippocampus, and pedunculo-pontine area after 96 h REM sleep deprivation in rats (Mehta, Khanday, & Mallick, 2015). They reported that following by REM deprivation, the orexin-A level will be significantly increased in LC, cortex and posterior hypothalamus. Interestingly, they observed that after recovery, the level of orexin-A returned to its normal state.

On the other hand, it has been demonstrated that increases in orexin due to chronic sleep deprivation is involved in the pathogenesis of AD (Scammell, Matheson, Honda, Thannickal, & Siegel, 2012). Liguori et al. illustrated that patients with moderate-to-severe AD have higher levels of orexin and facing more nocturnal sleep disorders (Liguori et al., 2014). In addition, orexin-A has been proposed to be associated with increased phosphorylated-tau and this may be related to a reduction in the ratio of deep sleep (Osorio et al., 2016).

The biological role of sleep deprivation in Alzheimer's pathology

Sleep and circadian rhythm disturbances possibly occur very early in the pathogenesis process of AD. Experimental models suggest that sleep deprivation may increase the soluble $A\beta$ levels and lead to chronic accumulation of $A\beta$, whereas improving time and quality of sleep has the opposite effect (Y.-E. S. Ju, Lucey, & Holtzman, 2013). Furthermore, It has also been proven that this relationship can be reversed, and the accumulation of beta-amyloid may cause a sleep-wakefulness imbalance (Y.-E. S. Ju et al., 2013).

Using in vivo microdialysis in mice, Kang et al. (2009) found that the amount of $A\beta$ in brain interstitial fluid is correlated with wakefulness and is increased during orexin infusion, but is decreased with infusion of a orexin receptor antagonist (KANG, LIM, BATEMAN, LEE, & SMYTH 2009). Hoon Roh et al. (2012) Reported that disruption of the sleep-wake cycle can accelerate beta-amyloid deposition in the mouse brain (HOON ROH, YAFEI, BERO, & KASTEN, 2012).

Spira et al (2013) found that among older adults, shorter duration and poorer quality of sleep are associated with greater $A\beta$ accumulation (Spira, Gamaldo, An, & et al., 2013). Sharon et al. (2014) reported that evening and morning $A\beta_{42}$ concentrations are differed between the individuals with unrestricted sleep and those

with sleep deprivation (S. Ooms, S. Overeem, K. Besse, M. Rikkert, et al., 2014). Ju et al. (2017) reports that specific disruption of slow wave activity may increase amyloid- β 40 and worse sleep quality is associated with higher tau levels (Y. S. Ju et al., 2017).

Meco et al. (2014) observed that SD decreases levels of postsynaptic density protein 95 and increases glial fibrillary acidic protein levels. Moreover, they investigated that total levels of the phosphorylated transcription factor cellular response element binding protein will be significantly diminished in brains of sleep-deprived mice compared with controls. They underlined the importance of SD as a chronic stressor, in modulating biochemical processes involved in the development of AD (Di Meco et al., 2014).

In general, sleep deprivation appears to increase the accumulation of beta-amyloid and tau proteins, thus accelerating the formation of amyloid plaques and neurofibrillary tangles. On the other hand, increased accumulation of beta-amyloids and Tau proteins in turn disrupt the sleep-wake cycle, thus forming a defective cycle. As a result, it seems that increasing the duration and improving the quality of sleep can slow down the progression of the disease. However, given the extensive study of animals in this field (Mahmoudi, Ahmadian, Farajdokht, Majdi, & Erfani, 2017), most results are derived from animal studies and human clinical studies are required to confirm them.

Conclusions

In this article, we reviewed the most important factors in the relationship between sleep deprivation and Alzheimer's disease. It was discussed that APOE ϵ 4 allele could be associated with sleep disorders, tau phosphorylation and A β deposition; Sleep deprivation can increase active oxygen species and, as a result, damage mitochondria and induce apoptosis; Sleep deprivation reduces the activity of the glymphatic system and, consequently, reduces the capacity to remove A β ; By activating kinases, sleep deprivation may increase tau phosphorylation and cause the formation of neurofibrillary tangles; and, that all of the pathways in question, eventually lead to the emergence of Alzheimer's through neuronal degeneration, A β deposition, and neurofibrillary tangles formation (Schema 1). Therefore, considering the important role of sleep in modulating the risk factors of Alzheimer's disease, it may be possible to prevent the emergence of Alzheimer's disease at aging by improving the quality of sleep and treat sleep disorders at early ages.

References:

- Ahnaou, A., & Drinkenburg, W. (2011). Disruption of glycogen synthase kinase-3-beta activity leads to abnormalities in physiological measures in mice. *Behavioural brain research*, 221(1), 246-252 .
- Albrecht, U. (2012). Circadian rhythms and sleep—the metabolic connection. *Pflügers Archiv-European Journal of Physiology*, 463(1), 23-30 .
- Anderson, K. N., & Bradley, A. J. (2013). Sleep disturbance in mental health problems and neurodegenerative disease. *Nat Sci Sleep*, 5, 61-75 .
- Avila, J., León-Espinosa, G., García, E., García-Escudero, V., Hernández, F., & DeFelipe, J. (2012). Tau phosphorylation by GSK3 in different conditions. *International Journal of Alzheimer's Disease*, 2012 .
- Cao, S. S., & Kaufman, R. J. (2014). Endoplasmic Reticulum Stress and Oxidative Stress in Cell Fate Decision and Human Disease. *Antioxidants & Redox Signaling*, 21(3), 396-413. doi:10.1089/ars.2014.5851
- Cedernaes, J., Osorio, R. S., Varga, A. W., Kam, K., Schiöth, H. B., & Benedict, C. (2016). Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. *Sleep medicine reviews* .
- Cheng, H.-C., Qi, R. Z., Paudel, H., & Zhu, H.-J. (2011). Regulation and function of protein kinases and phosphatases. *Enzyme Res*, 2011, 794089 .
- Cirelli, C., Shaw, P. J., Rechtschaffen, A., & Tononi, G. (1999). No evidence of brain cell degeneration after long-term sleep deprivation in rats. *Brain research*, 840(1), 184-193 .
- Cox, P. A., Davis, D. A., Mash, D. C., Metcalf, J. S., & Banack, S. A. (2016). Dietary exposure to an environmental toxin triggers neurofibrillary tangles and amyloid deposits in the brain. *Proceedings of the Royal Society B: Biological Sciences*, 283(1823). doi:10.1098/rspb.2015.2397
- Cui, S. Y., Li, S. J., Cui, X. Y., Zhang, X. Q., Yu, B., Sheng, Z. F., . . . Lin, Z. G. (2016). Phosphorylation of CaMKII in the rat dorsal raphe nucleus plays an important role in sleep–wake regulation. *Journal of neurochemistry*, 136(3), 609-619 .
- Datta, S., & Desarnaud, F. (2010). Protein kinase A in the pedunculo-pontine tegmental nucleus of rat contributes to regulation of rapid eye movement sleep. *The Journal of Neuroscience*, 30(37), 12263-12273 .
- Di Meco, A., Joshi, Y. B., & Praticò, D. (2014). Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. *Neurobiology of Aging*, 35(8), 1813-1820. doi:<https://doi.org/10.1016/j.neurobiolaging.2014.02.011>
- Dixon, S. J., & Stockwell, B. R. (2014). The role of iron and reactive oxygen species in cell death. *Nature chemical biology*, 10(1), 9-17 .
- Ebrahim, I. O., Howard, R. S., Kopelman, M. D., Sharief, M. K., & Williams, A. J. (2002). The hypocretin/orexin system. *Journal of the Royal Society of Medicine*, 95(5), 227-230 .
- El-Helaly, M., & Abu-Hashem, E. (2010). Oxidative stress, melatonin level, and sleep insufficiency among electronic equipment repairers. *Indian Journal of Occupational and Environmental Medicine*, 14(3), 66-70. doi:10.4103/0019-5278.75692
- Elmore, S. (2007). Apoptosis: A Review of Programmed Cell Death. *Toxicologic pathology*, 35(4), 495-516. doi:10.1080/01926230701320337
- Eugene, A. R., & Masiak, J. (2015). The Neuroprotective Aspects of Sleep. *MEDtube science*, 3(1), 35-40 .
- Fribley, A., Zhang, K., & Kaufman, R. J. (2009). Regulation of apoptosis by the unfolded protein response. *Methods Mol Biol*, 559, 191-204. doi:10.1007/978-1-60327-017-5_14
- Ghosh, A., & Giese, K. P. (2015). Calcium/calmodulin-dependent kinase II and Alzheimer's disease. *Molecular brain*, 8(1), 1 .

- Giau, V. V., Bagyinszky, E., An, S. S., & Kim, S. Y. (2015). Role of apolipoprotein E in neurodegenerative diseases. *Neuropsychiatr Dis Treat*, *11*, 1723-1737. doi:10.2147/ndt.s84266
- Giese, K. P., & Mizuno, K. (2013). The roles of protein kinases in learning and memory. *Learning & memory*, *20*(10), 540-552.
- Graves, L. A., Hellman, K., Veasey, S., Blendy, J. A., Pack, A. I., & Abel, T. (2003). Genetic evidence for a role of CREB in sustained cortical arousal. *Journal of neurophysiology*, *90*(2), 1152-1159.
- Grewal, S. S., York, R. D., & Stork, P. J. (1999). Extracellular-signal-regulated kinase signalling in neurons. *Current opinion in neurobiology*, *9*(5), 544-553.
- Guan, Z., Peng, X., & Fang, J. (2004). Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. *Brain Res*, *1018*(1), 38-47. doi:10.1016/j.brainres.2004.05.032
- Hanger, D. P., Byers, H. L., Wray, S., Leung, K.-Y., Saxton, M. J., Seereeram, A., . . . Anderton, B. H. (2007). Novel phosphorylation sites in tau from Alzheimer brain support a role for casein kinase 1 in disease pathogenesis. *Journal of Biological Chemistry*, *282*(32), 23645-23654.
- Harrison, J. R., & Owen, M. J. (2016). Alzheimer's disease: the amyloid hypothesis on trial. In: RCP.
- Hellman, K., Hernandez, P., Park, A., & Abel, T. (2010). Genetic evidence for a role for protein kinase A in the maintenance of sleep and thalamocortical oscillations. *Sleep*, *33*(1), 19-28.
- Hickie, I. B., Naismith, S. L., Robillard, R., Scott, E. M., & Hermens, D. F. (2013). Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. *BMC medicine*, *11*(1), 1.
- HOON ROH, J., YAFEI, H., BERO, A. W., & KASTEN, T. (2012). Disruption of the Sleep-Wake Cycle and Diurnal Fluctuation of β -Amyloid in Mice with Alzheimer's Disease Pathology. *SCIENCE TRANSLATIONAL MEDICINE*, *4*(150), 28. doi:10.1126/scitranslmed.3004291
- Huang, Y., & Mahley, R. W. (2014). Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiology of disease*, *72*, 3-12.
- Hungs, M., & Mignot, E. (2001). Hypocretin/orexin, sleep and narcolepsy. *BioEssays*, *23*(5), 397-408. doi:10.1002/bies.1058
- Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., . . . Nedergaard, M. (2012). A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β . *Science translational medicine*, *4*(147), 147ra111-147ra111. doi:10.1126/scitranslmed.3003748
- Ittner, A., Chua, S. W., Bertz, J., Volkerling, A., van der Hoven, J., Gladbach, A., . . . Stevens, C. H. (2016). Site-specific phosphorylation of tau inhibits amyloid- β toxicity in Alzheimer's mice. *Science*, *354*(6314), 904-908.
- Ju, Y.-E. S., Lucey, B. P., & Holtzman, D. M. (2013). Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nature Reviews Neurology*, *10*, 115. doi:10.1038/nrneurol.2013.269
- Ju, Y. S., Ooms, S. J., Sutphen, C., Macauley, S. L., Zangrilli, M. A., Jerome, G. . . . Holtzman, D. M. (2017). Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. *Brain*, *140*(8), 2104-2111. doi:10.1093/brain/awx148
- Kadavath, H., Hofele, R. V., Biernat, J., Kumar, S., Tepper, K., Urlaub, H., . . . Zweckstetter, M. (2015). Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. *Proceedings of the National Academy of Sciences*, *112*(24), 7501-7506.
- Kadotani, H., Kadotani, T., Young, T., Peppard, P. E., Finn, L., Colrain, I. M. . . . Mignot, E. (2001). Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. *Jama*, *285*(22), 2888-2890.
- Kanemoto, S., & Wang, H. (2012). Roles of endoplasmic reticulum stress in neurodegenerative diseases. *Translational Medicine*, *2012*.

- KANG, J.-E., LIM, M. M., BATEMAN, R. J., LEE, J. J., & SMYTH, L. P. (2009). Amyloid- β Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle. *Science*, 326(5955), 1005-1007. doi:10.1126/science.1180962
- Kelly, Á., Laroche, S., & Davis, S. (2003). Activation of mitogen-activated protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. *Journal of Neuroscience*, 23(12), 5354-5360.
- Leoni, V., Solomon, A., & Kivipelto, M. (2010). Links between ApoE, brain cholesterol metabolism, tau and amyloid β -peptide in patients with cognitive impairment. *Biochemical Society Transactions*, 38(4), 1021-1025. doi:10.1042/bst0381021
- Liguori, C., Romigi, A., Nuccetelli, M., Zannino, S., Sancesario, G., Martorana, A., . . . Bernardini, S. (2014). Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA neurology*, 71(12), 1498-1505.
- Lim, A. S. P., Yu, L., Kowgier, M., Schneider, J. A., Buchman, A. S., & Bennett, D. A. (2013). Sleep Modifies the Relation of APOE to the Risk of Alzheimer Disease and Neurofibrillary Tangle Pathology. *JAMA neurology*, 70(12), 10.1001/jamaneurol.2013.4215. doi:10.1001/jamaneurol.2013.4215
- Lim, M. M., Gerstner, J. R., & Holtzman, D. M. (2014). The sleep-wake cycle and Alzheimer's disease: what do we know? *Neurodegener Dis Manag*, 4(5), 351-362. doi:10.2217/nmt.14.33
- Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nature reviews. Neurology*, 9(2), 106-118. doi:10.1038/nrneurol.2012.263
- Mahley, R. W. (2016). Central Nervous System Lipoproteins: ApoE and Regulation of Cholesterol Metabolism. *Arterioscler Thromb Vasc Biol*, 36(7), 1305-1315. doi:10.1161/atvbaha.116.307023
- Mahmoudi, J., Ahmadian, N., Farajdokht, F., Majidi, A., & Erfani, M. (2017). A Protocol for Conventional Sleep Deprivation Methods in Rats. *Journal Of Experimental and Clinical Neuroscience*, 4(1). doi:10.13183/jecns.v4i1.61
- Manoharan, S., Guillemin, G. J., Abiramasundari, R. S., Essa, M. M., Akbar, M., & Akbar, M. D. (2016). The Role of Reactive Oxygen Species in the Pathogenesis of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease: A Mini Review. *Oxidative Medicine and Cellular Longevity*, 2016, 8590578. doi:10.1155/2016/8590578
- Massaad, C. A. (2011). Neuronal and Vascular Oxidative Stress in Alzheimer's Disease. *Current Neuropharmacology*, 9(4), 662-673. doi:10.2174/157015911798376244
- Mathangi, D. C., Shyamala, R., & Subhashini, A. S. (2012). Effect of REM sleep deprivation on the antioxidant status in the brain of Wistar rats. *Annals of Neurosciences*, 19(4), 161-164. doi:10.5214/ans.0972.7531.190405
- Mehta, R., Khanday, M. A., & Mallick, B. N. (2015). REM sleep loss associated changes in orexin-A levels in discrete brain areas in rats. *Neurosci Lett*, 590, 62-67. doi:10.1016/j.neulet.2015.01.067
- Mieda, M., & Sakurai, T. (2016). Orexin (hypocretin) and narcolepsy. In *Narcolepsy* (pp. 11-23): Springer.
- Morris, J. C., Roe, C. M., Xiong, C., Fagan, A. M., Goate, A. M., Holtzman, D. M., & Mintun, M. A. (2010). APOE predicts amyloid - beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of neurology*, 67(1), 122-131.
- Naidoo, N. (2009). Cellular stress/the unfolded protein response: relevance to sleep and sleep disorders. *Sleep medicine reviews*, 13(3), 195-204.
- Navara, K. J., & Nelson, R. J. (2007). The dark side of light at night: physiological, epidemiological, and ecological consequences. *Journal of pineal research*, 43(3), 215-224.
- Nichol, K. E., Parachikova, A. I., & Cotman, C. W. (2007). Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. *Behavioural brain research*, 184(2), 124-132.

- Nunomura ,A., Perry, G., Aliev, G., Hirai, K., Takeda, A., Balraj, E. K., . . . Shimohama, S. (2001). Oxidative damage is the earliest event in Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*, *60*(8), 759-767 .
- Okazawa, H., & Estus, S .(2002) .The JNK/c-Jun cascade and Alzheimer's disease. *Am J Alzheimers Dis Other Demen*, *17*(2), 79-88. doi:10.1177/153331750201700209
- Ooms, S., Overeem, S., Besse, K., Rikkert, M., Verbeek, M., & Claassen, J. R. (2014). Effect of 1 night of total sleep deprivation on cerebrospinal fluid β -amyloid 42 in healthy middle-aged men: A randomized clinical trial. *JAMA Neurology*, *71*(8), 971-977. doi:10.1001/jamaneurol.2014.1173
- Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M., & Claassen, J. A. (2014). Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA Neurol*, *71*(8), 971-977. doi:10.1001/jamaneurol.2014.1173
- Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek ,M., & Claassen, J. A. (2014). Effect of 1 night of total sleep deprivation on cerebrospinal fluid β -amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA neurology*, *71*(8), 971-977 .
- Osorio, R. S., Ducca, E. L., Wohlleber, M. E., Tanzi ,E. B., Gumb, T., Twumasi, A., . . . de Leon, M. J. (2016). Orexin-A is Associated with Increases in Cerebrospinal Fluid Phosphorylated-Tau in Cognitively Normal Elderly Subjects. *Sleep*, *39*(6), 1253-1260. doi:10.5665/sleep.5846
- Ramanathan, L., Gulyani, S ,Nienhuis, R., & Siegel, J. M. (2002). Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. *Neuroreport*, *13*(11), 1387-1390 .
- Ranjan, A., Biswas, S., & Mallick, B. N. (2010). Cytomorphometric changes in the dorsal raphe neurons after rapid eye movement sleep deprivation are mediated by noradrenalin in rats. *Behavioral and Brain Functions*, *6*(1), 62. doi:10.1186/1744-9081-6-62
- Ray, P. D., Huang, B.-W., & Tsuji, Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cellular signalling*, *24*(5), 981-990. doi:10.1016/j.cellsig.2012.01.008
- Roh, J. H., Huang, Y., Bero, A. W., Kasten, T., Stewart, F. R., Bateman, R. J., & Holtzman, D. M. (2012). Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med*, *4*(150), 150ra122. doi:10.1126/scitranslmed.3004291
- Rothman, S. M., Herdener, N., Frankola, K. A., Mughal, M. R., & Mattson, M. P. (2013). Chronic mild sleep restriction accentuates contextual memory impairments, and accumulations of cortical A β and pTau in a mouse model of Alzheimer's disease. *Brain research*, *1529*, 200-208 .
- Ryu, S., Atzmon, G., Barzilai, N., Raghavachari, N., & Suh, Y. (2016). Genetic landscape of APOE in human longevity revealed by high-throughput sequencing. *Mechanisms of ageing and development*, *155*, 7-9 .
- Sadigh-Eteghad, S., Sabermarouf, B., Majdi, A., Talebi, M., Farhoudi, M., & Mahmoudi, J. (2015). Amyloid-beta: a crucial factor in Alzheimer's disease. *Med Princ Pract*, *24*(1), 1-10. doi:10.1159/000369101
- Sakagami, Y., Kudo, T., Tanimukai, H., Kanayama, D., Omi, T., Horiguchi, K., . . . Takeda, M. (2013). Involvement of endoplasmic reticulum stress in tauopathy. *Biochemical and biophysical research communications*, *430*(2), 500-504 .
- Sakurai, T., Pandi-Perumal, S. R., & Monti, J. M. (2015). Orexin and sleep. In: Springer.
- Scammell, T., Matheson, J., Honda, M., Thannickal, T., & Siegel, J. (2012). Coexistence of narcolepsy and Alzheimer's disease. *Neurobiology of aging*, *33*(7), 1318-1319 .
- Scheper, W., & Hoozemans, J. J. (2015). The unfolded protein response in neurodegenerative diseases: a neuropathological perspective. *Acta Neuropathol*, *130*(3), 315-331. doi:10.1007/s00401-015-1462-8

- Shanavas ,A., & Papasozomenos, S. C. (2000). τ kinases in the rat heat shock model: Possible implications for Alzheimer disease. *Proceedings of the National Academy of Sciences*, 97(26), 14139-14144 .
- Singh, T. J., Wang, J.-Z., Novak, M., Kontzekova, E., Grundke-Iqbal, I., & Iqbal, K. (1996). Calcium/calmodulin - dependent protein kinase II phosphorylates tau at Ser - 262 but only partially inhibits its binding to microtubules. *FEBS letters*, 387(2-3), 145-148 .
- Somarajan, B. I., Khanday, M. A., & Mallick, B. N .(2016) .Rapid Eye Movement Sleep Deprivation Induces Neuronal Apoptosis by Noradrenaline Acting on Alpha1 Adrenoceptor and by Triggering Mitochondrial Intrinsic Pathway. *Frontiers in Neurology*, 7, 25. doi:10.3389/fneur.2016.00025
- Spira, A. P., Gamaldo, A. A., An ,Y., & et al. (2013). Self-reported sleep and β -amyloid deposition in community-dwelling older adults. *JAMA Neurology*, 70(12), 1537-1543. doi:10.1001/jamaneurol.2013.4258
- Takashima, A. (2006). GSK-3 is essential in the pathogenesis of Alzheimer's disease *Journal of Alzheimer's Disease*, 9(3 Supplement), 309-317 .
- Tisko, R., Sopkova, Z., Habalova, V., Dorkova, Z., Slaba, E., Javorsky, M., . . . Tkacova, R. (2014). Effects of apolipoprotein E genotype on serum lipids in obstructive sleep apnoea. *European Respiratory Journal*, 43(4), 1097-1105. doi:10.1183/09031936.00098513
- Viana, R. J., Nunes, A. F., & Rodrigues, C. M. (2012). Endoplasmic reticulum enrollment in Alzheimer's disease. *Mol Neurobiol*, 46(2), 522-534. doi:10.1007/s12035-012-8301-x
- Wilckens, K. A .,Woo, S. G., Kirk, A. R., Erickson, K. I., & Wheeler, M. E. (2014). Role of sleep continuity and total sleep time in executive function across the adult lifespan. *Psychology and aging*, 29(3), 658 .
- Xie, Z., Wei, M., Morgan, T. E., Fabrizio, P., Han, D ,.Finch, C. E., & Longo, V. D. (2002). Peroxynitrite mediates neurotoxicity of amyloid beta-peptide1-42- and lipopolysaccharide-activated microglia. *J Neurosci*, 22(9), 3484-3492. doi:20026340
- Zhao, Y., & Zhao, B. (2013). Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxidative medicine and cellular longevity*, 2013 .

Figure Captions

Schema 1. The pathways discussed in this study that relate sleep deprivation and Alzheimer's disease. The red arrows show the stimulatory effect and the blue arrows indicate the inhibitory effect.

Accepted Manuscript