Age Associated Sleep Loss: A Trigger For Alzheimer’s Disease

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ABSTRACT:
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Alzheimer’s disease (AD) is an untreatable, multifactorial, chronic, progressive, neurodegenerative disorder, which is the principal cause of dementia throughout the world and the fourth most important cause of death in developed economies after cancer, cardiovascular diseases, and vascular stroke. The so-called Alzheimer’s epidemic inevitably represents a major health problem to most nations, because there is no effective cure or preventive measure. Present cholinergic and glutamatergic drugs for the treatment of AD are largely symptomatic with temporary clinical benefits regarding cognitive, functional and behavioral manifestations of the disease but with no effect on its progression. Thus, there is a crucial need to discover new and efficient therapeutic strategies. Targeting behavioral aspects of AD represents an approach that may bear fruit, taking a cue from the success of cholinergic treatments in AD. Loss of sleep is a common problem associated with aging and with AD in particular. Clinical evidence has showed that people who suffer from chronic insomnia are about 11 times more likely to develop Alzheimer’s disease in later life. Sleep, a behavioral state exhibited by nearly all species, is common in the animal kingdom and has been well preserved in the course of evolution. Sleep is widely considered to be instrumental in maintaining health and cognitive functions. It is a major modulator of several developmental processes including hormone release, glucose regulation, cardiovascular functions, neurogenesis, immune functions, and physiologic balance and resilience. Reduced sleep duration and quality appears to be endemic in modern society; it is a stressor affecting the brain in many ways, including loss of memory and cognitive functions. Alzheimer’s disease is typically accompanied by daytime sleepiness and napping as well as severe disruption of nighttime sleep patterns; indeed, disruption of nighttime sleep is often cited as the primary reason for institutionalization of patients. In this review, recent and updated evidence linking sleep disruption to pathological factors playing a decisive role in the progression of Alzheimer’s disease is discussed.

Keywords: Alzheimer’s disease, amyloid β, cytokines, excitotoxicity, hippocampus, sleep


INTRODUCTION

Sleep began to be understood when it was associated with rapid eye movement (REM) by Aserinsky and Kleitman in 1953¹. A complex behavioral state and one of the great mysteries of modern neuroscience², sleep is thought to be a process that serves neuronal recovery and synaptic plasticity, which in turn are crucial for brain function and performance³⁴.
In addition, sleep appears to be essential for the survival and integrity of most living organisms. Many non-mutually exclusive roles have been attributed to sleep, including brain thermoregulation\(^5\), neuronal detoxification\(^6\), energy conservation\(^7\), tissue restoration\(^8\), immune defense\(^9\) and brain plasticity\(^10\).

**Sleep Cycle and Its Regulation**

Normal human sleep consists of two main states: rapid eye-movement (REM) sleep and non-REM sleep. Non-REM sleep can be further divided into light (S1-S2) and deep (S3-S4) stages. Each sleep stage can be recognized by its distinct characteristics in polysomnography, electroencephalography, electrooculography and electromyography recordings. S3 and S4 together are called slow-wave sleep (SWS) or delta sleep, based on the presence of high-amplitude, slow (2 Hz or slower) delta waves. During the night, the non-REM and REM sleep phases alternate cyclically. Sleep normally begins with S1, progresses through S2 and S3 to S4, and finally to REM sleep. This cycle is repeated every 70 to 110 min, four to six times a night. SWS predominates during the first third of the night, whereas REM sleep predominates during the last third\(^11,12\).

According to the current and widely accepted model of sleep regulation, sleep is controlled by two separate components: a circadian component C and a homeostatic component S\(^13\). Process C affects the appropriate timing of sleep and is mainly controlled by the genetically driven rhythmic activity of the suprachiasmatic nucleus (SCN) in the hypothalamus.

Process S accounts for a sufficient amount of sleep: it accumulates during wakefulness and declines during sleep. It is controlled by several interacting neural systems in the hypothalamus, basal forebrain and brainstem nuclei\(^13,14\).

A number of different neurotransmitters participate in the regulation of sleep. The wake promoting system, which shows high activity levels during wakefulness, consists of neuronal networks producing acetylcholine, amines, and orexins. The sleep-promoting neurons located in the anterior hypothalamus ventrolateral preoptic area contain the inhibitory transmitters gamma-aminobutyric acid (GABA) and galanin, and these produce sleep by inhibiting the wake-promoting brain regions. REM sleep is controlled mainly by an interaction of cholinergic and aminergic brainstem neurons\(^15,16\).

Disturbances of sleep-wake cycles are related to alterations in the suprachiasmatic nucleus,\(^17\) which is a small nucleus of the anterior hypothalamus located directly dorsal to the optic chiasm (from which it receives direct retinal innervations) that is composed of a neurochemically and functionally heterogeneous assembly of neurons\(^18\).

**Sleep Deprivation and Consequences**

Our sleep time has decreased by 20% over the last century\(^19\). Importantly, not only adults experience sleep loss. The incidence of sleep loss and excessive daytime sleepiness is becoming a great issue in children and adolescents as well\(^20\).

For a variety of reasons, either by lifestyle choice, imposed by work or family demands, or due to physical or psychological problems, chronic sleep deprivation is increasingly common\(^21,22\). Societal changes, such as an increase in television viewing and internet use, have affected sleep patterns, leading to chronic sleep deprivation in a substantial proportion of the population\(^21\). Furthermore, the quality of sleep declines with age, with a major reduction in the duration of slow wave sleep and increased sleep fragmentation\(^23\).

Virtually all forms of sleep deprivation result in increased negative mood states; especially feelings of fatigue, loss of vigor, sleepiness, confusion and feelings of irritability, anxiety, and depression are believed to results from inadequate sleep\(^24\).

Sleep deprivation affects the homeostatic component S of sleep regulation. It impairs the ability to maintain consolidated waking\(^25\) and is followed by a rebound increase in sleep. The increases in SWS and delta power during recovery
Age associated sleep loss: a trigger for Alzheimer's disease

Sleep correlate with the duration of the preceding sleep-deprivation period\textsuperscript{12,26}. SWS is thus thought to represent the vitally important component of sleep, which has to be primarily replenished after sleep deprivation.

**Age-Associated Changes in Sleep Pattern**

Aging leads to important circadian rhythm changes that are thought to manifest themselves as rather characteristic behavior patterns\textsuperscript{27}. One of these disrupted mechanisms is the melatonin system, in which five main changes have been noticed\textsuperscript{28}. The first change refers to a consistent decrease of pineal function with age.

The second change concerns the light input pathway. In fact, with age there is an unconscious reduction in photoreception due to pupillary miosis and impaired crystalline lens light transmission (especially blue light) by melanopsin-containing retinal ganglion cells. This is thought to lead to sleep problems and contribute to the development of affective disorders\textsuperscript{29}.

The third change takes place in the central nervous system, and consists of impaired pineal innervation/interconnection between the suprachiasmatic nucleus and the pineal gland, due to age or generalized central nervous system dysfunction. This impaired connection can cause dephased or flattened melatonin rhythms with decreased secretion\textsuperscript{30}.

Fourthly, localized pineal dysfunction (mainly pineal calcification) can reduce melatonin secretion by itself and can cause poor feedback on the SCN\textsuperscript{28}. Finally, SCN degeneration also takes place. The number of cells does not actually change; however, gene expression is dramatically altered\textsuperscript{31}.

Other age-related changes that can disrupt the circadian system are obesity, memory problems\textsuperscript{32}, the degeneration of the peripheral oscillators (as opposed to a main degeneration of central circadian controllers\textsuperscript{33}), and the presence of multiple chronic diseases (chronic pain, chronic inflammatory diseases such as arthritis) associated with a greater risk of developing sleep problems\textsuperscript{32,34}. Ageing of the circadian system results in a further decline of mental performance, but it is also involved in specific age-associated neurodegenerative diseases such as Alzheimer’s, Parkinson’s and Huntington’s\textsuperscript{35}.

Disruptions of sleep and circadian rhythms are common and early signs of these neurodegenerative diseases. Abnormalities in the circadian clock and in sleep quality worsen as these diseases progress\textsuperscript{35,36}.

Additionally, many pathways involved in neuro-degeneration, such as metabolism, reactive oxygen species (ROS) homeostasis and oxidative stress response, DNA damage repair and, potentially, autophagy, are controlled by the circadian clock. Therefore, defects in circadian clock functions may have etiopathogenic roles in the diseases referred to above\textsuperscript{31}.

**Sleep Deprivation and Neurodegeneration**

Loss of sleep is the most common sleep complaint in older adults\textsuperscript{37} and increases as a function of age\textsuperscript{32}. Alzheimer’s disease (AD) is typically accompanied by daytime sleepiness and napping as well as severe disruption of night time sleep patterns, and the latter is often cited as the primary reason for the institutionalization of patients\textsuperscript{38,39}.

During aging, brain volume and weight decline, while the ventricular volume increases. At the subcellular level, changes related to aging include decreased levels of neurotransmitters and impaired maintenance of intracellular ATP levels. Furthermore, calcium dysregulation, mitochondrial dysfunction and the production of reactive oxygen species have been described. In addition, in women, the declining levels of estrogen in menopause can have negative effects on brain energy metabolism.

Sleep serves neuronal recovery and synaptic plasticity. It is generally thought that lack of sleep has harmful effects that may impair neuronal integrity and perhaps contribute to neurodegeneration.
During most of the 20th century, neurodegenerative diseases have remained among the most enigmatic disorders known to medicine, with AD being the most common neurodegenerative disease. Aging and AD are characterized by episodic memory impairment and changes in global sleep architecture. Patients with AD have been described as having radical sleep architectural alterations.

**Sleep Deprivation and Alzheimer’s Disease**

Forty-five percent of Alzheimer patients have disruptions in their sleep and sundowning agitation. Clinical evidence has showed that people who suffer from chronic insomnia are about 11 times more likely to develop AD in later life. Factors that may underlie this increased prevalence include depression, anxiety, pain, sleep disorders and other medical disorders that disturb sleep, and menopause.

AD is a progressive dementia that manifests in early stages primarily as a profound inability to form new memories. The basis for this specificity is unknown, but evidence suggests the involvement of neurotoxins derived from the self-associating amyloid β peptide (Aβ). The original amyloid cascade hypothesis, developed from these findings, thus attributed AD memory loss to neuron death caused by fibrillar Aβ.

Several factors that contribute to the pathogenesis of AD are discussed here, and their interactions with sleep are compiled to present the evidence that advocates for a prominent influence of sleep on the progression of AD.

**Amyloid β**

The deposition of amyloid β protein in brain areas involved in cognitive functions is assumed to initiate a pathological cascade that results in synaptic dysfunction, synaptic loss, and neuronal death in AD. Sleep is the homeostatic method responsible for the clearance of toxic metabolic by-products accumulated during wakefulness. There exists a marked difference between physiological clearance of cellular waste from the central nervous system and peripheral tissues. Systemic waste interstitial proteins are transported via lymph vessels and the systemic circulation to the liver for degradation. The brain lacks this mechanism and relies on the recirculation of cerebrospinal fluid, which acquires waste proteins as it flows through the interstitial spaces surrounding brain cells before interfacing with the systemic circulation at the arachnoid granulations. This convective mechanism constitutes the glymphatic system and relies on aquaporin 4 (AQP4) water channels for effective clearance of waste solutes. Many of the proteins putatively associated with neurodegeneration are found in the interstitial fluid surrounding brain cells and knocking out AQP4 channels reduces the clearance of Aβ by 65%.

Given the fact that Aβ aggregation is associated with poor sleep-wake patterns and occurs years prior to clinical manifestations of AD, alterations in sleep may be an early event in AD.

Kang and colleagues showed that brain interstitial fluid Aβ concentrations increase during the hours of wakefulness and decrease during sleep. Chronic sleep deprivation significantly raises Aβ levels in the hippocampus, and within 3 weeks leads to greater plaque deposition. Via a destructive positive feedback loop, aggregation of Aβ for longer stretches will then disrupt the sleep-wake cycle, increase time spent awake, and decrease SWS. In contrast, the concentration of amyloid beta in the cerebrospinal fluid (CSF) decreases during sleep, a period during which the brain is minimally sensitive to environmental factors. As the production of Aβ peptides in the brain is intimately linked to neuronal activity, these findings suggest that nocturnal sleep may function as an offline period (i.e., a period with low sensory output) during which the brain recovers from daytime Aβ peptide accumulation.

Furthermore, neuronal damage has also been found to be indicated by elevations of two other
Age associated sleep loss: a trigger for Alzheimer's disease

With this in mind, the increase in morning serum concentrations of NSE and S-100B observed after a single night of sleep loss in experimental subjects might be caused by an increased nocturnal ROS production in the brain.

**Mao and Melatonin**

Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan metabolite synthesized mainly in the pineal gland, has a number of physiological functions, including regulating circadian rhythms, clearing free radicals, improving immunity and generally inhibiting the oxidation of biomolecules. Decreased melatonin in serum and CSF and the loss of the melatonin diurnal rhythm are observed in AD patients.

Patients with AD have lower melatonin levels versus age-matched controls and display irregularities in cyclic melatonin secretion. Serotonin, a key independent regulator of circadian sleep-wake cycles and a precursor of melatonin, is altered in AD via several proposed mechanisms, including serotonergic denervation and alterations in tryptophan availability. Changes in the sleep-control clock, the suprachiasmatic nucleus and the pineal gland are associated with normal aging but are even more pronounced in AD.

In addition, monoamine oxidase A (MAO-A) is the X-linked gene responsible for the degradation of several neurotransmitters. The gene has been shown to play a wide-ranging role in several aspects of circadian rhythm, including sleep regulation. Inhibition of monoamine oxidase via monoamine oxidase inhibitors (MAOIs) results in a variety of altered sleep patterns, such as insomnia, sedation and rapid eye movement sleep suppression. Recent research has demonstrated that in AD, upregulation of MAO-A facilitates oxidation of serotonin (5-HT) to 5-hydroxyindoleacetic acid (5-HIAA), thus reducing the direct influence of 5-HT on sleep regulation and also via its availability for conversion to melatonin. Linked to this, there is evidence that MAO-A and related genes play a neuro-chemical markers: neuron-specific enolase (NSE), an enzyme found in all neurons, and S100 calcium binding protein B (S100B), a protein which is mainly found in the glial cells of the peripheral and central nervous system. It has been demonstrated that in healthy young men a single night of sleep loss increases morning serum concentrations of NSE and S-100B by about 20% relative to values obtained after one night of sleep. These findings therefore suggest that a good night’s sleep may possess a neuroprotective function in humans.

**Oxidative Stress**

Oxyradical-induced damage to macromolecules (lipids, proteins, nucleic acids, etc.) is considered to be an important factor in the acceleration of aging and age-related neurodegenerative disorders such as Alzheimer’s disease. Sleep might involve the elimination of toxic compounds (e.g. free radicals) and the replenishment of energy stores. Sleep deprivation might reduce antioxidant defenses, since the activity of antioxidant enzymes such as superoxide dismutase (SOD) in the brainstem and hippocampus is also decreased by sleep deprivation.

Indeed, increases in hypothalamic and thalamic oxidative stress levels have been found in sleep-deprived rats.

Mitochondrial gene expression is also altered, which may lead to oxidative stress.

In addition, during a normal sleep-wake cycle, sleep represents a period during which brain glucose metabolism drops by approximately 30%, compared with values obtained during wakefulness. One reason for this sleep-related drop in central nervous system energy expenditure might be that the thalamic relay of environmental information to sensory cortical areas is dampened. In contrast, during nocturnal wakefulness, this relay of sensory information is nearly as high as it is during daytime. Substrate oxidation ultimately leads to the production of reactive oxygen species (ROS), such as hydrogen peroxide, and ROS can damage neurons and even induce cell death.
causative role in disease states\textsuperscript{86}.

Direct depletion of serotonin and its diversion into the MAO-A degradation pathway consequently lowers the overall rate of melatonin synthesis, with subsequent additional effects on the sleep-wake cycle\textsuperscript{87}.

It is known that melatonin levels in the cerebrospinal fluid fall dramatically in AD, compared with controls\textsuperscript{89,90}. Neurodegeneration may directly deplete pineal melatonin levels via damage to the suprachiasmatic nucleus-pineal axis\textsuperscript{87}.

**Serotonin**

Insufficient sleep may also affect brain vulnerability through changes in neurotransmitter systems, mainly the serotonergic system. The serotonergic system plays an important role in the regulation of the sleep wake cycle\textsuperscript{91}. The extracellular concentration of serotonin in the brain stem and in cortical and sub-cortical areas receiving serotonergic projections is highest during waking, decreases during slow wave sleep and reaches its lowest values during REM sleep. This reflects the discharge pattern of the serotonergic neurons in the dorsal raphe nucleus, which show the highest activity during the waking period, decrease their firing in slow wave sleep and are silent in the phase of REM sleep\textsuperscript{91,92}. The serotonergic system is sensitive to sleep loss; sleep deprivation in rodents increases the firing rate of serotonergic neurons in the dorsal raphe\textsuperscript{93} and increases the release and concentration of serotonin in some of the projection areas such as the hippocampus. It also enhances the serotonin turnover and decreases serotonin transporter binding in some brain areas\textsuperscript{94}.

These results indicate a potentiated serotonergic signaling following sleep deprivation. Chronic sleep restriction in animals has been shown to cause a gradually developing desensitization of serotonin-1A receptors (5-HT1A)\textsuperscript{95}. Reduced sensitivity of the 5-HT1A receptor system due to sleep loss may also alter neuronal plasticity and enhance the sensitivity to neurodegeneration\textsuperscript{96}.

**Sleep Deprivation and Excitotoxicity**

Aβ not only induces neuronal death but also enhances glutamate-induced excitotoxicity. Excessive amount of glutamate would cause NMDA receptor mediated Ca\textsuperscript{2+} overload, disrupt homeostasis, and induce neuronal death\textsuperscript{97}.

Wakefulness and prolonged wakefulness by sleep deprivation are associated with synaptic potentiation, which is in part the result of enhanced expression of glutamate receptors\textsuperscript{98}. The stimulation of glutamate receptors on neurons induces the influx of calcium, which has important signaling functions inside the cell but may also lead to neuronal damage through different pathways when concentrations become too high\textsuperscript{99}.

Expression of molecules that take part in calcium-dependent neurodegenerative and neuroprotective pathways such as Ca\textsuperscript{2+}/calmodulin-dependent protein kinase and calcineurin\textsuperscript{100,101} are altered in sleep deprived animals\textsuperscript{102}. Molecules having a function in neuroprotection to prevent calcium toxicity like cAMP response element-binding, brain derived neurotrophic factor and nerve growth factor\textsuperscript{103,104} show different expression during sleep deprivation\textsuperscript{102,105}.

**Sleep Deprivation and Cytokines**

In the AD brain, Aβ proteins, neurofibrillary tangles and neuronal degeneration seem to be the most likely sources of inflammation\textsuperscript{106}. Inflammatory responses within the brain are mainly given by activated microglia and reactive astrocytes. Once activated, microglia phagocytose foreign substances and release pro-inflammatory molecules, such as cytokines including interleukins (ILs), interferons (INFs), tumor necrosis factors (TNFs), and growth factors that further activate other inflammatory responses and thus potentiate the cycle\textsuperscript{107}.

The number of monocytes, a major source of cytokines, has been shown to increase during sleep deprivation of 39 hours\textsuperscript{108}. Prolonged sleep deprivation of 5 days causes IL-6 levels to increase compared to control individuals\textsuperscript{109}. 
Neurogenesis and Sleep Loss

The generation of new neurons in the adult brain has been associated with hippocampal functioning, memory formation and emotional regulation. Sleep loss can inhibit cell proliferation and neurogenesis in the dentate gyrus of the hippocampus.

The levels of neurogenesis in the hippocampus is regulated by a wide variety of molecules, including neurotransmitters, hormones, cytokines and growth factors. These factors are sensitive to various conditions including stress, inflammation, and aging. Sleep loss could decrease neurogenesis levels by activating stress systems. Sleep depravation decreases neurogenesis by increasing circulating levels of the adrenal stress hormone corticosterone. However, other studies showed that the negative effects of sleep loss on neurogenesis do not depend on corticosterone levels. Other potential mechanisms underlying the effect of sleep loss may involve changes in neurotransmitter systems, inflammatory processes, neurotrophic factors and cell signals that regulate neurogenesis.

Sleep Loss and Changes in the Hippocampus

One of the brain regions which appears to be particularly sensitive and vulnerable to sleep loss is the hippocampus. The hippocampus plays an important role in cognition and emotion regulation and is one of the few brain regions that display consistency in neurogenesis from adolescence into adulthood. Diminished hippocampal neurogenesis and its reduced volume have been implicated in the etiology and symptomatology of depressive and emotional disorders including AD.

Evidence suggesting a link between sleep loss and neurodegeneration comes from the diminished volume of the hippocampus and some other brain regions both in sleep-restricted humans and in experimental animals. Studies have indicated an enhanced expression of hippocampal glutamate receptors and Ca2+-induced excitotoxicity following sleep deprivation. Earlier findings have reported that the activity of the antioxidant enzyme superoxide dismutase (SOD) in the brainstem and hippocampus can be decreased by sleep deprivation. Thus conditions which activate reactive oxygen species can trigger a cascade of events which facilitate the release of proinflammatory factors such as TNFα and interleukins (IL-1 and 6) in different brain areas including the hippocampal region.

Furthermore, these substances have been shown to attenuate the secretion of brain-derived neurotrophic factor (BDNF) which is a neuroprotective factor. Hippocampal BDNF has been shown to contribute critically to synaptic plasticity, long-term potentiation (LTP) and hence memory function. There are reports indicating that after sleep deprivation, BDNF secretion and therefore its concentration is diminished in areas of the brain including brain stem, hippocampus and cerebellum. This suggests that sleep plays a role in the secretion of BDNF. Due to the BDNF contribution to learning and memory processes, sleep deprivation is perceived to affect memory function negatively.

Concluding Remarks

Humans spend one third and rats half of their lives asleep. In January 1965, Randy Gardner, a San Diego high school student, created a new Guinness World Record by staying awake for 264 hours – or 11 whole days. This review summarizes the evidence linking age-associated sleep deprivation with neurodegeneration in general and with Alzheimer’s disease in particular. The literature reviewed in the present article makes the case that sleep influences several factors like oxidative stress, neurogenesis, excitotoxicity, inflammation and mainly amyloid β, which are inseparable and constitute the main causes of Alzheimer’s disease. The present article advocates sleep loss as a prominent diagnostic feature of Alzheimer’s disease and also argues that treatment of insomnia should be given due consideration when choosing therapeutic options for AD.
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Age associated sleep loss: a trigger for Alzheimer’s disease

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87


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Age associated sleep loss: a trigger for Alzheimer’s disease


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