

Sleep Disturbances Generate Alzheimer's Disease Through Inflammation

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Abstract. As the world's population ages, more and more people are suffering from Alzheimer's disease. Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss and dementia. In recent years, the research on Alzheimer's disease has gradually extended to other directions, among which the relationship between neuroimmunity and Alzheimer's disease has attracted attention. The pathological features of AD include deposition of β -amyloid ($A\beta$), neurofibrillary tangles TAU, and neuronal loss. Studies have shown that sleep disturbances are factors that induce cellular and molecular inflammatory changes. Most people with Alzheimer's disease (AD) experience some form of sleep disruption, including nighttime sleep fragmentation, increased daytime napping, decreased slow-wave sleep (SWS, stage N3), and decreased rapid eye movement sleep (REM). In recent years, increasing evidence has shown that sleep disturbances can lead to cognitive decline and may increase the risk of Alzheimer's disease dementia by triggering inflammation through increased beta-amyloid burden. This article will explain the connection between sleep disorders, inflammation, and Alzheimer's disease. It also elaborates on the mechanisms by which inflammatory factors trigger Alzheimer's disease, sleep disorders activate inflammatory pathways, and prevention and treatment of Alzheimer's disease by means of anti-inflammatory and sleep therapy. In the future, research and exploration of drugs to treat inflammation in sleep disorders will also be important for preventing Alzheimer's disease.

Keywords: Sleep disturbances, Alzheimer's disease, Inflammation.

1. Introduction

The most common neurodegenerative diseases affecting sizable portions of the cerebral cortex and hippocampus are Alzheimer's disease [1]. It begins slowly and progresses insidiously. Progressive memory loss and other cognitive dysfunctions are its hallmarks. Extraneuronal toxic amyloid oligomers and proteins, as well as intraneuronal neurofibrillary tangles which constitute hyperphosphorylated tau, are blamed for neurodegeneration [2].

There is a bidirectional relationship between Sleep disturbance and Alzheimer's disease. Sleep disorders are frequent in Alzheimer's disease (AD). Micro-architectural sleep alterations, nocturnal sleep fragmentation, decrease in nocturnal sleep duration, diurnal napping and even inversion of the sleep-wake cycle are the main disorders observed in patients with AD [3].

Sleep issues were qualitatively comparable across AD dementia patients and healthy aged people. However, the REM sleep exhibited particular abnormalities, and the degree of the changes was often higher. With an increase in the frequency and length of awakenings, AD dementia is frequently characterized by increased wakefulness, which makes sleep more interrupted at night and leads to shorter total sleep time and worse sleep efficiency. As a result, these individuals showed a larger percentage of stage 1 and stage 2 sleep and a lower percentage of slow-wave sleep.

Although several early research in the 20th century suggested that sleep disruptions might serve as a risk factor for dementia occurrence, the predominate belief at the time was that both disorders developed simultaneously as aging progressed. This idea was challenged lately when it emerged from a few studies of incident dementia that those who reported sleep problems in middle age had a higher chance of developing Alzheimer's disease (AD) than those who did not.

Alzheimer's disease and sleep disorders manifest in the excitation or suppression of inflammatory factors. The markers tumor necrosis factor alpha (TNF- α), interleukin (IL)-1 β , and CD86, for example, were found to be increased in A β -stimulated microglia in an in vitro investigation [4]. Inflammation of the astrocytes also activates the NF- κ B and Stat6 pathways. Excretory/secretory substances trigger the NF- κ B pathway, which in turn induces the production of IL-1 β and IL-6 [5]. Research shows that Higher levels of CRP and IL-6 were linked to sleep disruption. In a meta-analysis of Alzheimer's disease, it was associated with considerably higher levels of IL-1 β than controls.

2. Implications of inflammatory factor for AD

2.1. Transcription factor---NF- κ B expression

Numerous neurodegenerative diseases, including Alzheimer's disease, are linked to NF- κ B activation [4]. NF- κ B has been postulated to play both neurotoxic and neuroprotective roles, with the outcome probably depending on the timing, duration, and intensity of activity. P2X7/NLRP3/caspase1 pathways activate the nuclear factor-kappa B (NF- κ B) and NLRP3 inflammasome which are closely related to Alzheimer's disease (AD) through inflammation. Hence, targeting these proteins to combat the AD pathogenesis may be a sensible tactic. NF κ B is strictly controlled by its inhibitor protein I κ B, which isolate NF κ B in the cytoplasm, under the normal circumstances. After I κ B is degraded, NF κ B moves to the nucleus where it triggers the expression of κ B genes, including I κ B, to create an autoinhibitory feedback loop. It makes sure NF κ B is properly silenced after each activation. As a result, abnormal NF κ B activation and a range of immunological phenotypes arise.

2.2. Pro-inflammatory factors: TNF- α , IL-6, [IL]-1 β

Several types of cells can create TNF- α , a 25 kDa transmembrane protein. However, macrophages which are located in the brain can synthesize the monocytic cell. The immune response in numerous target organs, including the brain, has been regarded to as being master-regulated by TNF- α [5]. The level of this pro-inflammatory cytokine is increased in the cerebrospinal fluid of AD patients, and it is directly correlated with the development of the illness. The chronic generation of TNF- α by microglia causes a neuro-inflammatory reaction linked to multiple sclerosis, Parkinson's disease, and Alzheimer's disease [6]. The amyloid- β plaques and tau protein, which are known to worsen AD patients' brains' condition, may also be caused by this TNF- α mediated inflammation. Genetic and pharmaceutical techniques that increase TNF-signaling aggravate A β and tau-protein accumulation in animal models. According to a growing body of research, Targeting TNF- α may be a biologically feasible way to enhance cognition among the elderly that would possibly treat or prevent AD.

Involved in several neurological illnesses including Alzheimer's and Parkinson's disease, inflammatory colon cancer, arthritis, and inflammatory bowel disease, IL-6 trans-signaling is more connected to its pro-inflammatory effects. IL-6 is produced by macrophages, T-lymphocytes, endothelial cells, smooth muscle cells and adipocytes.

There are three signaling pathways for IL-6: In the classic signaling, IL-6 triggers dimerization of gp130 and subsequent downstream JAK/STAT signaling by binding to a particular membrane receptor (mIL-6R). In the trans-signaling, IL-6 activates gp130 by binding to the soluble version of the mIL-6R (sIL-6R). The majority of cells in the body can be activated by this procedure since gp130 is widely expressed. The soluble version of gp130, or sgp130, selectively inhibits the trans-signaling of IL-6. The third pathway is referred to as cluster signaling, It is thought to be the only mechanism of communication between DCS and T cells [7].

According to earlier studies, elevated levels of the cytokine IL-6 were discovered to occur before Alzheimer's disease. Studies using the so-called GFAP-sgp130Fc mice, which express sgp130Fc in astrocytes, have shown that inhibiting IL-6 trans-signaling with the sgp130Fc protein reduces inflammation-related damage in peripheral tissues and in the CNS. Additionally, it has been found IL-6R mutation p. D358A, which increases the quantity of sIL-6R produced as a result of its increased

proteolysis by ADAM10 and ADAM17, may get Alzheimer's disease in APOE 4 carriers in advance [8].

Macrophages, endothelial cells and astrocytes generate IL-1 β . Griffin et al. discovered that IL-1 β has a significant impact on the development of neurological alterations in Alzheimer's disease. The blood-brain barrier have been through by IL-1 β , which changes the HPA axis. Therefore, Alzheimer's patients' brains produce and accumulate amyloid plaques and tau phosphorylation as a result of IL-1 β 's role due to creation of amyloid precursor protein (APP), which is a crucial process in Alzheimer's disease. Our team have demonstrated that IL-1 β lead to chronic inflammation which aggrandize pathological tau phosphorylation. Futhermore, Ada et al. discovered in a Systematic Review and Meta-Analysis that the aged with Alzheimer's disease had elevated peripheral blood IL-1 β levels.

2.3. Anti-inflammatory cytokines:IL-4(-), IL-10(-), IL-13

IL-4 is a cytokine that is largely secreted by mast cells, basophils, Th2 cells, and eosinophils and acts as a powerful immune system regulator. Few papers have discussed the role of IL-4 about aging and Alzheimer's disease (AD). However, the consistency of the findings across research suggests that IL-4 plays a role in preventing age-related inflammatory alterations in the brain. Butovsky et al. observed that IL-4-stimulated microglia boosted the portion of new neurons and oligodendrocytes in neural progenitor cells. Interestingly, IL-4 stimulation of microglial cells raised their production of the neurogenesis-supporting hormone IGF-1. Maher et al. (2005) reported that a decline in hippocampal IL-4 is associated with an increase in IL-1 and IL-6 in the hippocampus of elderly mice.IL-4 has been demonstrated to reduce A β -related neuroinflammation in both in vitro and vivo, as well as to stimulate evacuation of oligomeric A peptides. In fact, enhanced expression of the A β degrading enzymes neprilysin (NEP)and the scavenger receptor CD36 which induce rat microglial cells resulting in the removal of oligomeric A β . Additionally, amyloid precursor protein transgenic mice that received an in vivo injection of an IL-4/IL-13 combination and there is a decrease in brain A β levels and an improvement in cognitive performance. In APP+PS1 transgenic mice, IL-4-based therapy and vaccination have been shown to decrease A β deposition and evoke a neuroprotective effect.A viral vector encoding IL-4 was introduced into the hippocampus of AD mice models, which led to prolonged IL-4 expression, not only it decreased microgliosis, but also reduced A β formation and accumulation and increased neurogenesis.

Fiorentino et al. referred to the 36-KDa homodimeric cytokine interleukin-10 as a "cytokine synthesis inhibitory factor" since it can prevent all T cell types from producing cytokines. Monocytes, macrophages, mast cells, T-cells, neutrophils, and eosinophils are the major in vivo sources of IL-10. IL-10 affects phagocytosis, immunological mediator release and antigen presentation in monocytic cells. The results support the idea that IL-10 may lessen neuroinflammation, cognitive impairment, and neurodegeneration, based on the authors. According to Bagyinszky et al.22, IL-10 medication may be a possible treatment for AD becauseit can reduce amyloid by causing the creation of anti-inflammatory molecules and inhibiting pro-inflammatory cytokines, most likely by reducing their expression.

Richwine et al. found that a peripheral injection of lipopolysaccharide results in a significant cognitive loss in IL-10-deficient mice as compared to wild-type mice. In transgenic AD mice models, Kiyota et al. showed that IL-10 dramatically decreased neuroinflammation, increased neurogenesis, and improved spatial cognitive impairment. They demonstrated that treating double-transgenic mice which have a treatment with IL-10-adenovirus might inhibit microgliosis. Henderson proposed that estrogen treatment could prevent or postpone the onset of AD by boosting microglial cells' production of IL-10. Resveratrol, a natural polyphenol with anti-inflammatory effects, may also elevate IL-10 levels and gene expression, which may help to explain its neuroprotective effects.

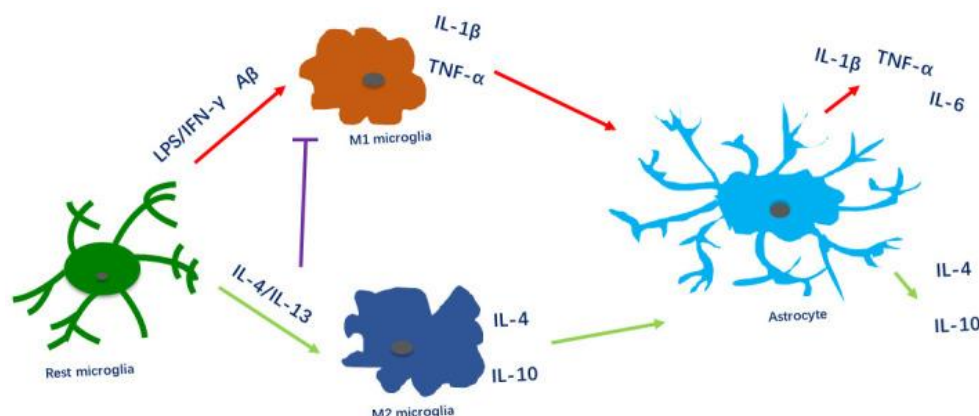


Figure 1. Different types of IL.

3. Sleep disorders alter signaling pathways

3.1. Sleep disorders affect pro-inflammatory cytokines signaling in AD

TLRs are a subclass of pattern-recognition receptors that can distinguish between self- and non-self-microorganisms based on their chemical patterns. Inflammatory cytokines including IL-1, TNF- α , and IL-6 are produced as a result of nuclear factor κ -B (NF κ B) gene transcription being stimulated by the activation of TLRs and receptor complexes.

Increased white blood cell counts are assumed to indicate host defenses are being activated in these sleep deprivation trials. Later research revealed that acute sleep deprivation also increased levels of IL-1, IL-6, and TNF- α , albeit the precise mediators may vary from trial to trial.

Research demonstrating that a night of insufficient sleep induces monocytes to create more IL-6 and TNF- α messenger RNA is a crucial first step in the quest to identify the mechanism of inflammation linked to sleep loss[9]. Despite not being the only source of IL-6 and TNF- α , monocytes are potent producers, and this study contends that sleep loss activates a molecular pathway in which monocytes play a key role. Additionally, sleep deprivation raises TNF- α levels, which have a circadian pattern. Targeted disruption of TNF- α receptors or their inhibition in the CNS would reduce spontaneous NREM sleep [10].

In children with OSA, both local and systemic inflammatory markers have been shown to be elevated. The tonsil tissues of kids with OSA have also regularly been observed to have elevated production of inflammatory mediators like cysteine leukotrienes and glucocorticoid receptors. Children with OSAS frequently have higher hs-CRP levels, which are unrelated to the level of obesity. Elevated IL-6 release from adipose tissue is caused by intermittent hypoxia and chronic sleep fragmentation, and adipocyte-derived mediators like IL-6 may interact with endothelial cells to enhance NF- κ B-dependent endothelial dysfunction.

OSAS promotes a long-lasting low-intensity inflammatory state in both adults and children, according to analysis of the inflammatory cytokines IL-6 and TNF- α .

IL-1, TNF- α , IL-6, and CRP, well-known indicators of the acute inflammatory system, have all been demonstrated to respond to changes in sleep in humans.

3.2. Sleep disorders change the neuroinflammatory signal transduction pathways of AD

Nuclear factor- κ B (NF- κ B) is a transcription factor that regulates a variety of physiological processes, including immunological response, cell growth and proliferation, synaptic plasticity, and other pathogenic processes brought on by stressors, trauma, infections, and inflammatory disorders. Activation of NF- κ B has also been shown in studies on local neuronal processes, such as the activation and release of several cytokines implicated in sleep regulation.

The number of NF-B p65-IR neurons was likewise raised by SD in the lateral hypothalamic macrocellular area, indicating that the sleep-wake cycle alters NF- κ B expression. Irwin et al. carried

out a clinical investigation in the beginning of 2008 to investigate the impact of sleep loss on NF- κ B signaling. Activation of NF- κ B and PBMC gene expression was seen in partial SD. In a different clinical investigation, healthy male volunteers were subjected to a four-hour sleep restriction for five nights, which led to changes in 117 genes. Interesting, among the 25 up-regulated genes linked to immune function is NF- κ B. Children with obstructive sleep apnea syndrome had higher levels of NF- κ B, demonstrating the molecular connection of sleep deprivation-induced inflammation pathway activation. Leukocytes express more inflammatory genes as a result of increased NF- κ B activation brought on by sleep loss, which raises the risk of inflammation. These findings help to partially explain how sleep deprivation causes inflammatory pathological conditions.

TNFR1 is a receptor for TNF(α) and also binds to TNF(β). The function of the cytokines IL-1 and TNF- α in sleep regulation has been well studied among all sleep regulating substances (SRS). Numerous factors, such as sleep, inflammation, and infection, affect TNF- α expression. Non-rapid eye movement (NREM) sleep is inhibited by TNF, while rapid eye movement (REM) sleep has also been demonstrated to be inhibited by TNF at greater concentrations. NREM sleep is also impacted by pathological conditions that directly or indirectly cause TNF-production. As a result, sleep disruption raises TNF-expression, which activates pathways involved in chronic inflammation. Such chronic inflammatory pathways are typical of neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), in which neuroinflammation results in cell death and apoptosis.

Key functions in sleep homeostasis are played by MAPK and its cell activators Ras, Raf, p38MAPK, MEK, and ERK. The consolidation of hippocampal-dependent memories is facilitated by enhanced MAPK activity during REM sleep as compared to the waking state.

Rats given 6 hours of SD had lower ERK/P44/P42 levels in the hippocampus, but after 2 hours of restorative sleep, these levels went back to normal. Due to reduced ERK activation, SD rats also have poor spatial memory. The actin remodeling, synaptic plasticity, proteinopathy, dopaminergic neurodegeneration, and neuroinflammation linked to numerous neurodegenerative illnesses, such as AD and PD, are also supported by evidence.

4. Potential treatments for AD

4.1. Anti-inflammatory treatment

Take non-steroidal anti-inflammatory drugs, of which aspirin and ibuprofen are the most commonly used. It also includes Naproxen, melofenamate, sulindac, fenoprofen and piroxicam. The other cases were not taken. There are more than 20 distinct NSAIDs that are offered on the market. In several medical diseases, they serve as anti-inflammatory, analgesic, and antipyretic agents. It is debatable whether or not NSAIDs lower the risk of AD based on the facts.

Among those who took aspirin plus NSAIDs for two or more years, one significant epidemiological investigation revealed a 60% sparing effect. Another study showed that using NSAIDs lower 55% venture of AD, and that the risk continued to decrease with a longer treatment. In the Rotterdam research, there was a sparing of 80%. Moreover, the MIRAGE investigation revealed a 36% sparing.

In recent years, more and more scholars have paid attention to the theory of inflammatory response, which makes NF- κ B, an important transcription factor in vivo, become another way for the treatment of AD. Natural products have the characteristics of multiple effects, multiple targets and multiple ways of action. The possible mechanism of natural products with the effect of reducing AD inflammation is mainly through reducing A β Toxicity, reduce inflammatory factors, regulate the expression of key proteins in NF- κ B/NF- κ B signal pathway, and improve the inflammatory response and cognitive ability of AD animals in multiple ways.

Natural product active ingredients are classified into five groups: polyphenols, flavonoids, terpenoids, alkaloids, and others.

For instance, Curcumin is a polyphenolic substance present in the roots and stems of Zingiacae and Araceae plants. It can cross the blood-brain barrier and has anti-amyloid formation and aggregation, anti-inflammatory and antioxidant effects on the nervous system, which can play a neuroprotective effect [8].

4.2. Sleep treatment

Bright light therapy (BLT) has been studied for its effectiveness in treating dementia patients since the early 1990s by a number of studies. These research have mostly concentrated on the impact of light on circadian rhythms and sleep. Few researchers have, however, examined its impacts on cognition, emotion, and behavior.

The majority of these trials revealed positive results despite the fact that there was significant variety in the type of light treatment, length of each intervention, and duration of light exposure. Over the course of ten days, Ancoli-Israel et al. compared bright morning light to brilliant evening light and dim morning light. They discovered that only the first two conditions resulted in longer overnight maximum sleep duration, demonstrating that strong light in the morning and evening can improve the consistency of nocturnal sleep. Patients with dementia who experience sleep difficulties may benefit from bright light therapy. The theory behind this therapy is that exposure to bright light of more than 2500 lx raises a person's plasma melatonin levels.

Rhythmic Sensory Stimulation (RSS) therapy encouraged greater alertness, spurred conversation and storytelling, improved perception of the environment, and boosted capacity for engagement in individuals with Alzheimer's disease, according to one study's descriptive and qualitative data. The subjects' SLUMS ratings demonstrated statistically significant results of the treatment in extremely brief treatment trajectories (six 40 Hz treatments).

The impact of 40hz RSS on 18 AD patients at three phases of the disease was examined in a similar study. SLUMS, emotional rating scales, and the researchers' behavioral observations were used as outcome measures. The outcomes demonstrated that the 40 Hz treatment significantly raised the slope of both the entire sample and the subgroup. The improvement of AD patients' mental function as determined by SLUMS may result from 40 Hz therapy.

Transcranial communication stimulation (tACS) has been demonstrated to modulate higher cognitive functions in healthy persons by entraining brain rhythms at particular frequencies in predetermined brain areas [12].

A G-TAC exposure over Pz or a sham TAC was given to participants at random in a 1:1 ratio, with the stimulation being reversed one week later. Each tACS stimulation lasted 60 minutes. The outcome showed that using tACS over Pz as a non-invasive treatment is an efficient way to improve memory in MCI-AD.

4.3. Non-drug therapy

The Nighttime Insomnia Treatment and Education for Alzheimer's Disease (NITEAD) project's initial findings were published in 2003. In this randomized controlled study, caregivers were taught to practice good sleep hygiene and engage in daily physical activity for 30 minutes in order to treat the patient without the need of drugs. General sleep education was provided to the control group. The trained carers were more successful in modifying AD patients' habits ($p < 0.01$). Three individuals underwent actigraph evaluations and NITEAD assessments a year later. After two months, there was a reduction in daytime somnolence and nocturnal awakenings (with a mean gain of 8%), as well as an improvement in sleep efficiency [13].

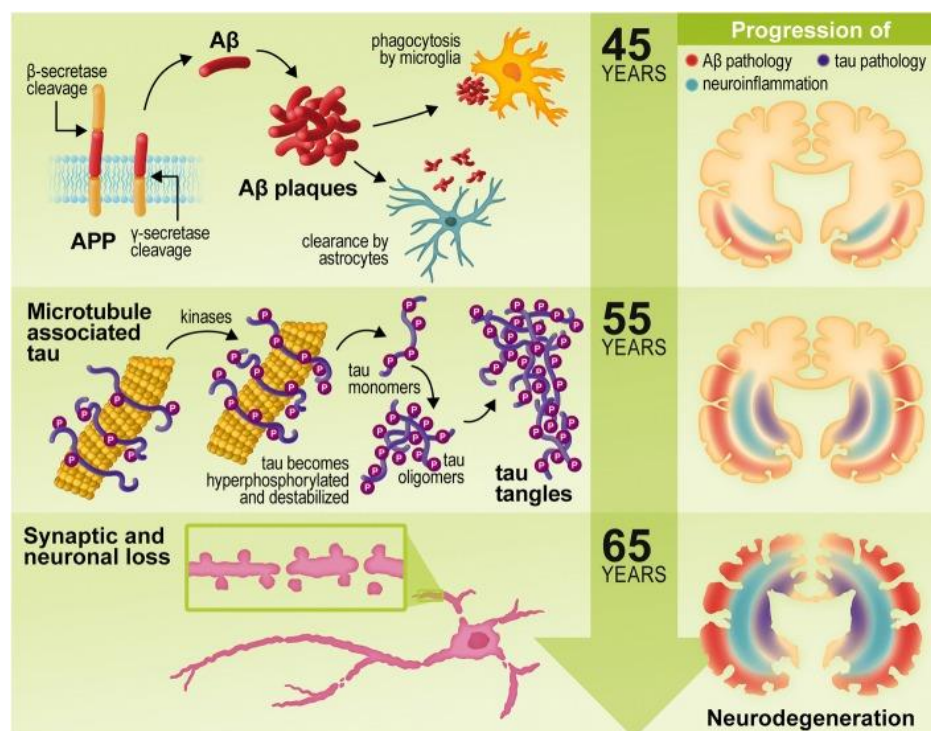


Figure 2. The process of neurodegeneration.

5. Conclusion

In conclusion, inflammation is the link between sleep disorders and Alzheimer's disease. Studying inflammation can give us more ways to understand the connection between sleep disorders and Alzheimer's disease and the mechanism of Alzheimer's disease specific discovery, so as to find new treatments and delay the progression of the disease. At the same time, clinical drugs to improve sleep disorders and inflammatory response are developed to control the onset and timely treatment of Alzheimer's disease. It is suggested that finding drugs that target the key sites of microglial activation and have good BBB permeability should be the next key research target. In addition, sleep therapy and non-drug therapy can also alleviate Alzheimer's disease, and its specific mechanism and practicability still need further research and experiments.

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