FUTURE PERSPECTIVES
PREVENTING ALZHEIMER'S DISEASE WHILE SLEEPING

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ABSTRACT

Short Perspective

BACKGROUND: Alzheimer´s disease is an incurable neurodegenerative disease where the brain is clogged with amyloid beta plaques. Patients have to cope with memory loss and problems with praxis and visual recognition. Two forms of Alzheimer's disease, early onset and late onset, are caused by genetic factors and several risk factors respectively. Since there is no medicine to cure Alzheimer disease, insight into risk factors which can contribute to effective prevention is crucial. It is thought that sleep might play an important role in the development of late onset Alzheimer's. Sleep is regulated by orexin molecules and their receptors. A high number of orexin receptors induces insomnia and disrupts sleep. When sleep is disturbed, the brain is not given enough time to clear the accumulated amyloid beta plaques, leading to increased wakefulness and an increased risk of developing Alzheimer´s disease. Nowadays orexin antagonists are used to treat insomnia and they might therefore also have potential to prevent Alzheimer disease. Studies in which mice were treated with orexin antagonists have shown promising results. Therefore we suggest to design a clinical trial to explore if the use of this medicine has an effect on the sleep-wake cycle leading to a better removal of amyloid beta and thereby decreasing the risk for Alzheimer´s disease.

WHAT'S KNOWN: Studies in mouse models have demonstrated that there is an association between extracellular accumulations of amyloid beta, wakefulness and orexin. The administration of orexin in mice models showed that both wakefulness and amyloid beta levels increased significantly. After the treatment with an orexin receptor antagonist, the amyloid beta deposition decreased. Another recent study showed that infusion of an orexin antagonist led to a decrease in amyloid beta level in the interstitial fluid. It is known that amyloid beta dynamics in mice are comparable to the dynamics in humans. Furthermore, the same relationship between sleep and amyloid beta as seen in mice is present in humans as well.

WHAT'S NEW: Although orexin antagonists are used as a treatment for sleeping disorder, to the best of our knowledge, so far no study has been published investigating the effects of orexin antagonist treatment in humans on the deposition of amyloid beta. Investigation of this effect can be a crucial step forward in the prevention of Alzheimer's disease.

KEY WORDS: sleep, Alzheimer's disease, orexin, amyloid bèta

Introduction

Alzheimer´s disease is an age-related neurodegenerative disease [1]. In the Netherlands, around 250.000 people suffer from this disease [2]. The number of patients is certain to rise in the coming decades because more people reach a higher age. In the beginning patients suffer from progressive memory loss, which later develops into dementia [1]. They have a reduced sense of orientation in space and time, language problems, problems with praxis and with visual recognition [2]. The memory loss is caused by atrophy of the hippocampus. This brain structure is involved in the storage of new information.

Alzheimer´s disease is mainly caused by the emergence of amyloid plaques in the limbic cortex and neocortex, which consist of the protein amyloid beta [3]. According to the amyloid cascade hypothesis, increasing concentrations of plaques in the cortex lead to the magnitude of cognitive decline [3,4]. Another neuroanatomical change of Alzheimer´s disease is the emergence of neurofibrillary tangles in the neocortex and the limbic cortex caused by tau protein [3].

Although different treatments are available to slow down the process of disease, there is currently no medicine for curing Alzheimer´s disease [3].

Besides searching for treatment strategies, scientists are also searching for potential causes of the disease, including personal lifestyle. A recent point of interest is the relation between sleep and the development of Alzheimer's disease. During sleep amyloid beta plaques are thought to be cleared. Therefore people suffering from sleeping disorders might have a reduced clearance of these plaques, resulting in a higher risk of developing Alzheimer's disease. Since insomnia is a common condition, with an estimated prevalence of 14% in the Netherlands [5], this potential cause is worth further exploration. In this article, we will discuss what is currently known about the relationship between sleep and Alzheimer's disease and suggest future research directions.

Pathophysiology

Amyloid beta protein (Aβ) is part of the Amyloid precursor protein (APP) [4]. Normally the APP is cleaved by alpha- and gamma-secretase. In Alzheimer's disease APP is cleaved by beta and gamma-secretase, leading to three cleavage products: sAPPβ, Amyloid β and C99 [2]. Aβ has different isoforms, the most important for Alzheimer´s disease is Aβ-42 [6]. Aβ-42 can aggregate fast to form plaques and is the most toxic one, leading to vascular damage and dementia. Scientists suggest that the formation of Aβ-42 leads to the hyper-phosphorylated form of tau [2]. Normally, tau is a protein that binds to microtubule and stabilizes them. In patients with Alzheimer's disease tau is hyperphosphorylated by kinases. This leads to a collapse of the microtubules and essential metabolites cannot be transported. In a later stadium it causes neuronal loss.

Causes for Alzheimer's disease

Mainly, two forms of Alzheimer's disease exist. Early onset Alzheimer's, which is caused by genetic factors and late onset Alzheimer's, caused by several risk factors. Early onset familial Alzheimer´s disease is associated with mutations in the amyloid precursor protein (APP) [6]. This gene is encoded on chromosome 21 [2]. There could be mutations on the N- or C-terminal of Aβ increasing Aβ and Aβ42 production. Mutations in the Aβ sequence itself affect Aβ aggregation and cause vascular variants of Alzheimer´s disease. There can also be different presenilin mutations, which lead to Alzheimer disease. Presenilin protein is part of the γ-secretase complex. Mutations in presenilin-1 increase the ratio Aβ42/Aβ40 or total amount of Aβ.

Late onset Alzheimer´s disease, also called sporadic form of Alzheimer´s disease, is caused by many non-genetic risk factors. Since there is no effective treatment against Alzheimer's disease yet, prevention is crucial. Mapping of risk factors is therefore important. Several known risk factors are age, alcoholism, atherosclerosis, chronic stress, diabetes, eating disorders, high cholesterol, hypertension, apolipoprotein E4 gene, obesity and smoking [7].

Sleep

One other risk factor that has only been discovered recently is sleep deprivation. Several theories about this relation have been developed. The clearance of Amyloid-beta(Aß) happens during sleep [8]. The sleep-wake cycle has been disrupted in patients with Alzheimer's disease (AD) [9]. The quality and quantity of sleep is observed to be decreased in humans with preclinical evidence of AD. The relationship between sleep and AD is however still poorly understood. It is known that hormones are involved in the initiation and the maintenance of wakefulness. These hormones are orexins. They play an important role in arousal and regulation of sleep [10]. The current theory is that the orexins act as excitatory neurotransmitters [11]. on the orexin receptors found on the orexins neurons. Orexin neurons are specifically found in the hypothalamus. Individuals with a high percentage of orexin receptors are found to suffer from insomnia while individuals with a low percentage of receptors are found to suffer from narcolepsy [12,13]. It is thought that orexins are not directly involved in the development of Alzheimer's disease, but indirectly through the maintenance of wakefulness and the decreased Aß clearance during wakefulness. A study performed in mice where the orexin gene was knocked out showed a decrease in the amount of Aß found in the brain with an increase in sleep time. It was also shown that the rescue of hypocretin neurons in APP/PS1 mice which lacked the neurons, Aß was increased in the brain. According to this research it seems that hypocretins and their effects on sleep modulate the Aß pathology in the brain [14]. Moreover, a study including 298 women without dementia showed that the 105 women with sleeping disorder had an OR 1.85 of developing cognitive impairment or dementia [15].

Although the relationship between sleep and Alzheimer's disease might seem clear, it is more complicated. The relationship is bidirectional [16]. Sleep deprivation can lead to Alzheimer's, but at the same time, Alzheimer's leads to sleeping problems. This relation involves the same mechanism. The deposition of Aβ in the brain causes wakefulness and less sleep. This consequence starts to develop when Aβ plaques accumulate in the hippocampus and the cortex. Increased wakefulness is a heavy burden for patient as well as caregivers, since patients start wandering around during the night [17]. This dangerous consequence of Alzheimer's disease is often a cause of institutionalization.

Future research directions

Nowadays orexin antagonists can be used as a treatment for insomnia. These orexin antagonists might have a potential to prevent Alzheimer´s disease as well. Studies in mouse models have demonstrated that there is an association between extracellular accumulations of Aß, wakefulness, and orexin. Administration of orexin in mice models showed that both wakefulness and Aß levels increased significantly [15]. After treatment with an orexin receptor antagonist, the Aß deposition decreased. To the best of our knowledge, so far no study has been published investigating the effects of orexin treatment in humans on the deposition of Aß. It is known that Aß dynamics in mice are comparable to the dynamics in humans. Prospective studies show the same relationship in humans between sleep and Aß as seen in mice. If it is proven that the orexin antagonist could improve sleep quality and also reduce Aß concentrations in patients, it will be possible to provide preventive care for people with high risk for Alzheimer's disease.

A possible approach to investigate the effect of Suvorexant (an orexin antagonist) on amyloid bèta levels in cerebrospinal fluid is to design a clinical trial including patients with insomnia (figure 1). Participants will be asked to stay in a sleeping centre for three nights. All participants are randomly split into two groups. One group will receive Suvorexant. The control group will receive a placebo. Treatment will be given before the third night. The two groups will be compared with regard to the Aß concentration in cerebrospinal fluid. Possible secondary outcome measures are: orexin concentration, tau protein concentration, sleep quality.

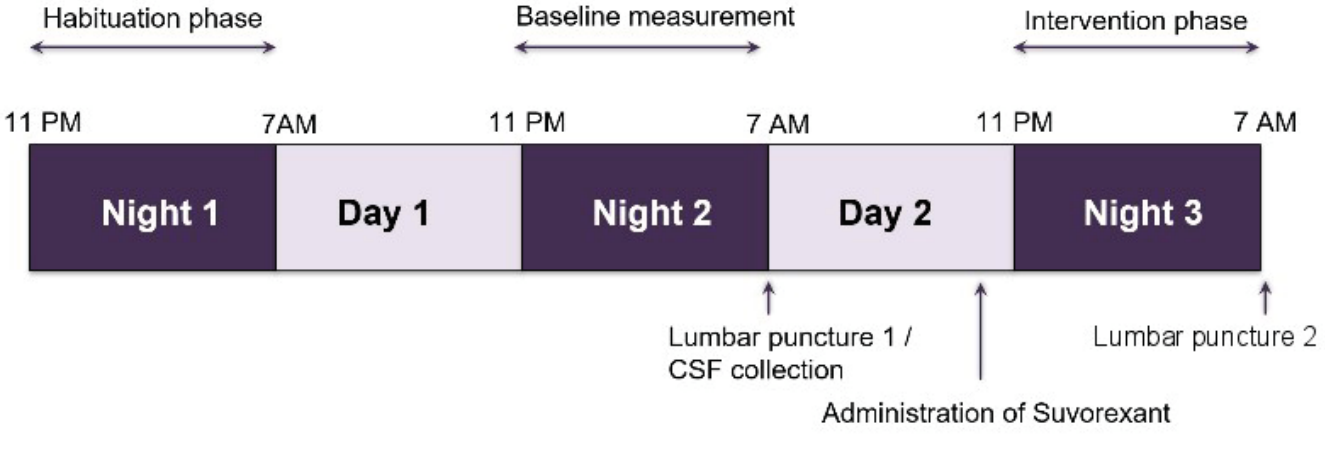

Figure 1: *Workplan of the clinical trial including patients with insomnia. CSF = Cerebrospinal fluid.*

Discussion and conclusion

The main cause of Alzheimer's disease is the presence of plaques of the amyloid beta protein. Aggregation of this protein leads to hyperphosphorylation of the tau protein which ultimately leads to neuronal loss causing Alzheimer's symptoms. Sleep deprivation is a recently discovered risk factor, leading to an increase of Aβ concentration and accumulation. In turn, Alzheimer's disease causes sleeping problems as well. This bidirectional relationship indicates the importance of sleep for the prevention of Alzheimer's disease. Treatment with Suvorexant might proof to be usable in the prevention and/or curation of Alzheimer's disease. If Suvorexant can improve sleep quality and thus also improve the clearance of Aβ during sleep, Suvorexant can be used as a prevention therapy. It might also be worthwhile investigating the effects of suvorexant on patients with Alzheimer's disease or even other forms of dementia. If sleep quality improves in patients with AD and Aβ aggregates diminish, Suvorexant might be used for curing patients with AD as well. When these studies show positive results, large trials can help the clinicians decide on whether to implement these treatments or not.

It should, however, first be proven that a lack of sleep does in fact greatly increase the chance of Alzheimer's disease. It might be possible that the observed relationship is actually pointing in the wrong direction. Patients with sleeping disorders might have a preclinical stage of Alzheimer's disease. That would mean the disease is causing sleeping problems, instead of the other way around. This doubt can be taken away by following people who sleep irregularly or hardly sleep at all due to their occupation (instead of sleeping disorders). If they show an increased risk of developing Alzheimer's disease, the existence of the relationship becomes highly likely.

It is definitely worthwhile exploring the relationship between sleep and Alzheimer's disease in order to be able to prevent or even contribute to curing this devastating disease.

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