The influence of sleep deprivation on the development of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and is the principal cause of dementia in elderly people. The disease is characterized by neuronal senile plaques and neurofibrillary tangles in the patients brain. These plaques consist out of aggregated Aβ. In 2012 a new clearance system, the glymphatic system, used to remove toxic metabolites has been discovered. The glymphatic system is able to eliminate Aβ from the brain, hereby preventing it from aggregating. Because the system is highly active during sleep, it is considered that sleep deprivation contributes to an increase in Aβ. Research is now focusing on the possibility of a relationship between sleep deprivation and the development of AD. This thesis will highlight several possibilities on how sleep, especially sleep deprivation, could influence the development of AD.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and is the principal cause of dementia in elderly humans. The disease is characterized by the progressive loss of neurons, which causes the loss of memory and other cognitive functions. Due to the fact there is minimal treatment, AD is a growing public health problem[1–3]. The economic consequence of AD is immense, the annual cost of dementia in 2010 was valued at 206 billion US dollars[4,5]. Approximately 70% of the cost arose in Western Europe and North America[5]. At the same time the prevalence of AD was estimated to be 35,6 million cases worldwide. The number of AD cases seems to rise, and is expected to double every 20 years. The amount of AD patients is expected to reach approximately 115,4 million by 2050, unless something changes. The worldwide prevalence for individuals aged 60 or above is estimated between 5 and 7%[4,6].

The first case of AD was discovered over 100 years ago by Aloïs Alzheimer in a patient named Auguste D. Alzheimer described the unusual symptoms of his patient and the presence of neuronal senile plaques and neurofibrillary tangles in the patients brain[7,8]. A number of breakthroughs have been made since then, for instance the linkage between AD and genetics and the early onset forms of AD[7]. However, only 5% of the AD patients have a clear autosomal dominant (familial) form of AD[9]. While, the remaining 95% occurs with no apparent family history, the so called "Sporadic AD"[10]. Sporadic AD does not rise from a genetic disruption, the exact cause is not yet known. The factors involved in this type of AD may be something other than genetics[11]. For example, disruption of sleep seems to impair the quality of life in AD patients and there appears to be a bidirectional connection between sleep and AD[12]. This thesis will review the possible influences of sleep deprivation on the development of AD.

2. AD Pathology

The brain consist out of neurons, the most important cells in the brain. AD causes the loss of neurons, leading to the loss of brain weight and volume[3]. The pathological processes begin years to decades prior to any symptoms appear[12,13]. At first soluble amyloid-β (Aβ) become insoluble plaques in the brain. These plaques represent the first identifiable pathological change in AD patients, but dementia occurs 10-15 years afterwards[12]. The manifestation of the disease starts slowly with mild cognitive impairment. In time, AD will lead to gradual loss of cognitive skills, identity and even activity[10]. Some brain regions are more affected then others, mostly affected are the cerebral cortex and the hippocampus[10]. As seen in figure 1 the progression of tau and Aβ has a different starting point. Aggregation of tau starts in the locus coeruleus and spreads to the medial temporal lobe, hippocampus and neocortex. The deposition of Aβ starts in the neocortex and spreads to the inside of the brain[14].

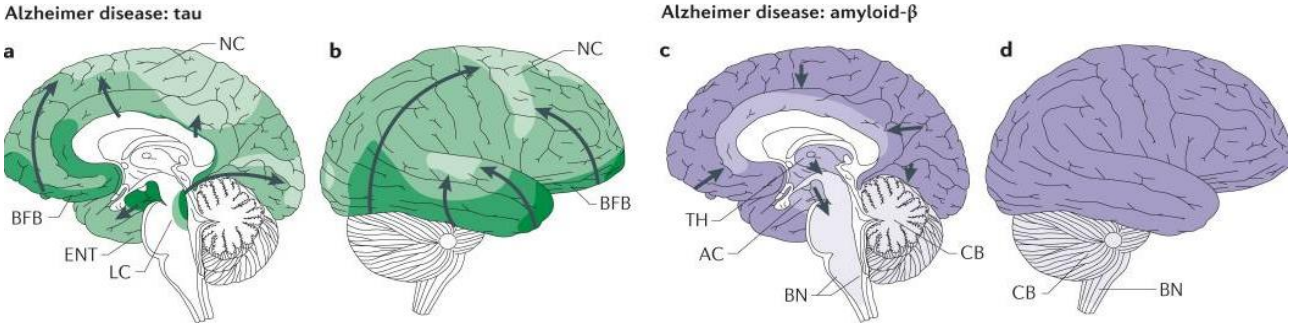

Figure 1 Progression of tau and amyloid-beta in Alzheimer's disease. a,b) Tau aggregation occurs in the locus coeruleus (LC), then in the transentorhinal and entorhinal regions and later in the hippocampus and in the neocortex (NC). c,d) Aβ deposits start in the NC and are then observed in allocortical, diencephalic and basal ganglia structures and in the brainstem[14].

3. Mechanisms

Like multiple other neurodegenerative disorders, AD is associated with the formation and accumulation of abnormally folded proteins. As for AD, there is an increased formation of extracellular amyloid plaques and intracellular neurofibrillary tangles in the brain[15]. However, there are different supporting mechanisms of AD pathogenesis and progression. Based on various causative factors multiple theories have been formed, such as the Amyloid-β hypothesis, tau hypothesis and cholinergic hypothesis (fig. 2)[10,16].

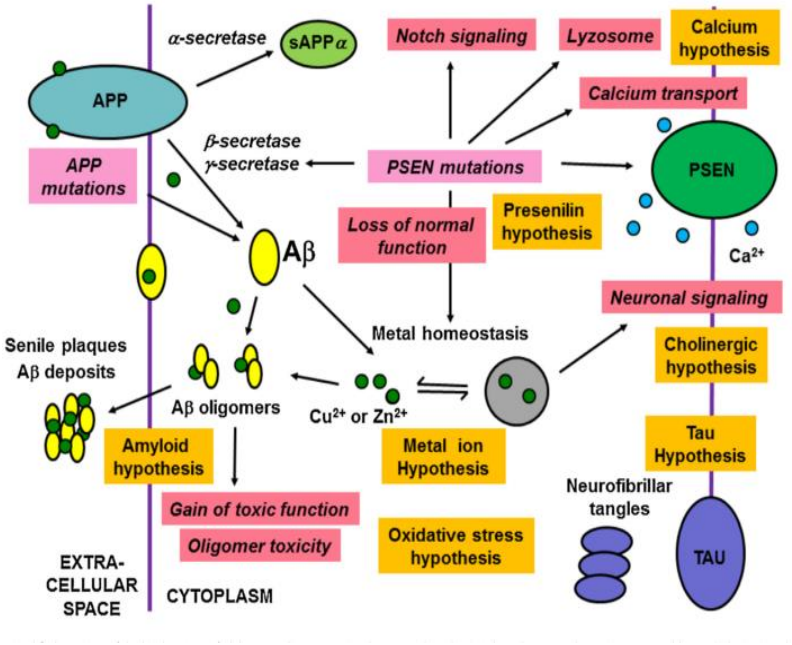

Figure2 *Overview of the biochemistry of Alzheimer's disease. The mechanistic hypotheses are shown in yellow and the key pathologies in red. APP, PSEN and Aß are shown in light blue, green and yellow. Metal ions are shown as green or blue*

3.1. Amyloid-β hypothesis

The most influential theory for Alzheimer's disease is the amyloid-β hypothesis[17]. In which Aβ is believed to be the main contributor to the dysfunction and loss of neurons[7,18]. Aβ is a natural metabolism product and consist of 38 to 43 amino acids[7,19] and is produced by all cells in the body. Although the main function remains to be determined[7]. Under normal circumstances, the main Aβ species (Aβ1-40) is 40 amino acids long. In case of AD, there is an accumulation of Aβ1-42, which is a longer form of Aβ[7].

Aβ is derived from the amyloid precursor protein (APP) by cleavage (fig. 3)[7,13,15,19]. Cleavage of APP can occur by two different pathways, the non-amyloidogenic and the amyloidogenic APP processing pathway. The first pathway occurs through cleavage by α-secretase, releasing a large amyloid precursor protein (sAPPα) and leaving an 83-residu carboxy-terminal fragment(C83) behind[19]. The cleavage site of α-secretase lies within the Aβ sequence, α-secretase thus prevents Aβ formation[18]. Afterwards γ-secretase digests C83 and liberates extracellular p3 and the amyloid intracellular domain (AICD)[19]. A different pathway is the amyloidogenic APP processing pathway, this pathway is regulated by β- and γ-secretase[10,19]. One of the main β-secretases is beta-site amyloid precursor protein-cleaving enzyme 1(BACE-1)[18], this enzyme releases a shortened sAPPα. The remaining part, C99, is a γ-secretase substrate, which results in Aβ and AICD. Then AICD is targeted to the nucleus, where it signals transcription activation[19]. The formed Aβ could be either Aβ1–38, Aβ1–40 or Aβ1–42, depending on the cleavage site of γ-secretase. The degree of aggregation is determent on the type of formed Aβ, because Aβ1–42 displays a higher propensity for aggregation[10,15]. Researchers also believe that Aβ1-42 is a more toxic form compared to Aβ1-40, because it aggregates more easily[7].

Aβ proteins are able to spontaneously self-aggregate into oligomers (2 to 6 peptides) or fibrils. Fibrils can then be arranged into β-pleated sheets, forming insoluble fibers of advanced amyloid plaques. The soluble forms of oligomers appear to be the most neurotoxic forms or Aβ[19]. Thus, the severity of the

cognitive defect does not correlate with the total Aβ amount, but with the levels of oligomers in the brain[19].

The degradation of Aβ is regulated by proteases. This hypothesis is built on the proposition that AD is caused by an imbalance between Aβ production and clearance, which results in an increased amount of Aβ in various forms such as monomer, oligomer, insoluble fibrils and plaques all in the central nervous system[20]. Proteases such as neprilysin and insulin-degrading enzyme regulate the levels of Aβ. Neprilysin is known to degrade Aβ mono- and oligomers. Insulin degrading enzyme is known to degrade small peptides, like insulin and monomeric Aβ. Overexpression of these enzymes prevent plaque formation[19,21].

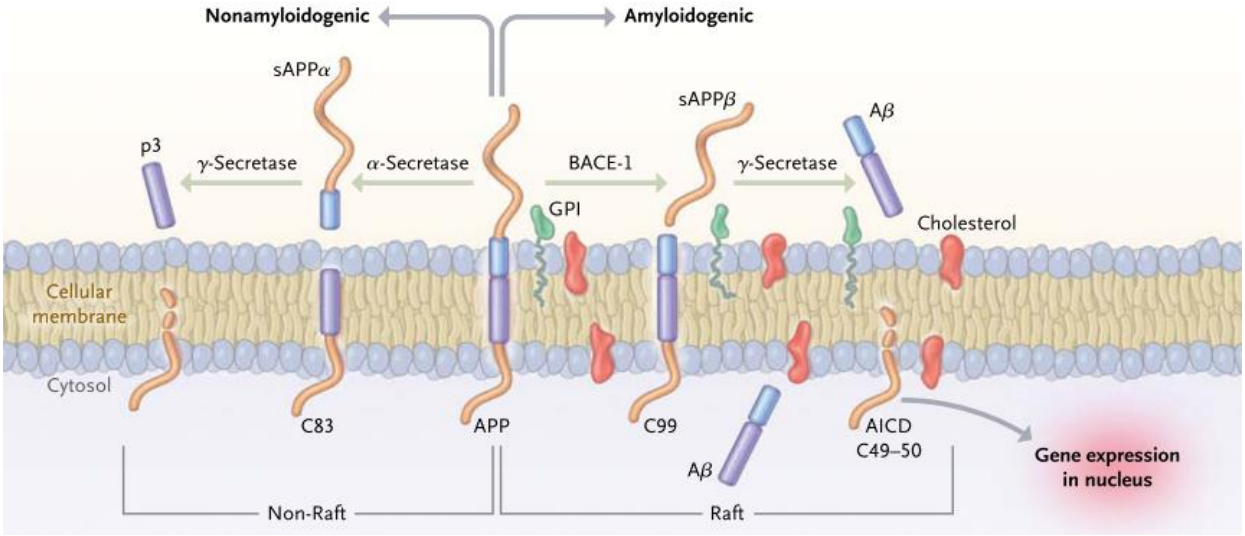

Figure 3 *Processing of Amyloid Precursor Protein(APP). Cleavage of APP can occur in two different manners. The non-amyloidogenic pathway (left) occurs through cleavage by α-secretase, generating a large amyloid precursor protein (sAPPα) and an 83-residu carboxy-terminal fragment(C83)[19]. The cleavage site of α-secretase lies within the Aβ sequence and thus prevents Aβ formation. Following γ-secretase extracts C83 and liberates extracellular p3 and the amyloid intracellular domain (AICD)[19]. The amyloidogenic pathway (right) is the second manner through which cleavage can occur, regulated by β- and γ-secretase. The amyloid precursor protein-cleaving enzyme 1 (BACE-1) then releases sAPPβ. The remaining C99 is a substrate for γ-secretase, cleavage will generate AICD and Aβ. AICD will then activate transcription in the nucleus[10,19].*

3.2. Tau hypothesis

Another important model for AD is the tau hypothesis, since the earlier mentioned intracellular neurofibrillary tangles in the brain are caused by abnormal phosphorylation (hyperphosphorylation) of tau. Tubulin-associated unit (tau) is a microtubule-associated protein (MAP) in neurons, it is an abundant soluble protein[19] and promotes the assembly and stability of microtubules[8]. The gene encoding for tau is microtubule-associated protein tau gene (MAPT)[3,8].

The cytoskeleton of the neuron is composed of microtubules, which maintain the neuronal structure, axonal transport and neuronal plasticity[22]. These microtubules are vital for transport of organelles and vesicles containing proteins and neurotransmitters, which are transported from the neuron cell body (soma) to the synapses[22]. Microtubules are formed by accumulation of α- and β-tubulin, this accumulation is stabilized by phosphorylated tau[8,22]. The stabilizing activity of tau is regulated by its degree in phosphorylation[8]. Enzymes regulate the extent of tau posphorylation[19], increases

phosphorylation by glycogen synthase-3 (GSK3) activity and decrease by phosphatases (PP2A and PP2B)[8]. In case of AD, tau is abnormally hyperphosphorylated[22], this is caused by kinases, like GSK3, and affects its ability to bind to tubulin[8]. Resulting in the detachment of tau[4,8] and thus destabilizing the microtubule structure[8]. Hyperphosphorylated tau is, in contrast to normal tau, insoluble and self-aggregates into paired helical filaments(PHF)[19]. Neurofibrillary tangles consist of these PHF's and thus tau[16].

Interestingly, there is evidence that Aβ oligomers induce oxidative damage and promote tau phosphorylation[16,17]. What seems to suggest that hyperphosphorylation of tau and the formation of neurofibrillary tangles in the neurons are secondary events[17]

Several kinases are implicated in the hyperphosphorylation of tau. Hyperphosphorylation can also occur via the extracellular signal-regulated kinase (ERK) pathway and may occur under conditions where oxygen is lacking, like hypoxia. Whereas hypoxia is a common feature of Obstructive Sleep Apnoe(ASO), one of the most common sleep disorders. This disorder could trigger neuronal degeneration and axonal dysfunction in the cortex and brainstem[23].

3.3. Cholinergic hypothesis

In the late 1960s and early 1970s, the first systematic biochemical investigation of the AD brain began. This is how researchers considered the cholinergic hypothesis. In the mid-1970s researchers reported a neocortical deficit in Choline acetyltransferase (ChAT), which is responsible for the synthesis of acetylcholine(ACh). This deficit was confirmed by discoveries of reduced ACh release, choline uptake and loss of cholinergic soma in the nucleus basalis of Meynert, the cortex and the hippocampus[24–28]. Thereafter, it prompted researchers to believe that the loss of neurons was due to the loss of cholinergic stimulation[29].

The neurotransmitter Ach is involved in learning and memory[30]. ACh release and synthesis are depressed in AD and the ACh degradation is altered in the presence of Aβ[31]. Furthermore, attachment of amyloid fibers to Acetylcholine esterase (AChE), catalyzes the breakdown of ACh[24–28], can trigger an alteration in its characteristics. For example, changing its pH sensitivity and thus its activity[32]. Apart from this, it has been noticed that the AChE levels in AD patients are decreased, while its activity is increased around plaques and NFT[33].

To test this hypothesis researchers used AChE inhibitors, which could reduce the hydrolysis of ACh. Testing these AChE inhibitors, patient's showed a lot of side effects. To fairly test the cholinergic hypothesis, scientists developed a 'second generation' of AChE inhibitors[34,35]. The use of these inhibitors showed a delayed progression of the symptoms of AD, equal to 6-12 months deterioration[36–38]. The fact that the AChE inhibitors only reduce the progression of the disease indicates that the cholinergic dysfunction may not cause AD related cognitive impairment directly[35,39].

3.4. Inflammation hypothesis

Another hypothesis is the inflammation hypothesis. Neurodegenerative diseases are all accompanied by the activation inflammatory and neuroinflammatory systems. The inflammation hypothesis for AD is built on assumptions that the immune system accompanies the AD pathology and could be a contributor to the pathogenesis of the disease[40,41]. The link between inflammatory processes and the pathogenesis of AD has been supported by epidemiological studies, describing a reduced risk in the development of AD when non-steroidal anti-inflammatory drugs are used chronically[42].

Neuroinflammation is characterized by the activation of microglia and astrocytes. Astrocytes are part of the blood-brain barrier, functioning as the modulators of structure and of the brain[43–45]. They play an important role in the trophic and metabolic support of neurons, neuronal signal transmission and in the formation and plasticity of the synapses[46–49]. The microglia are considered the principal immune cells of the central nervous system (CNS), functioning as the macrophages of the brain by the ability to migrate into different parts of the brain, phagocytose, process and present antigens[45,50–52]. They can be triggered by detection of protein aggregation or neuronal death. In case of AD, the microglia are able to bind to soluble Aβ oligomers and Aβ fibers through receptors. This process is followed by phagocytosis.[53,54] In cases of sporadic Alzheimer, downregulation of expression of Aβ phagocytosis receptors are suggested to be responsible for inefficient clearance of Aβ.[53,55] Normally, the presence of Aβ can prime microglia, making them susceptible to a secondary stimulus or promoting their activation. In AD, microglial cells are chronical activated by Aβ[56,57]. Resulting in continuous production of inflammatory cytokines and chemokines[41,58,59]. Whereas, cytokines and chemokines maintain the activation of primed microglia. This process affects surrounding CNS cells: astrocytes, oligodendrocytes and neurons. Possibly leading to the hyper phosphorylation of tau, and thus leading to neurodegeneration[41,45]. Adding to this, that it is possible that these inflammatory processes contribute to the sleep associated development of neurocognitive disorders[60]

4. Sleep and AD

It has been noticed that sleep of patients with AD is altered[12,61]. It is even suggested that fragmented sleep could be an early sign of Alzheimer or even a contributor to the development of the disease. This chapter will explain if the bidirectional relationship is possible and the research that does and doesn't support it. However, first the processes underlining sleep will be described.

4.1. Sleep

Sleep is a fundamental biological process, commonly observed throughout the animal kingdom. Although, the systems generating sleep are poorly understood. Sleep takes up to one third of our lifetime, which could mean it plays a special role in our existence, otherwise it would have disappeared through evolution. Insufficient sleep can impair our cognitive performance during wakefulness[62]. Long term or chronical sleep deprivation is linked to many health issues, for example obesity, cardiovascular diseases and neurocognitive disorders[4,62]. The exact mechanism or order of incidence is not always known.

Sleep consists of two types of sleep, rapid eye movement (REM) and non-REM[62]. NREM consists of three stages (N1, N2 and N3), which are progressively deeper. Stage one is a transition state consisting of light sleep, at this point there is a reduced brain-wave activity and slow eye movements. In stage two the body is in a low energy state; muscle relaxation, decreased body temperature and a reduced heart rate. This stage is defined by spindles and K-complexes, less than 3 min apart on electroencephalographs. In deep sleep, stage 3, sleep is characterized by slow-wave-spindles (SWS). This stage of sleep is thought to be the most restorative form of sleep. The next stage, REM, is characterized by Rapid Eye Movement, vivid dreaming, active inhibition of muscles and an increased brain activity, heart rate and respiratory rate. Overall, adults go through all four stages in 90-100 minutes during the night. However, the time spent in one stage changes as the night progresses[4,63–65].

4.2. Glymphatic system

Until a few years ago Aβ was thought to be cleared only by the following mechanisms; uptake by microglial phagocytes, receptor-mediated transport across the blood vessel walls and degradation by enzymes[66]. Comparable mechanisms occur for tau[67]. However, in 2012 the discovery of the glymphatic system provided new insights in the clearance of the brain[68–70].

The glymphatic system is a biomolecule clearance system used to remove toxic metabolites in the brain via the cerebrospinal fluid (CSF) and interstitial fluid(ISF)[71]. The CSF is found in the brain and spinal cord and is produced by the choroid plexuses of the ventricles of the brain. The interstitial fluid is located between tissue cells[70–72]. However, the glymphatic system does not just eliminate soluble proteins and metabolic waste. The system also takes care of distribution, e.g. lipid distribution by releasing Apolipoprotein E[73]. Though this is literature study will focus on the clearance of biomolecules, since this is a potential important mechanism for AD.

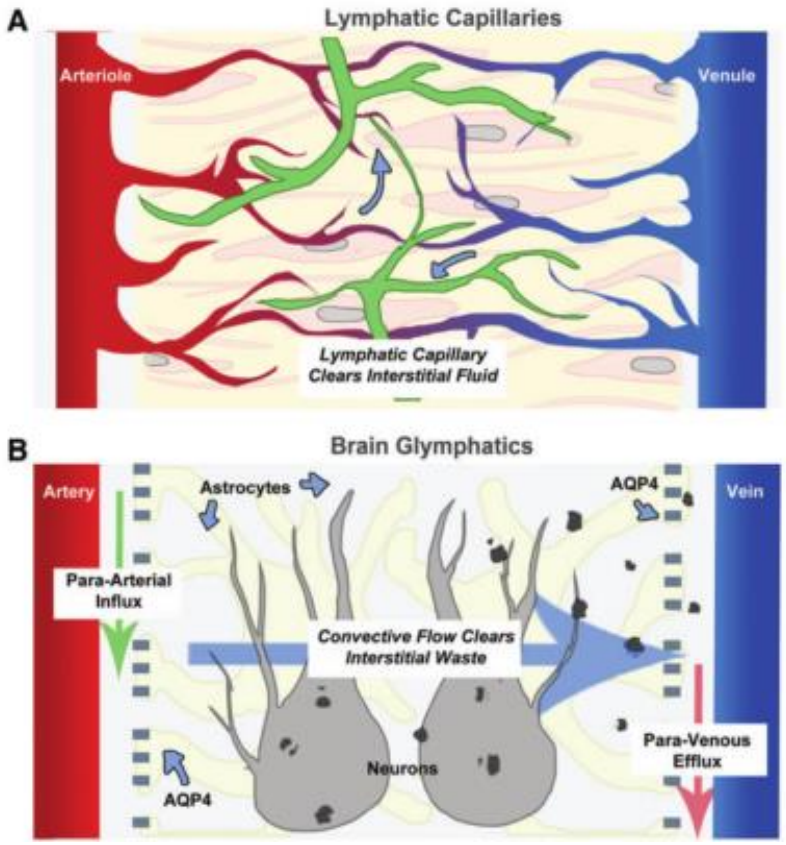

Figure 4 The lymphatic system is comparable to the glymphatic system. The lymphatic vessels eliminates waste from the interstitial fluid(A). In the brain, the glymphatic system, there is a convective flow between entering cerebrospinal fluid through the arteries and exiting interstitial fluid through the veins removing biomolecular waste from the brain[71].

The glymphatic system clears biomolecules from the brain by a convective flow (fig 4). The CSF enters the brain parenchyma via a para-arterial influx. The movement of CSF into the parenchyma drives interstitial fluid between tissue towards the perivenous spaces[72,74,75]. This way the extracellular solutes are removed through drainage of the interstitial fluid along the para-venus efflux to the cervical lymph system via the olfactory bulb and along cranial and spinal nerves. The interchange between CSF and ISF is driven by a combination of respiration, arterial pulsatility and CSF pressure occurring through constant production of CSF by the choroid plexus [69,70,72]. The transport of CSF into the brain parenchyma is facilitated by Aquaporin 4 (AQP4) water channels[69–72]. The AQP4 water channels are expressed in the endfeet of astrocytes located in the brain vasculature[69,70,72]. The channels are required for glymphatic functioning and facilitate clearance of soluble proteins, waste products and excess extracellular fluid[69–71]. The glymphatic system takes care of 65% of the Aβ clearance, most of which occurs during sleep. It has been tested in mice that clearance occurs twice as fast in sleeping and anesthetized fase[69,76]. Natural sleep and anesthesia facilitate a 60% increase in interstitial space, leading to a convective flow between CSF and ISF[76,77]. The increase in interstitial space leads to an increased clearance of Aβ[69,76].

The biomolecular clearance is probably not regulated by circadian rhythms, due to the fact that anesthesia can be administered at any time inducing clearance. One hypothesis is that arousal itself is responsible. To be precise, the locus coeruleus noradrenergic signaling, which is linked to wakefulness. Thus, adrenergic signaling is possibly able to reduce interstitial volume followed by a decreased clearance. After treatment of adrenergic antagonist, mice showed an increase in CSF influx as well as an increase in interstitial space. The researchers even administered more slow wave patterns, indicating a more relaxed sleep-like state[76].

4.3. Aging, sleep deprivation and AD

As people age, it is often seen that people need more time to fall asleep, wake up more often and earlier and have excessive daytime napping[4,78,79]. Additionally, Elders tend to have a reduced threshold for arousal resulting in fragmented sleep with multiple arousals[65]. Aging individuals also seem to awake less from REM sleep and more from NREM sleep, compared to young adults, and have less sleep spindles and K-complexes in NREM sleep[4,78,80,81]. Studies have indicated that aging is associated with reduced SWS and NREM[82], this occurs in combination with structural brain atrophy (mainly in the frontal lobe regions)[83]. A study in 2013 even demonstrated that the degree of age-related atrophy in the medial prefrontal gray matter is linked to the degree of reduced SWS activity[84]. Furthermore, Mander et. al hypothesize that Aβ accumulation within the medial prefrontal cortex (mPFC) is significantly correlated with the severity of impairment slow-wave activity(SWA) during NREM sleep[85].

As for the link between SD and AD development. It has been reported that excessive daytime sleepiness, at a baseline, have a higher probability to be diagnosed with incident dementia later on, compared to those without EDS. Likewise, individuals with sleep disturbances were more likely to develop or be diagnosed with AD or cognitive decline at a follow up[86–88]. Another study found that reduced sleep was associated with a 75% increased risk for all cause dementia and doubled the risk for AD. In which no effect of sleeping pills has been administered, because they may not result in quality sleep[89]. Another study also underlined that markedly fragmented sleep could increase the risk at developing AD, by 1,5 fold, compared to those with the smallest amount of fragmented sleep[90]. Other studies in humans also suggested that sleep disruption and disorders could be a possible risk factor for the development in cognitive deterioration and dementia[88,91]. A study in 70 year old's reported a correlation between shorter sleep duration or poorer sleep quality and greater Aβ burden assessed by PET[92].

In AD patients imaging and pathological studies showed abnormalities in brain regions that are known to regulate sleep[93]. This explains the changed sleep pattern seen in AD patients. Even at early stages, before clinical onset, disruptions of NREM and SWS have been detected[85,94]. In patients with AD, insomnia is very common, the severity of this symptom even correlates with the degree of dementia[95]. As explained before, sleep facilitates in the clearance of metabolic waste by the glymphatic system[76]. With the changed sleep pattern this clearance mechanism could be suppressed[12]. The amount of Aβ is directly affected by how much people are awake or asleep. Likewise, it has been reported that individuals with AD and sleep disruption are more likely to become symptomatic compared to AD patients with a healthy sleep pattern[12]. Correspondingly, animal models for AD have shown that manipulation of sleep and circadian behavior can modify the progression of the disease. As sleep deprived mice had 25% more β-amyloid plaques compared to control mice, implying that disruption in the sleep-wake cycle and orexin may play a role in the pathogenesis of AD[96].

4.3.1. Amyloid-β

The release of Aβ is facilitated by neuronal firing, or synaptic activity[97]. Aβ concentrations show diurnal variation, the levels rise during wakefulness and fall during sleep[2,98,99] in mice[99] and humans[98], due to its glymphatic system. Therefore, it has been suggested that sleep facilitates in the removal of Aβ[4,99,100]. Neurons are predicted to have the less neuronal activity during sleep, especially during SWS and thus release less Aβ compared to other stages of sleep or wakefulness. In case the quality of sleep is poor and an individual may not reach and sustain SWS, this could this result in a greater release of Aβ[99] and possibly to Aβ accumulation[100].

In case of sleep deprivation, the amount of Aβ will not decrease as much compared to normal sleep, which may be important in the pathogenesis of AD. A research by Ooms et al. (2014) indicates that one night of sleep deprivation increases cerebral Aβ42 levels, which could elevate the risk at AD. Though this research also found that one night sleep deprivation does not increase the levels of Aβ40 and tau [100]. Furthermore, Di Meco et al. (2014) investigated the impact of sleep deprivation on an AD mouse model with plaques and tangles and found significant memory impairments, altered tau metabolism and synaptic pathology[1].

Transgenic models of AD have shown that environmental or pharmacological manipulation of sleep and circadian behavior can modify disease progression[96,99,101]. Furthermore, it is seen in mice that the diurnal Aβ level variation seems to disappear when Aβ plaques are present and this also applies to humans, particularly the levels of Aβ42 remains even[98]. Evidence has shown that individuals with plaque formation have worse sleep quality compared to individuals without plaque formation. The affected subjects, have a lower sleep efficiency and the wake up time after sleep onset is affected[102]. However, it is not known whether the plaque formation is a result of reduced sleep quality or the other way around. Though, it has been said that chronic sleep deprivation accelerates Aβ deposition into insoluble Aβ plaques[99].

4.3.2. Tau

Evidence has shown that tau indirectly participates in the regulation of the sleep and wake cycle. Tau deficient mice show an increase in wakefulness and a decrease in NREM sleep time, a higher number of state transitions from NREM to wakefulness and shortened sleep bouts[103].

Microtubules are able to modulate the sensitivity states of different melatonin receptors, and can thereby influence the activity of circadian patterns[104,105]. As a result, impaired functioning of melatonin receptor could trigger sleep disturbances in AD patients. This finding is supported by the discovery of increased wakefulness in tau deficient mice[103].

A research by Holth et. al (2017) also indicated that tau pathology is associated with sleep disturbances. This research showed not only a decrease in NREM sleep but also a decrease in REM sleep. Tau related changes in sleep could negatively affect disease progression. As well as Aβ, tau levels in the brain interstitial fluid increase by neuronal activity. Suggesting it could be a possibility that increased wakefulness may elevate tau secretion and maybe even worsen tau pathologies[106]. Though, the function of tau in the extracellular space is not well understood[107,108].

Sleep deprivation has shown to reduce the phosphorylated isoform of soluble tau, which is related to the increase of its insoluble form. These data suggest that SD could accelerate the tau pathology, by inducing conformational changes and thereby accelerating tau aggregation[1]. This change could be associated with

the reduced activity of cdk-5, a kinase involved in the post-transcriptional phosphorylation of tau and AD[109,110]. Considering the contradiction between the cdk5 activity and the percentage of phosphorylated tau, it is believed that other kinases and/or phosphatases may be involved. Though, it is also possible that the lower percentage of phosphorylated tau results from hyperthermia, which is a consequence from SD[1]. Another study in a mouse model for AD showed elevated Aβ and tau-p levels in the cortex (not hippocampus) after chronic mild sleep restriction[111].

4.3.3. Insulin

Sleep deprivation has not only been associated with a reduced glymphatic metabolism, but also with the glucose metabolism. Research has shown that the glucose metabolism is also altered in sleep deprived patients, contributing to increased blood glucose and an decreased insulin level, which can lead to insulin resistance like type 2 diabetes mellitus[112]. This insulin resistance, has already been observed after one night of SD in healthy subjects[113]. Interestingly is the fact that diabetes mellitus is also associated with an increased risk for the development of AD[114,115]. Though, it has been shown that insulin resistance is not always involved in the pathogenesis of AD. For instance, a mouse model carrying an insulin receptor mutation did not display acceleration in plaque formation or memory abnormalities[116].

4.3.4. ApoE4

ApoE4 is a major risk factor for late onset AD, especially in homozygous cases[117] with an increased risk of 50%[118]. ApoE is thought to play a critical role in Aβ clearance, through binding to Aβ. ApoE4 is known to form less stable complexes compared to ApoE3 and ApoE2, hereby decreasing Aβ clearance.

Some studies propose that ApoE4 could make MCI or demented patients more susceptible for sleep alterations (e.g. reduction of REM sleep, increased fragmentations of SWS or sleep apnea)[94,119,120]. Decreased sleep efficiency could be due to a lower CSF melatonin rate in homozygous 4/4 compared to heterozygote patients[121]. Other studies associate homozygous 4/4 genotypes with an even more increased risk of developing sleep disorders and cognitive impairment related to sleep diseases[120,122–124]. A study among older women indicated that sleep disordered breathing could be associated with the increased risk of developing dementia, particularly if the allele Apolipoprotein E epsilon4 is present. [91,125]

Though, other research has shown a protective effect of ApoE4 on sleep in AD[126], or either no effect[61]. However, it has been shown that better sleep consolidation could reduce the risk on AD conferred by ApoE4[11]. Though, research has indicated that the negative effect of ApoE4 might be amplified by sleep disruption[92,123,124,127,128].

4.3.5. Melatonin

Melatonin is a hormone produced by the pineal gland at night. This hormone plays an important role in the regulation of the biological clock and sleep wake cycle, by promoting sleep onset[4]. Melatonin has a protective role as an antioxidant and anti-amyloid properties as well. It can arrest the formation of amyloid fibrils and is able to attenuate the AD-like hyperphosphorylation of tau. Melatonin also seems to play a role in the protection of the cholinergic system and in anti-inflammation[129,130].

Research has shown that the total level of melatonin in the body decreases with age[131]. In AD patients levels of melatonin are even more decreased[132], these reduced levels of melatonin correlate with the severity of mental and sleep impairments[133,134]. Interestingly enough, the homozygous ApoE4 patients display a significantly lower amount of melatonin compared to patients with only one copy[121].

The results supplementation of melatonin to AD patients have been contradictory. Some studies have shown little to no effect on sleep in AD patients[135,136]. Though, these patients had more severe AD, with probably a higher level of Aβ. As for normal aged individuals, improving effects have been seen[137]. Though, there are studies that do report a reduced variability of sleep onset time and a reduced percentage of nighttime activity. Especially long-term administration of melatonin showed improvement of sleep quality in AD patients[138–140]. Even the cognitive alterations in AD patients seemed to be halted in melatonin receiving patients compared to non-receiving patients[139,141]. Studies with APP transgenic mice have indicated that early long-term melatonin treatment provides anti-amyloid and antioxidant effects. However, it is seen that when treatment is given after amyloid formation there is no such effect[142–144]. Melatonin seems to be useful in symptomatic treatment, concerning sleep, sundowning (agitated behavior during the evening) and cognitive impairment[145]. As for sleep specific phases, melatonin treatment has shown to improve REM sleep in elders[146] and is found to improve the restorative phases of sleep in AD patients[145,147]. Which is interesting considering the decrease in REM sleep in AD patients[148].

4.3.6. Orexin

Orexin (hypocretin) is a neurotransmitter that is responsible for regulating arousal, wakefulness and is able to suppress REM sleep. The loss of orexin-producing neurons causes narcolepsy[99]. Furthermore, it has been reported that the orexin system is affected in advanced AD, could be a consequence of the loss of orexin-producing neurons[149]. Since the glymphatic system rinses the brain from toxins during sleep, excessive wakefulness regulated by orexin could possibly be a key regulator in AD.

For instance, infusion of a dual orexin receptor antagonist (almorexant) led to a decreased Aβ level in the interstitial fluid in mice and to a 10% decrease in wakefulness. Research shows that the knockout of the wake-promoting orexin gene reduces Aβ accumulation. This effect is reversed by sleep deprivation[150]. Indicating that sleep might be a modulatory factor for the degree of Aβ toxicity[151]. Which, suggest that chronic sleep deprivation may contribute to the pathogenesis of AD[99]. Though, patients whom have narcolepsy-cataplexy (thus, orexin deficient) don't seem to be protected against AD[152], which is interesting considering the effect of orexin antagonist's in AD mice.

4.3.7. Immune system

Sleep deprivation will provide a deregulation of the immune system. Study findings in general, suggest that SD is accompanied by immune activation. For example, increased white blood cells, granulocytes, monocytes, lymphocytes, NK cells and NK activity in the blood circulation have been reported[153]. Studies also found a changed balance in cytokine production. Some research suggested that the production of IL-6 and TNF-α is increased by prolonged sleep restriction[154,155], for which saturable transport systems over the blood-brain barrier are described[156]. There are also studies that outlined the effects of 24 h of continued wakefulness on cytokine production. Though these result are very conflicting[157,158]. Some research found increased levels of IL-1, IL-2 and IL-10[155,159]. Which is interesting, considering the firing rate of wake-active serotonergic neurons are reduced by IL-1 through enhancing inhibition of the axon terminals[160]. Furthermore, studies have shown that IL-1 and TNF are able to increase NREM sleep[161,162], which promotes immune function and occurs SWS. IL-1 is also found to cause fragmentation of NREM sleep[163] , in which it's effect magnitude and duration depends on the dose and time and time of administration[163–165]. Highlighting the contradictory of these studies.

Research highlighting the role of glial cells and SD revealed some interesting results. For example, a recent study by Bellesi et al. (2017) found that after normal sleep, astrocytes are active in 5,7% of the brain's synapses of mice. While, in sleep deprived mice, astrocytes were active in 8,4% of the synapses compared to 13,5% in chronically sleep deprived mice. Suggesting that chronical sleep loss results in more debris breakdown, but also in an elevated demolition of neuronal connections in the brain. Furthermore, their research found that after chronic sleep deprivation even microglial cells were more active. Excessive activation of microglial cells has also been seen in AD[166]. Previously, research had already reported astrocytic activation in the hippocampus of sleep deprived rats[167].

Inhibition of microglial activation in a study by Wisor et al. (2005) resulted in a reduced rebound in SWS after 3 hours of SD. Hereby they suggested that the microglial activation could contribute to the need for sleep[96]. Although another study by Bellesi et al. (2015) presented that 6-8 h of sleep deprivation led to an increased rebound of SWS activity, without finding evidence for microglial activation[168]. Which could indicate that microglial activation does not necessarily play a role in sleep homeostasis. The activation, however, could be a physiological response to worn synapses by extended wakefulness. Though, this could also be due to the reduced clearance of Aβ by the glymphatic system as a result of SD[76], leading to the aggregation of Aβ[99], by which microglial cells can be activated[169,170].

5. Discussion & Conclusion

Looking at the overall findings it is clear that AD is a complex disease, in which multiple factors can play a major role. In all of the AD subjects tangles and Aβ plaques are important markers for the disease[7,8,15]. Because the cause of sporadic AD is not yet identified, this literature research focused on the possibility of sleep deprivation as a risk factor for AD.

Sleep is known to facilitate the removal of toxic metabolites, like Aβ molecules, from the brain using the glymphatic system. Sleep deprivation could reduce the clearance of Aβ by the glymphatic system[68–71,76,100]. Furthermore, aging is associated with a reduced sleep quality[4,65,78,79], while aging is also associated with an increased risk of AD[19]. Elders seem to have a reduced SWS and NREM sleep[82]. As for AD patients, a decrease in SWS and REM sleep and some alterations in spindles and K complexes has been noted[148]. Considering that SWS is thought to be the most restorative state of sleep, because there is less activity of the neurons, a decrease in sleep and SWS sleep could result in a higher amount of Aβ levels in the brain[4,63–65]. Apart from speculating, research has shown that AD patients with sleep disruptions are more likely to become symptomatic than patients with a healthy sleep pattern[12]. Adding to this that sleep deprived animal models for AD have a 25% increase in Aβ plaques compared to non-sleep deprived controls[96].

As for tau, it is seen to indirectly regulate the sleep and wake cycle. Tau deficiencies and tau-p appears to increase wakefulness and decreases NREM and REM sleep[1,103,106]. Because tau is taught to increase neuronal activity, presence of tau in the ISF could negatively affect AD progression[106]. Furthermore, SD has shown to result in elevated tau-p levels[111].

SD has also been associated with reduced insulin level, possibly leading to diabetes mellitus[112]. Which is thought to increase the risk of AD[114,115]. Though one research has indicated that an insulin receptor mutation in mice did not exacerbate AD-like phenotypes[116].

For people caring the ApoE4 gene, research has shown that better sleep could reduce the risk of AD[11]. And that increased fragmented sleep in ApoE4 carriers increase the risk at AD by 1,5 fold[90]. Indicating that sleep is important in the development of AD for people at risk nonetheless.

Levels of melatonin seem to decrease in elders[131] and even more in AD patient[132]. Melatonin supplementation studies have shown contradictory results[135,136,138–140]. Though, it could be that long term administration showed better improvement. Furthermore, it could be possible that in severe AD patients already have a Aβ level that is too high, resulting in plaques. The presence of plaques has shown to disable clearance[98], which could be the reason why supplementation of melatonin doesn't work in severe patients.

As for orexin, suppressing the orexin system should lead to an increase of sleep and thus possibly to an increase of Aβ clearance. Research has indicated that a dual orexin receptor antagonist decreased the Aβ level. Furthermore, knocking out the orexin gene also reduced Aβ accumulation. This effect could also be reversed by sleep deprivation[150]. Again indicating that sleep deprivation can contribute to the stockpiling of Aβ.

Looking at the immune system, research shows an increase of microglia and astrocytes after chronic SD[166,167]. This activation of microglia has also been seen in AD[166]. In SD, the increased level of Aβ could possibly trigger the activation of microglial cells by self-aggregation[99,169,170].

Overall, it is fascinating to consider SD as a major risk factor so far. However, research does support the idea of SD as an influence on the development of AD, especially in people with a high risk at AD. To what extend SD influences the development is not well understood. What can be concluded is that normalization of sleep-wake patterns contribute to the clearance of metabolic waste in the brain and reduces the risk at AD. As for moderate AD patients, this potential therapy target could be of major influence on the prognosis of the disease. Considering, it is proven that patients with AD and SD are more likely to get symptomatic. To extent the impact of sleep treatment it is of importance to find a way to diagnose AD as early as possible.

6. References

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