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Aberrant waste disposal in neurodegeneration: why improved sleep could be the solution

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ABSTRACT

Sleep takes up a large percentage of our lives and the full functions of this state are still not understood. However, over the last 10 years a new and important function has emerged as a mediator of brain clearance. Removal of toxic metabolites and proteins from the brain parenchyma generated during waking activity and high levels of synaptic processing is critical to normal brain function and only enabled during deep sleep. Understanding of this process is revealing how impaired sleep contributes an important and likely causative role in the accumulation and aggregation of aberrant proteins such as β-amyloid and phosphorylated tau, as well as inflammation and neuronal damage. We are also beginning to understand how brain slow-wave activity interacts with vascular function allowing the flow of CSF and interstitial fluid to drain into the body's lymphatic system. New methodology is enabling visualization of this process in both animals and humans and is revealing how these processes break down during ageing and disease. With this understanding we can begin to envisage novel therapeutic approaches to the treatment of neurodegeneration, and how reversing sleep impairment in the correct manner may provide a way to slow these processes and improve brain function.

Introduction to sleep

It is estimated that by 2027 the number of people living over the age of 75 will exceed 10% of the UK population, and by this age they will have spent 25 of those years asleep. Sleep plays an essential role in daily living by restoring numerous metabolic and immunological processes to maintain our brain's normal function. The majority of animals maintain a roughly 24 hour cycle governed primarily by light and dark, with corresponding phases of activity and inactivity. Humans spend their inactive phase in consolidated sleep, generally during the dark period. Sleep however, is not just a single process, but consists of cycles of different brain activity which have been described as light sleep, deep sleep and rapid eye-movement or REM sleep. During a normal night we cycle through these different sleep stages several times together with short wake bouts that we do not register. The majority of deep sleep typically occurs in the first half of the night with the latter part being primarily spent in light sleep and REM. A young adult usually spends 15-25% of the time in deep sleep, and 20-25% in REM sleep. The amount of sleep per night can vary, but the general recommendation is 7-8 hours for a healthy individual, irrespective of age. These stages of sleep can be clearly characterised by measuring brain activity using electroencephalography (EEG). Light sleep is characterized by low-voltage, high frequency waves, coupled with variable electromyography (EMG) amplitude. Deep sleep is characterized by high amplitude slow waves, or delta-activity (1-4 Hz), and low muscle activity. REM sleep or paradoxical sleep is exemplified by low amplitude, mixed frequency EEG dominated by theta (4-8Hz) activity, with pronounced eye-movements and muscle atonia.

Sleep and wakefulness are governed by two processes that interact to create a propensity for the level of arousal. The first is the circadian process which oscillates on a 24 hr cycle and is generated as a daily rhythm entrained to light and dark. The second process is that driven by a homeostatic mechanism reflecting the sleep drive which increases during periods of wakefulness, dissipates during sleep, and is particularly sensitive to deep or 'restorative' sleep. The opposing interaction between these two processes creates the rapid switching to sleep at night

Abbreviations: Aβ, beta amyloid; CSF, Cerebrospinal fluid; EEG, electroencephalography; REM, rapid-eye movement; EMG, electromyography; BOLD, blood-oxygen level dependent imaging; CAA, cerebral amyloid angiopathy; OSA, obstructive sleep apnea; PET, positron emission tomography; MRI, magnetic resonance imaging; ISF, interstitial fluid; MCI, mild cognitive impairment; SWA, slow wave activity; SWS, slow-wave sleep; AQP4, aquaporin-4; NOS, nitric oxide synthase; NREM, non-rapid eye movement; iNPH, idiopathic normal pressure hydrocephalus.

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and waking in the morning.

Slow-wave sleep

Slow-waves originate in the prefrontal cortex, generally travel in a rostral to caudal direction, and are linked to activity in the thalamus and hypothalamus, producing highly synchronised firing activity [84]. These slow oscillations in turn coordinate high frequency oscillations called spindles (11-16Hz) which also couple with hippocampally generated high frequency events called ripples (140-220Hz). This phase locking of activity is proposed to underlie the consolidation of memories acquired during preceding wakefulness, and the transfer of information from the hippocampus to the cortex.

Sleep and wake states are controlled by a variety of midbrain and brainstem circuits. The ventrolateral preoptic area (VLPO) of the hypothalamus has been demonstrated to play a major role in promoting sleep via inhibitory projections onto wake-promoting brain areas such as the lateral hypothalamus (LH), dorsal raphe nucleus (DRN), locus coeruleus (LC) and ventral periaqueductal grey (vPAG). A detailed review of the circuitry controlling sleep was published by Weber & Dan [85].

Slow-waves may originate locally and are likely mediated by layer 5 cortical neurons. However, the thalamus is thought to be strongly linked and may also form an intrinsic component of slow-wave generation [27]. The more global effects that slow-wave activity can have on bodily functions such as blood flow and respiration [39] suggest that involvement of deeper brain structures and links to the autonomic nervous system are important factors.

Slow-wave activity (SWA), or the extent of delta power in sleep, is regarded as a general marker of sleep homeostasis. Delta power is low during the day and highest at the onset of sleep, declining throughout the sleep period. Sleep deprivation results in a subsequent increase in SWA, compensating for the lack of prior sleep. The mediator of sleep pressure is still debated, however, adenosine is thought to play a major role; accumulating during wakefulness, and declining during sleep. Recent evidence has strongly implicated the role of astrocytes in sleep homeostasis and imaging astrocyte activity during normal sleep processes has shown changes in calcium signalling occur in astrocyte processes in proportion to the sleep need. Manipulating astroglial calcium can change the response to sleep deprivation [56] as well as the architecture of SWS [18]. Indeed, ATP and adenosine, as well as other transmitters, are regulated by astrocytic networks [16].

The structure of slow-wave sleep, and the synchronous link with spindles and hippocampal ripples have been shown to be conducive to synaptic modulation and memory consolidation. It is thought that ripples represent memory trace events that are replayed during sleep, and this process transfers memory representations to cortex for long term storage [49,136]. The sleep homeostasis hypothesis (SHY) posits that slow waves can facilitate synaptic downscaling, which rebalances the high level of synaptic stimulation during active waking [126]. This process would reduce synaptic strength at the majority of synapses, but enhance the strength of others that are important for maintaining recent memories.[158]

Sleep changes with ageing

The structure of sleep tends to change during the ageing process. There is a gradual decrease in the amount of slow-wave sleep and sleep becomes more fragmented, often with more nocturnal awakenings [158] . The circadian clock also advances slightly, with the trend towards earlier wakening in the morning and greater tiredness in the evening. There may also be the tendency for more daytime naps, which can in turn reduce sleep propensity at night. In addition, there is a decrease in the number and amplitude of sleep spindles, and slow wave activity as measured by delta power is reduced. More detailed analysis has also demonstrated that the precise phase-coupling of the circuits active during slow-wave sleep become uncoupled in older brains which is correlated with both atrophy in the medial prefrontal cortex, and decreased overnight consolidation of memories [159].

Brain homeostasis and glymphatics

Normal resting brain activity consumes approximately 20% of the body's energy. Maintaining healthy neurons and glia together with continuous signalling throughout the brain is highly energetic, and until recently little was known about how the brain managed the high metabolic load and waste elimination required on a daily basis. The meninges covering the brain do have lymphatic drainage [7,77], but the brain itself contains no lymphatic vessels. Recent work has shown that glia play a major role in facilitating the flow of solutes and dissolved waste products through the brain, providing a mechanism known as the 'glymphatic system' – a perivascular transport route that allows cerebrospinal fluid (CSF) and interstitial fluid (ISF) to mix and drain metabolic waste out of the brain via meningeal and extracranial lymphatic vessels. Interestingly, this process appears to be least active during wake but enhanced during sleep; particularly slow-wave or deep sleep. This was first reported in 2013 using tetramethylammonium diffusion and two-photon imaging in mice, where the authors reported a 60% increase in interstitial space and increased flux of interstitial fluid during sleep [145]. Sleep was also shown to enhance the clearance of β-amyloid from the CNS by tracking intra-cortically injected ^{125}I-A$\beta_{1\text{-}40}$ [54]. This study also went on to show a strong link with delta power in sleep by modulating noradrenergic tone to increase delta power and consequently CSF flux. Since then, this finding has been replicated and extended to humans [30,46,79,112]. The drivers of this glymphatic flow have been the subject of much discussion in the literature, and there is still debate around the advective (bulk flow) or diffusive nature of these processes [25,109,122]. It has been suggested that diffusion may be important for the CSF-ISF exchange, but that advection drives flow along perivascular pathways [1], however, this is still an area of active research. A recent study of this process used modelling combined with directly measured tracer movement following cisternal injection [68]. Modelling of the data using optimal mass transport analysis supported the hypothesis that CSF solute movement was primarily advective while parenchymal transport utilized both advective and diffusive components. Another study modelling diffusion and bulk flow (advection) in light of measured data again concluded that both processes play a role in interstitial transport, however bulk flow may be more relevant in transporting large molecules such as Aβ [110]. Recent evidence has demonstrated a clear pulsatile nature to the perivascular flow that is linked to arterial pulsations [11,55,92]. In addition, slow oscillations have been identified in the basement membrane of capillaries suggested to facilitate perivascular drainage [131], and the reduced vasomotion found in App/PS1 mice was associated with impaired clearance of waste products. Using particle tracking through a cranial window, Mestre et al. linked the pulsatile flow of CSF in the perivascular compartment to the cardiac cycle and showed that this flow was also sensitive to blood pressure, with acute hypertension induced by angiotensin II dampening the waveform and reducing flow [92]. Others have utilized the spontaneous hypertensive rat (SHR) where chronic high blood pressure produces stiffening of arteries and microvessels [68,97]. These SHR animals were reported to show a reduction of glymphatic flow of approximately 30% relative to the normotensive Wistar Kyoto strain (WKY) using MRI imaging of the tracer Gd-DOTA in adult animals [97]. Application of solute diffusion/advection modelling to these data revealed regional changes in flow along the medial cerebral artery (MCA) route indicating obstruction in some parts of the pathway [68]. This link of reduced glymphatic flow to hypertension suggests a potential mechanism contributing to the known association between hypertension and dementia [74,130]. Interestingly, this hemodynamic/CSF pharmacodynamic relationship has also been linked to sleep EEG oscillations in humans by simultaneously measuring EEG together with BOLD fMRI

measures of CSF flow and hemodynamics. During wake, the CSF signal synchronised with respiration, however during NREM sleep, the CSF oscillations increased in amplitude and were synchronised with and preceded by the EEG slow-wave oscillation, suggesting that these oscillations are biophysically coupled. This data strongly suggest that slow oscillations occurring specifically during NREM sleep drive both oscillations in blood and CSF flow [40]. These important findings now demonstrate that as well has having an important role in cognition, slow-wave sleep enables large, low frequency, brain-wide pulsations in blood volume and CSF flow, increases CSF/ISF mixing, and facilitates solute clearance. Early imaging studies suggested that cerebral blood flow decreased during sleep [20], implying a drop in metabolic need and decreased neural activity, however more recent studies indicate this may vary across brain region and more detailed imaging techniques are starting to show how blood and CSF flow are linked to neuronal activity (Turner et al., 2021). These factors may combine to facilitate optimal exchange of CSF/ISF and perivascular flow both into and out of the brain.

Slow-wave sleep (SWS) drives clearance

This newly discovered role for slow-wave sleep is being explored in both preclinical and clinical settings. One obvious focus is the potential for facilitating the removal of waste products, including proteins such as β-amyloid and tau, from the brain [98]. Several groups have now demonstrated that sleep deprivation in rodents increases the levels of β-amyloid and tau in interstitial fluid, and proposed this to be due to reduced clearance and potentially overproduction during prolonged waking neural activity [51,63]. Indeed, chronic sleep restriction over 6 weeks increased cortical accumulation of β-amyloid and phospho-tau in male 3xTgAD mice [114]. Both sleep deprivation and chemogenetically induced wakefulness in mice produced increases in interstitial fluid levels of β-amyloid, tau and lactate [51]. These authors also demonstrated that sleep deprivation was able to increase the rate of tau spreading following hippocampal injection of recombinant P301S human tau fibrils in young P301S mice. In this same P301S model (rTg410) which overexpresses human tau P301S protein, reductions in CSF-ISF exchange were observed in a regionally specific manner in 8-9 month old animals, using MRI and injected contrast agent, as well as reduced brain clearance of tau. These effects were strongest in areas markedly affected by tauopathy [47]. Other proteins associated with neurodegeneration, for example, alpha-synuclein [51] and Apolipoprotein E [2] , as well as metabolites such as lactate [81] also show reduced clearance after sleep deprivation, suggesting this process is not limited to β-amyloid and tau.

In addition to homeostatic sleep drive there is some level of circadian control over brain waste clearance. Clearance of CSF in mice was greater during the day (inactive period) than during the night (active period), and conversely drainage to the mandibular lymph nodes was highest during the night [45]. This process was independent of light/dark cycle, persisting in constant light, and interestingly was lost in aquaporin-4 channel null mice implicating this channel in the clearance process.

Other recent studies have demonstrated impairment of CSF tracer influx in aged mice, as well as reduced clearance of ^{125}I-β-amyloid, suggesting that glymphatic function declines with increased age [69].

Slow-wave sleep appears to be a critical factor for clearance activity and this is also reflected in the brain activity under anaesthesia. An analysis of glymphatic transport under different anaesthetics demonstrated the greatest level of transport using ketamine/xylazine and the lowest using isoflurane, Avertin and α-chloralose [46]. This distribution correlated exactly with the extent of delta-power change in the corresponding EEG spectrum. It also correlated inversely with the heart-rate when measured under anaesthesia, in contrast to respiratory rate or blood-pressure, again suggesting a strong link between cardiovascular activity, CSF clearance and slow-wave power. This difference between anaesthetics has been replicated and used to illustrate differences in CSF flow [14], most recently demonstrating distinct efflux pathways under different anaesthetics, along the vagus nerve with isoflurane and via the olfactory bulb under ketamine/xylazine [124].

Several groups have shown similar effects of sleep loss in humans [9,51,79,100,120]. The first studies utilized serial sampling of lumbar CSF to look for changes in different Aβ variants, demonstrating an increase associated with daytime and a decrease at night, while sleep deprivation prevented the night-time drop or increased levels further during the sleep restriction period [79,100]. Ju et al. went on to demonstrate that specific disruption of slow-wave sleep was responsible for increased β-amyloid and that with disruption of sleep quality over 6 nights, CSF tau levels were also increased [61]. Subsequent studies have utilised brain PET imaging to look at both amyloid and tau levels. Shokri-Kojori et al. demonstrated that one night of sleep deprivation increased β-amyloid burden as measured using ^{18}F-florbetaben, with increases in hippocampus and thalamus [120]. In addition Lucey et al. showed that NREM slow-wave sleep, cognitive performance, and CSF tau-Aβ42 ratio were correlated with tau brain expression using ^{18}F AV-1451 (flortaucipir). In a relatively large cohort of individuals ranging from those with no AD markers to those with amyloid and tau present, SWA was inversely related to the level of pathological markers [80]. In addition to CSF changes, it was possible to measure an increase in total tau in blood plasma following a period of acute sleep deprivation in healthy young adults. However, no changes in amyloid were observed in plasma in this study [12].

That sleep changes perivascular flow in humans was recently demonstrated directly [40]. A combination of blood-oxygen level dependent imaging (BOLD) and EEG, was the first study to demonstrate a clear connection between slow wave sleep, hemodynamic oscillations and CSF clearance [40]. Interestingly, during sleep, the CSF flow dynamics were anticorrelated to haemodynamic oscillations, suggesting an alternation of blood flow and CSF flow which was coherent with, and preceded by, the neural slow wave rhythm. There are also indirect suggestions that CSF flow is increased during sleep. For example, uptake of gadolinium into perivascular spaces was more rapid during the night than the day [113]. In addition, patients with disrupted sleep appear to have enlarged perivascular or Virchow-Robin spacing [15] suggesting reduced fluid clearance. This increased perivascular space appears also to be associated with an increased risk of dementia [157]. Most recently, a study monitoring tracer clearance from the brain compared the speed of clearance during wakefulness and following sleep, directly demonstrating that in humans, sleep significantly increased the rate of glymphatic clearance compared to wake [73].

Alternative routes of clearance

There is still much debate regarding the clearance routes of CSF from the brain, and the relative importance of these for clearing aberrant proteins. There are currently at least three known routes; (1) into the subarachnoid space and via arachnoid granulations and villi into the major venous sinuses, (2) along the olfactory nerve, passing through the cribriform plate to the nasal mucosa reaching the cervical lymphatic vessels; (3) along the perineural sheaths surrounding cranial and spinal nerves and into the dura mater lymphatic vessels [7,37,135]. Drainage in the perivascular space could occur via the perivenous or periarterial route. Some evidence suggests the perivenous route [54], with tracer studies showing exit via the medial internal cerebral veins and lateral-ventral caudal rhinal veins. Other tracer studies have suggested that drainage occurs primarily along capillary basement membranes and arteriolar smooth muscle cell basement membranes against the direction of blood flow and without involving perivenous spaces [3,95], a route christened IPAD (Intramural Peri-Arterial Drainage). Studies following clearance of fluorescent-labelled β-amyloid directly injected into the cisterna magna have demonstrated labelling in the walls of arteries and smooth muscle cell basement membranes up to 30 minutes later, and suggest these as rapid routes of clearance [3]. Recent studies have also

shown that tau and α-synuclein proteins are also able to be cleared along the same pathway, but with different dynamics [99]. Further evidence that the periarterial route is important for clearance of proteins such as β-amyloid comes from the predominance of amyloid depositions in arteries resulting in cerebral amyloid angiopathy (CAA), whereas there is little evidence for deposition around veins [137], although recent reports do describe some venular deposition albeit to a lesser extent [96]. The question still remains as to the proportions of CSF and ISF that are cleared via the different routes and the contribution they make to clearing toxic agents and this is an active area of research [23]. Several imaging studies have attempted to follow either PET tracers or MRI contrast agents as they travel through the CSF into the lymphatic system in both animals and humans [29,34,113,119].

Wang et al. [134] found that blocking the deep cervical lymph node drainage of APP/PS1 double-transgenic AD mice resulted in a significant deterioration of Aβ-related pathophysiology highlighting that this as an important exit route for brain clearance. While the olfactory route appears to be a major clearance route in animals, [19,53,107] recent evidence has questioned this in humans [90,111]. Both studies, which looked at the clearance of the MRI tracer gadobutrol, found little tracer in the nasal mucosa. This contrasts with a study using dynamic PET imaging of a tau tracer ^{18}F-THK5117 and an amyloid tracer ^{11}C-PiB [29]. This group studied the clearance of both tracers over 80 minutes and found the highest density labelling accumulating in the nasal turbinate. They also demonstrated a 23% decrease in ventricular clearance of ^{18}F-THK5117 in Alzheimer's patients with a 66% decrease in superior turbinate binding. The level of ventricular clearance was directly correlated with the amyloid ^{11}C-PiB binding in the brain. This ventricular finding was replicated and extended by Schubert et al. who also found impaired clearance in MCI as well as in multiple sclerosis patients [119]. Another form of dementia, idiopathic normal pressure hydrocephalus (iNPH), which is characterised by progressive ventriculomegaly, problems with gait, dementia, and urinary incontinence is linked to enlargement of the brain ventricles and several other pathologies similar to Alzheimer's Disease. Twenty-four hour MRI tracking of intrathecally injected gadobutrol in controls and iNPH patients showed a delay to both brain influx and efflux suggesting a deficiency in glymphatic function in these patients [113]. In subsequent work, this group demonstrated impaired clearance within the entorhinal cortex [34], an area associated with cognitive function and early deposition of pathological proteins such as β-amyloid and tau. Further studies are clearly required to further investigate the exact route or routes of exit to the lymphatic system.

Vasomotion

An alternative driver of CSF was suggested by a study looking at vasomotion initiated by vascular smooth muscle dilations and constrictions [131]. This study in head-fixed awake mice looked at clearance of fluorescent dextrans injected intravenously. Continuous recordings over a 5-min time course revealed spontaneous vessel dilations and constrictions (on the order of 10%–15% diameter change) in individual pial arteries and arterioles in awake mice at ultra-low frequencies. Particles were observed moving alongside arterioles in the opposite direction to blood flow. Perivascular flow was reduced under isoflurane anaesthesia, consistent with previous studies [14]. Supportive of this hypothesis is the evidence that pericytes (cells found surrounding the capillary/basement membrane and in direct contact with astrocyte endfeet) have contractile capabilities, constrict and dilate in response to local neurotransmitters, and may also contribute to controlling blood and CSF flow [105]. Recent evidence also suggests that pericyte function is compromised by sleep restriction [89] and impaired in Alzheimer's disease [144]. Vasomotion appears to be linked to neural activity, particularly power in the gamma spectral band of EEG, which predominates during waking [33,87], and may drive fluctuations in blood oxygenation, potentially contributing to resting state BOLD measures [87]. Reports suggest that vasomotion itself is at its lowest level during sleep [156] suggesting that while it may provide some driving force, it probably does not underlie the sleep-mediated clearance process. A recent report utilized two-photon imaging in mouse sensorimotor cortex to follow hemodynamic changes in combination with EEG during the sleep/wake cycle. They describe large increases in blood volume and arteriole diameter during NREM and REM sleep states relative to wake, with rapid changes linked to vigilance state transitions. These changes were 2-5 times larger than those evoked by whisker stimulation during waking [128]. Correlations between neural activity and haemodynamic activity were strongest during NREM sleep relative to wake or REM states. These findings again show a dramatic link between hemodynamic activity and sleep state suggesting these changes are facilitating CSF flow during this state. Further studies to identify the neural mechanisms underlying neurovascular coupling suggest this is via NOS- expressing GABAergic interneurons rather than pyramidal neurons with involvement of inwardly-rectifying potassium channels [33]. Mechanisms may also differ between capillaries and arterioles, with capillaries depending more on astrocytic calcium and arterioles on interneuron NO release [8,94]. Clearly further work is required to understand the link between these processes and sleep state, and how they are controlled.

The importance of astrocytes and aquaporin-4

The process of brain fluid clearance starts in the neuropil, a dense structure of neurons and glia bathed in interstitial fluid into which metabolites and waste proteins are secreted. CSF, which surrounds the brain filling the subarachnoid space, flows into the brain along penetrating arteries into the perivascular space which are surrounded by astrocytic endplates. The end-plates which face the artery are filled with dense arrays of the aquaporin-4 (AQP-4) water channel, termed orthogonal array of particles or OAP's, which facilitate fluid flow into the interstitial space. Astrocytes surround both arteries and veins, and during slow wave sleep interstitial solutes including protein waste, are carried away along these perivascular routes into the lymphatic and cervical vessels. The role of astrocytes in this process appears to be critically important, and the AQP-4 water channel plays a major role in the transport process [60]. AQP-4 channels participate in transporting water and solutes across the perivascular layer, enabling rapid responses to changes in osmolarity, ionic concentration, and regulation of astrocyte volume. This volume change could play a role in enabling the increase in perivascular space observed during slow wave sleep [145], in addition to the increase in apparent diffusion coefficient [30] enabling CSF and interstitial fluid exchange. In addition, AQP-4 has been shown to play a role in extracellular potassium regulation, which again links to different extracellular ionic changes observed between sleep and wake vigilance states [32]. Characterization of AQP-4 knockout mice appears to confirm a role for this channel in CSF clearance and removal of aberrant proteins such as amyloid β and tau [54,91]. Changes in AQP-4 in human brain have also been reported in cases of dementia, with reductions in perivascular distribution reported in post-mortem Alzheimer's diseased tissue. These changes in AQP-4 correlated to increased amyloid-β burden and increased Braak stage [153]. Hasan-Olive also reported a significant reduction of AQP-4 density in astrocytic endfeet membranes in idiopathic normal pressure hydrocephalus (iNPH) patients, a subtype of dementia related to AD [48]. A recent study also investigated the levels of aquaporin-4 in the CSF of Alzheimer's disease and iNPH patients: significantly reduced levels were found in AD patients, and a trend to reduction in iNPH patients was observed [6]. Several groups have now identified single nucleotide polymorphisms (SNPs) in the aquaporin-4 gene that significantly associate with increased β-amyloid deposition, and the rate of cognitive decline in Alzheimer's Disease [22,108], as well as predicting transition from MCI to Alzheimer's [24]. These studies also reported an association with poor sleep [108,129]. The Ulv Larsen study showed that a common 8-SNP AQP-4 haplotype resulted in a difference in slow wave activity in

NREM sleep and changed reported sleepiness after prolonged waking, supporting the link between astrocyte driven brain clearance and slow-wave sleep. Preclinical studies incorporating AQP4 gene deletion into existing mouse models of Alzheimer's disease have demonstrated that removal of AQP-4 exacerbates β-amyloid plaque formation and cognitive deficits in APP/PS1 mice [147]. Direct effects on glymphatic clearance have also been shown, and AQP-4 deletion aggravates decreases of fluorescent tracer influx into, and efflux out of, the brains of 3 and 12 month old APP/PS1 mice [38,147]. In another model (5XFAD), AQP-4 deletion also increased β-amyloid deposition and plaque number [121]. As well as amyloid based models, the overexpressing human tau model (rTg4510) has recently been shown to exhibit impaired CSF/ISF exchange, decreased AQP-4 polarization to astrocyte endfeet as well as reduced clearance of tau. In addition, treatment of wild-type mice with the AQP-4 channel inhibitor TGN-020 reduced glymphatic inflow of total tau and phosphorylated tau, effects that were lost in the AQP-4 -/- mouse [47].

The interaction of AQP-4 and sleep restriction was investigated using control and AQP-4 -/- mice [154]. In control animals chronic sleep restriction over 7 consecutive days produced impairments in glymphatic tracer flow, abnormal distribution of AQP-4 away from blood vessels and cognitive impairments. In the AQP-4 -/- mouse sleep deprivation exacerbated these effects. In addition these mice demonstrated increases in hippocampal β-amyloid 1-40, total and phosphorylated tau, and evidence of increased microglial activation.

Interestingly the polarisation of aquaporin-4 to perivascular endfeet appears to be influenced by the circadian cycle, with much greater polarisation during the rest phase and associated with higher brain clearance [45]. The daily rest/active clearance rhythm was lost in AQP4-/- mice suggesting the importance of this channel in mediating glymphatic function.

Visualizing changes in brain clearance – preclinically and clinically

There are a number of techniques that have been employed to visualise brain clearance mechanisms both in rodents and humans. Several types of tracer have been used to investigate the rate of both influx into the brain and clearance into the lymphatic system. Tracers, for example a simple BSA fluorescent conjugate, can be injected into the cisterna magna and conventional fluorescent microscopy used to identify the tracer flux at set times after infusion [46]. This technique was extended to visualization using light-sheet microscopy in cleared whole brain providing robust analysis of how different anaesthetics affect rates of glymphatic flow [10]. It has also recently been possible to demonstrate active CSF flow in the perivascular space through a cranial window, using fluorescently labelled dextrans [54] or microspheres [92]. This approach does not rely on viewing fixed tissue, which the authors suggest causes the perivascular space to shrink and reverse direction of flow. Other methods studied in living animals have used MRI imaging of tracer flow injected into the cisterna magna [47,149]. These approaches demonstrated drainage of tracer into the cervical lymph nodes, as well as confirming decreased CSF flow under isoflurane anaesthetic compared to ketamine/xylazine. Unfortunately, none of these techniques have yet been able to demonstrate clearance during normal sleep in comparison to the wake state. The closest to this was a recent MRI imaging study in 25 healthy volunteers, comparing CSF clearance over a day cycle versus a night cycle following a normal night's sleep, demonstrating that clearance was significantly greater after a night's sleep [73].

Clinical measures of glymphatic function and CSF flow have been primarily developed around imaging methodology. There are however several studies that have incorporated measures of fluidic markers from CSF sampling that indirectly show the effects of sleep deprivation on clearance of these proteins [61,79]. In terms of clinical tracers, the MRI contrast agent Gadobutrol has been utilised where peak tracer was found after 24 hrs and one night's sleep [34,35]. Other studies have used the Aβ PET tracer ^{11}C-PiB with a view to looking at Aβ clearance from ventricles and superior nasal turbinate [29,119]. A recent technique of using ^{99}mTc-diethylene-triaminepentaacetic acid (DTPA) delivered intrathecally was shown to provide good resolution of flow into and out of the brain using SPECT imaging, while avoiding the toxicity issues with MRI contrast agents, and may be useful for future studies of sleep or drug effects [132]. Another approach has been to utilize BOLD imaging in conjunction with other measures such as EEG. Fultz et al. used this approach to directly study hemodynamic fluctuations and CSF flow. They could directly relate them to low frequency EEG oscillations demonstrating the related nature of these oscillations during NREM sleep [40].

Sleep and brain clearance impairments in other health conditions

Disruption of slow wave sleep is prevalent in a variety of neurodegenerative and other diseases. Besides its role in clearance, it also has a key function in memory consolidation [160]. Sleep is also strongly linked to neuroinflammation [43]. Thus, apart from sleep disruption itself possibly being a disease symptom, sleep disruption can also be an early sign of future disease progression.

Traumatic brain injury

In the case of traumatic brain injury (TBI) for instance, the early inflammatory response often leads to sleep disruption both acutely and chronically [86]. This disruption of sleep may lead to further elevation of pro-inflammatory cytokine levels such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, and to further cellular damage. These cytokines are also involved in sleep regulation and in turn affect sleeping patterns. Other studies suggest that those patients with long term sleep issues following mild traumatic brain injury have elevated biomarkers of neurodegeneration such as Neurofilament light chain and tau [139]. Levels of amyloid and IL-10 are also often increased [41]. It has been suggested that, given the overlap in this process and those operating in Alzheimer's Disease (AD), this may account for the increased risk of developing AD associated with TBI [43]. There is also clinical data suggesting a link between brain clearance, poor sleep and persistence of TBI symptoms [106].

Parkinson's Disease and dementia with Lewy Bodies

In Parkinson's patients it has been shown that sleep quality is a significant risk factor for the development of the disease [82,155]. Furthermore, global cognitive performance is correlated with sleep efficiency [123] as measured by wake after sleep onset (WASO). In particular, slow wave sleep has been linked with cognitive performance [117]. Both Parkinsons and dementia with Lewy bodies (DLB) are are commonly preceded by REM sleep behaviour disorder [57] and are both associated with deposition of alpha-synuclein protein accumulating in a similar fashion to β-amyloid and tau [93] which suggests an association with impaired clearance of aberrant protein from the brain. Sleep efficiency and slow-wave sleep can both be improved in Parkinson's patients by 16 weeks of chronic exercise [4], although the consequences of this for cognitive performance were not assessed. It is tempting to speculate that increasing slow-wave sleep and enhancing brain clearance mechanisms would be of clinical benefit for Parkinson's patients.

Frontotemporal dementia

Sleep disturbance is a common feature of other neurodegenerative diseases, such as frontotemporal dementia (FTD) [88] and amyotrophic lateral sclerosis (ALS) [17] . These diseases may be more genetically based but also involve aberrant proteins such as C9orf72 and TDP-43

[28]. In these cases, amyloid plays little or no role as a driver of disease or as a promoter of sleep disturbance. This may suggest that it plays little role in promoting sleep disorders in vascular dementia or Alzheimer's disease and that sleep disruption is a fundamental part of neurodegenerative disease progression and not a consequence of it.

Cardiovascular disease

As mentioned earlier, the developing connection with the cardiovascular system, glymphatic clearance and sleep suggests that cardiovascular dysfunction can also contribute to the development of neurodegenerative disease (Fig. 1). Loss of cardiac fitness has been shown to be related to cognitive decline [138], and in animal models of hypertension, glymphatic transport has been shown to be impaired, with enlarged perivascular spaces and dysfunctional aquaporin-4 polarity [97,148]. Hypertension is also often co-morbid with related conditions such as sleep apnea and obesity.

Cerebral amyloid angiopathy

The accumulation of β- amyloid in brain tissue is thought to represent an early or prodromal stage of Alzheimer's disease. However, amyloid is also deposited in the vascular compartment along the walls of cerebral and leptomeningeal vessels [125]. This process, known as cerebral amyloid angiopathy (CAA), is present in approximately 80% of AD patients, and probably occurs independently in a large proportion of the population aged over 80 [125]. CAA can lead to destruction of the vessel wall and loss of smooth muscle cells, producing fibrinoid necrosis and potentially microaneurisms. The reasons for accumulation in vessels are unclear, but it is thought that this may partly be due to the breakdown of perivascular clearance mechanisms and the impaired clearance of amyloid peptides and solutes along the IPAD pathways that drain solutes from extracellular compartments [23]. These deposits in the basement membranes of capillaries and arteries produce arterial and vascular stiffness, reducing the pulsatility that plays a role in driving CSF-ISF exchange in the perivascular space, as well as reducing the ability for glymphatic clearance, generating a positive feedback loop leading to more accumulation of β-amyloid. In both mouse models of CAA and in humans with AD and CAA, the vascular amyloid deposition has been reported to result in mislocalization of aquaporin-4 expression in astrocytes and decreased GFAP expression, as well as reduction in other ion channels important for normal homeostatic function, in particular potassium channels [141]. Furthermore, in another amyloid model, the APPJ20 mouse, amyloid was found in close association with cerebral vessels, and actually physically displaced astrocytic end-feet disrupting astrocyte/vascular coupling [66]. As a consequence AQP-4 expression was reduced and a likely consequence would be decreased brain clearance.

OSA and Alzheimer's

Obstructive sleep apnea (OSA) is a well-known sleep condition that has become more prominent in recent years with a worldwide estimate of 936 million adults aged 30-69 with mild symptoms, and 425 million with moderate to severe symptoms [13]. Prevalence in some countries is as high as 50%. This disorder is more prominent in men, and is linked to obesity as well as other common conditions such as hypertension and cardiovascular impairment. It is characterized by intermittent hypoxia, increases in intrathoracic pressure and sleep fragmentation, leading to daytime sleepiness and cognitive impairment. One consequence of sleep fragmentation is a large depletion of slow-wave sleep, which can be lost almost completely in severe OSA [44]. There is a considerable body of accumulated evidence to draw strong links between Alzheimer's disease and OSA. Studies have demonstrated that AD patients have a 5-fold increased risk of OSA, and at least 50% of AD patients will suffer from OSA [36]. More importantly, recent studies examining AD biomarkers have shown that many of these are elevated in OSA patients early on, including Aβ42, phospho-tau and total tau [21,31,151]. A recent study of post-mortem tissue from OSA patients identified Aβ plaques and neurofibrillary tangles in the hippocampus of these subjects as well as significantly reduced hippocampal volume, all characteristics of AD [102]. The extent of the pathology significantly correlated with OSA severity. This evidence again suggests that abnormal sleep can contribute to the development of Alzheimer's disease pathology. It should also be noted that in MCI and AD patients with OSA the presence of OSA appears to accelerate the increase in amyloid and tau [21,101]. Several groups have looked to see if continuous positive airway pressure (CPAP) therapy, which is the only currently available therapy for OSA, is able to affect either cognitive symptoms or these associated biomarker changes. Studies suggest that CPAP was able to reverse cognitive impairment in both MCI and AD patients with sleep apnea, slowing cognitive decline in mild to moderate patients [26,101,127]. More recently, CPAP was found to increase slow-wave sleep and lower β-amyloid after 1-4 months of treatment [62]. Another study, comparing normal, OSA and OSA-CPAP treated patients, showed that unlike the OSA patients, those treated with CPAP showed no neuropathological AD biomarkers [75]. These studies suggest that the OSA induced markers of early stage AD can be reversed by treatment of the underlying sleep disorder.

Cause or consequence - Sleep symptoms and Alzheimer's disease

There is considerable evidence that in a high proportion of patients sleep changes precede cognitive and other symptoms of dementia. Strong evidence comes from three recent studies; the first using sleep EEG records from 9,834 subjects ranging from normal to diagnosed dementia, to identify properties that might suggest mild cognitive impairment and progression to AD [150]. The study demonstrates a

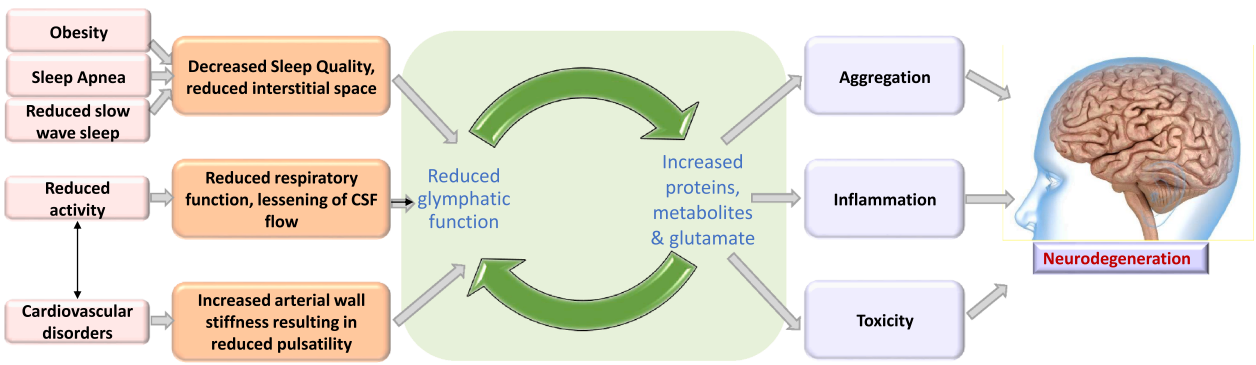

Fig. 1. The combination of sleep impairment with other co-morbidities such as cardiovascular disease lead to reduced glymphatic function and increased accumulation of toxic proteins, these will in turn lead to increased aggregation, inflammation and neurotoxicity, in addition to continued reduction of brain clearance.

number of spectral and feature changes that combine to form markers that are highly correlative with progression to Alzheimer's disease; the most predictive being sleep fragmentation and low frontal delta power. Secondly, another large study looking at subjective sleep quality in MCI patients and healthy elderly showed a direct correlation of poor sleep to plasma Aβ levels [76], and thirdly, a recent longitudinal study looking at sleep duration which showed that persistent short sleepers in their 50's 60's and 70's had a 30% increased chance of developing dementia, independent of other risk factors [115]. Another recent study demonstrated that slow wave sleep tracked longitudinally could forecast the trajectory of Aβ deposition in clinically normal adults, irrespective of other factors such as age and sex [143]. There are several earlier studies which again note that loss of SWS and sleep fragmentation frequently occur in MCI patients [133,140,142]. Recent evidence also suggests that levels of β-amyloid, amyloid plaque and tau tangle pathology start to appear in sleep apnea patients prior to emergence of any cognitive signs [102,151], OSA being an extremely strong risk factor for AD [5]. Where sleep has been studied in animal models of AD, decreases in slow-wave activity occur early and are linked to Aβ or tau levels [52,65]. Another important study that indicates a causative role of poor sleep, is that from Xie et al. In this study they applied a chronic sleep fragmentation paradigm to wild-type C57/Bl6 mice during the inactive phase for 2 months. Following this period they found that sleep restricted mice performed poorly on the Morris water maze, and novel object recognition task. They also found increased β-amyloid expression in hippocampus and cortex. In addition, they found dysregulated endosomes and lysosomes, as well as increased signs of autophagy and activated microglia [146]. This indicates that in the absence of any other factors, chronic sleep fragmentation can induce all the neuropathological signs of dementia, as well as impaired cognitive function, suggesting a causative role in the early stages of the disease.

Sleep as a therapeutic intervention

There are now some preclinical examples of the effects of increasing slow wave activity on brain clearance. Kastanenka demonstrated in APP/PS1 mice that firstly, slow wave activity was reduced compared to control mice at 3-6 months of age. Secondly by artificially driving slow-wave oscillations using optogenetic techniques to synchronize pyramidal cell firing, they could halt the deposition of amyloid plaques, and prevented calcium overload in cortical neurites [64]. They also showed that driving slow oscillations could restore aberrant GABA levels in APP/PS1 mice, that could reduce overall hyperexcitability. This suggests that it is the increase in slow-wave activity that has real effects on the pathophysiology of the disease. Pharmacological intervention can also affect pathology, as recent publications have demonstrated. In the same APP/PS1 model, chronic administration of pimavanserin or MDL100, 907 (both serotonin receptor 2A inverse agonists that increase slow-wave sleep) were able to lower both the level of CSF Aβ with a steady state reduction of 40% after 36 hrs, as well as reduce plaque load in the hippocampus and cortex [152]. The treatment also reduced anxiety and cognitive impairments in these mice. Another publication also suggested that 5-HT_{2A} antagonism could restore function in APP/PS1 mice via treatment with desloratadine, although this work attributed the improved function to reduced microglial inflammation [78].

Effects of sleep agents on brain clearance have not yet been reported. Most commonly-used approved sleeping aids do not increase slow wave sleep. In fact, the most widely used agents, such as benzodiazepines, have the opposite effect and reduce slow wave sleep. In addition, benzodiazepines (and related 'non'-benzodiazepines that act at the same site) are not recommended for use in elderly patients, due to impaired cognition, increased risk of falls and daytime hangover effects [118]. Suvorexant, and more recently lemborexant, are orexin antagonists and appear to be better tolerated in elderly. However, this mechanism has little effect on slow wave sleep [50]. The antidepressant trazodone is reported to increase SWS [161], and is often used off label to treat insomnia [58]. A recent report comparing elderly trazodone users and non-users demonstrated a slowing of cognitive decline with trazodone use in patients with sleep impairment [70]. This, together with earlier reports of improved neuropsychological function with trazodone [72], reinforces the potential therapeutic value of pharmacological modulation of improving slow-wave sleep and extending consolidated sleep. Brain penetrant antihistamines such as diphenhydramine have also been shown to increase slow-wave sleep and improve sleep quality, however these agents generally also have anticholinergic activity which would be inappropriate in this patient population [118].

Other approaches to increasing overnight slow wave sleep have also been proposed, originally from the perspective of improving cognition. Several studies have demonstrated that the exposure to essential oils may increase overnight slow-wave sleep. An initial study in 2005 demonstrated intermittent presentation of lavender oil increased the percentage of SWS relative to those subjects exposed to water [42]. This has recently been followed up in more detail where small but significant increases in deeper sleep stages were observed when exposed to lavender oil overnight [67].

It has also been demonstrated that slow-wave activity can be increased by direct stimulation of the brain either by acoustic or electrical stimulation. Several groups have shown that transcranial current stimulation (tCS) applied during NREM sleep can enhance slow oscillations and in turn promote memory recall [59,83]. Others have shown that this may be effective in MCI patients [71]. The same principal has been applied using acoustic stimulation to enhance slow wave activity [103,104], and demonstrated improvements in memory consolidation in healthy subjects and MCI patients. Effect sizes using these techniques are not huge and the literature is mixed (recently reviewed by [116]). The increase in slow wave activity has tended to be observed only over a single night, and the effects have generally been demonstrated on overnight recall. It is not known whether the pro-cognitive benefits would be maintained, or what the impact of longer-term stimulation would be, and there is a lot more work to be done in this area.

Conclusion

Dementia has become one of the greatest health challenges facing the world. With an ageing population and burden of care for those suffering from neurodegenerative disorders, the search for understanding causative mechanisms and developing effective therapeutics continues to thwart the scientific community. Efforts within the pharmaceutical industry have focussed on reducing the aberrant proteins such as β-amyloid and phosphorylated-tau that are thought to contribute to the neurodegeneration process. However, despite increasingly long and expensive clinical trials, these single target approaches have not been successful in either treating the symptoms or slowing the progress of the disease. In recent years, research has revealed the important role played by sleep in both the consolidation of memories and in enabling the brain to clear toxic metabolites and proteins, with a focus on those that may accumulate to cause damage to the CNS. We are starting to understand more about this process with the key involvement of astrocytes in controlling fluid flow, co-ordinating slow-wave activity as well as the importance of the neurovascular system and its relationship with neural activity. It is still early days in terms of our understanding of this process. However, sleep is a critical component in enabling the glymphatic process to occur and slow-wave sleep impairment is now well established as a key factor in the etiology of Alzheimer's disease as well as other neurodegenerative disorders. We can now start to explore how manipulation of sleep may be able to prevent the decline of these processes and potentially be a key factor in slowing disease progression.

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