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The role of sleep deprivation and circadian rhythm disruption as risk factors of Alzheimer's disease

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ABSTRACT

Emerging evidence suggests that sleep deprivation (SD) and circadian rhythm disruption (CRD) may interact and increase the risk for the development of Alzheimer's disease (AD). This review inspects different pathophysiological aspects of SD and CRD, and shows that the two may impair the glymphatic-vascular-lymphatic clearance of brain macromolecules (e.g., β-amyloid and microtubule associated protein tau), increase local brain oxidative stress and diminish circulatory melatonin levels. Lastly, this review looks into the potential association between sleep and circadian rhythm with stress granule formation, which might be a new mechanism along the AD pathogenic pathway. In summary, SD and CRD is likely to be associated with a positive risk in developing Alzheimer's disease in humans.

1. Introduction

It is a common experience that after a night of good-quality sleep we feel clear-headed, while if we do not go to bed at the time we feel is needed, our performance in daily tasks deteriorates. This experience is in fact supported by scientific evidence. Both sleep duration and quality (i.e. continuity and intensity) are essential for maintaining good human performance and cognition (reviewed in Goel et al., 2013). Human subjects with sub-optimal sleep duration (i.e. 0–6 h/night) (Gildner et al., 2014) or poor sleep quality, as in sleep apnea patients (Yaffe et al., 2011), tend to have poorer memory and other higher cognitive function deficits. Studies using animal models (Karatsoreos et al., 2011; Kwon et al., 2015) also showed similar findings. Recent research further linked sleep deprivation (SD) with the development of Alzheimer's disease (AD), the most common form of dementia (50–75% dementia cases) worldwide, which is estimated by the World Health Organization (WHO) to affect 81.1 million people by 2040 (Duthey, 2013). One systematic review and meta-analysis, involving 198,232 individuals in 12.14 ± 12.84 years of follow-up, found that subjects with sleep disturbances have a 1.49-fold increased risk of AD as compared to a baseline of no sleep disturbances (Shi et al., 2017). Patients with insomnia (risk ratio = 1.51), sleep-disordered breathing (risk ratio = 1.20) or other sleep disturbances (risk ratio = 1.76) were found to have higher risks of developing AD (Shi et al., 2017). A post-mortem study showed that chronic sleep fragmentation was associated with a decreased number of neurons in the intermedius nucleus of the anterior hippocampus compared to baseline, in both AD and non-AD cases (Lim et al., 2014).

Amyloid-β (Aβ) (Hardy and Selkoe, 2002; Selkoe and Hardy, 2016) and microtubule-associated protein tau (Bloom, 2014) are classic hallmarks of AD. Increased interstitial Aβ levels are reported to be positively associated with amyloid plaque formation (Thal et al., 2006). Increasing lines of evidence also show that extracellular tau may interact with intracellular tau and cause neuronal toxicity or various forms of tauopathy (Medina and Avila, 2014). The following human studies indicate that sleep duration and quality are associated with Aβ cerebrospinal fluid (CSF) or interstitial fluid (ISF) concentration. One study demonstrated, in healthy young males via a lumbar catheter, that the Aβ levels in CSF showed a diurnal pattern, increasing throughout the day, peaking at night and decreasing overnight (Kang et al., 2009a). Another study showed that among non-demented, late middle-aged adults, subjects with poorer self-reported sleeping quality also demonstrated increased amyloid burden (Sprecher et al., 2015). In mice, Holtzman's group further demonstrated a similar diurnal ISF-Aβ fluctuation pattern (Kang et al., 2009a). Mice that were forced to be awake during the first 6 h of a 12-hour light cycle showed an abnormal rise in ISF-Aβ compared to the baseline levels at the corresponding circadian time point, while being put to sleep after the 6 h of wakefulness had an

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immediate effect in depressing the ISF-Aβ levels. These results suggested that the duration of wakefulness, instead of circadian time point, is the factor affecting ISF-Aβ concentration (Kang et al., 2009a). Chronic SD in amyloid precursor protein (APP)/presenilin 1 (PS1)/orexin knockout (OR-/-) mice significantly increased Aβ pathology, while a 12% increase in the sleep time during the dark phase was associated with > 50% reduction in the development of Aβ pathology in the brain (Roh et al., 2014). Rodent studies further showed that SD correlates with extracellular concentrations of tau (Di Meco et al., 2014; Iliff et al., 2014; Liguori et al., 2014; Qiu et al., 2016; Rothman et al., 2013). From these studies, it could be inferred that there is at least some degree of association between SD and AD, and the underlying pathogenesis requires the integration of various studies to map out.

Apart from an optimal duration and good sleep quality, sleeping and waking up at the right time of the day, i.e. following the natural circadian rhythm, is also emphasized in health maintenance throughout human civilization. Misalignment of the internal clock with the environmental circadian rhythm could occur either in trans-meridian jet lag (i.e. long-haul flight crossing several time zones) (Noyek et al., 2016) or social jet lag, which is defined as the extension of daily activities into night resulting in "discrepancies in social and biological clocks" (Wittmann et al., 2006). Acute misalignment could lead to symptoms in jet lag disorder (Noyek et al., 2016), while misalignment in a chronic setting would also lead to cognitive impairment or features of dementia. Healthy female flight attendants exposed to regular trans-meridian jet lag showed a significant reduction in temporal lobe volumes on MRI and more prominent spatial cognitive deficits compared with their counterparts who were only required to work short-haul flights (Cho, 2001). Adolescents with chronic social jet lag showed impaired memory, concentration and school performance (reviewed in Touitou, 2013). A 4.9-year cohort study involving 1282 healthy elderly women showed an increased risk of developing dementia or mild cognitive impairment in subjects having delayed onset of peak activity in a day (Tranah et al., 2011). Although Kang et al. (2009a) previously concluded that it is likely wakefulness, instead of circadian time point, that affects the ISF or CSF Aβ levels in the body, the above studies suggest that CRD might have other underlying pathways that could be involved in the development of cognitive impairment and even potentially AD.

However, before a judgement can be made, the presence of chronotypic variation, which is the difference in preferred timing of activity and sleep among individuals in the society (Wittmann et al., 2006), should be taken into consideration. The literature mostly supports that late chronotypes (late sleepers) have poorer health outcomes and daytime cognitive functioning compared to early chronotypes (early sleepers) when they are forced to keep with the natural circadian rhythm socially and behaviorally, for instance by attending a daytime job or early-morning school after a night of late sleep (Reviewed in Golombek et al., 2013; Roenneberg and Merrow, 2016; Wittmann et al., 2006). Therefore, complying with the natural circadian rhythm is not definite for good health or cognition for all chronotypes. The relationship between the natural circadian rhythm, the human endogenous biological clock, and the associated cognitive health outcome remains to be elucidated. This review tries to investigate the issue by dissecting the molecular pathways involved in the internal clock and its interaction with the external environment.

It is worth noting, with the modernization of society, that the increase in night-life and shift-work (Boivin and Boudreau, 2014) causes a reduction of sleep time in people living in major cities. A population-wide health survey by the Hong Kong Government in 2014/15 showed that 35.4% of the total local population aged 15 or above slept less than 7 h per day in the past 30 days (Centre for Health Protection Hong Kong, 2017). Similar surveys in the U.S. (Centers for Disease Control and Prevention U.S.A, 2011; Ford et al., 2015) and Singapore (Tan et al., 2016) reported that over 30% of the local adult population slept less than 7 h on weekdays. The increase in nighttime activity and the use of electronic devices also puts modern metropolitans at chronic social jet lag (Czeisler, 2013; Hatori et al., 2017; Wittmann et al., 2006). The social trend of increasing SD and CRD in the population and the enormous future demographics predicted to be affected by AD leads to the question of whether these trends would aggravate future AD epidemics. Thus, it is of significant public health interest to investigate whether SD and CRD would be valid as positive risk factors for AD. This review aims to integrate the current scientific findings on the molecular mechanisms of SD and CRD that contribute to AD, thereby providing a reference for future public health policymaking.

2. A foreword on circadian rhythm and sleep

From plants and fruit flies to humans, a particular group of genes or molecules enabling the organism to respond to the day/night-light/dark cycle are preserved across species (Reviewed in Welsh et al., 2010; Crane and Young, 2014; Reddy and Rey, 2014). In humans, every cell possesses an internal biological clock that operates via the oscillation of a series of genes or molecules, termed "clock genes" or "clock proteins", in which the molecular oscillation "keeps" and "tells" the time for the organism in a biological setting (Yamazaki et al., 2000). The molecular oscillation of the clock genes could take place independently without any external cues such as light, with a rhythm of approximately 24–25 h (Yamazaki et al., 2000; Aton and Herzog, 2005). The circadian oscillation of molecules occurs individually in each cell. At the whole organism level, the cellular oscillation is ultimately coordinated by a master circadian pacemaker, the suprachiasmatic nucleus (SCN), located dorsally to the optic chiasm in the hypothalamus (Welsh et al., 2010; Van Erum et al., 2017). Although the biological clock in humans could function internally, the purpose of its existence is to detect and align the body's physiology to the rhythm of the Earth's rotation by resetting the rhythms of molecular oscillation, a process called "entrainment". This process is achieved by sensory input to the SCN via visual, dietary and social cues. The SCN would then integrate these environmental cues and give output projections to orchestrate the molecular oscillation of each somatic cell into a synchronized rhythm (Welsh et al., 2010; Van Erum et al., 2017). The 2017 Nobel Prize in Medicine and Physiology acknowledged the influence of the internal clock on human physiology. The internal body clock coordinated by the SCN entrains many physiological events, such as melatonin and cortisol secretion, and sleep (Reviewed in Crane and Young, 2014; Touitou et al., 2017; Van Erum et al., 2017; Welsh et al., 2010).

It is now widely accepted that two interlinked transcriptional-translational feedback loops (TTFL) form the core of the internal clock (reviewed in detail by Crane and Young, 2014; Reddy and Rey, 2014). In every nucleated body cell, the first loop begins with the dimerization of two nuclear proteins, BMAL1 (brain and muscle Arnt-like protein-1) and CLOCK (circadian locomotor output cycles kaput), starting in the subjective day (Landgraf et al., 2012). The complex serves as a transcriptional activator of two genes, namely *period (per)* and *crytochrome (cry)*. The PER and CRY proteins accumulate in the cytosol, reaching a critical concentration in the late afternoon (Landgraf et al., 2012), and are translocated back to the nucleus where they repress the transactivation of the BMAL1/CLOCK complex, forming a negative feedback loop (Hogenesch et al., 1998, Landgraf et al., 2012). The second feedback loop commences with BMAL1/CLOCK upregulating the translation of NR1D1 (nuclear receptor subfamily 1, group D, member 1, also known as REV-ERBα) and NR1D2 (nuclear receptor subfamily 1, group D, member, also known as REV-ERBβ), which then represses *Bmal1* gene transcription and controls the transcription of *per* and *cry* genes (Bugge et al., 2012; Cho et al., 2012; Preitner et al., 2002). Adding onto the TTFL model, several post-translational modifications e.g. phosphorylation of the PER protein by casein kinases (Lee, 2001; Gallego and Virshup, 2007), or non-transcription/translational processes e.g. the peroxiredoxin rhythms (reviewed by Reddy and Rey, 2014) are found to have a significant influence on the TTFL and determination of final circadian output.

The most prominent external cue in resetting the internal clock (known as Zeitgeber, meaning "time giver" in German) is light (Hendrickson et al., 1972; Moore and Lenn, 1972; Hughes et al., 2016). In humans, a specific group of cells in the retina, the intrinsically photosensitive retinal ganglionic cells (ipRGCs), are dedicated to light detection for circadian entrainment

(Berson et al., 2002). Human ipRGCs specifically express the photopigment melanopsin (Opn4), which acts as a G-protein coupled receptor (GPCR), and upon photic signaling, opens TRPC6 and TRPC7 ion channels via Gq/11 type G-protein - PLCβ4 cascade, leading to calcium influx and action potential generation (reviewed in Hughes et al., 2015). The ipRGCs project to the SCN via the retinohypothalamic tract (RHT), and at the axonal terminal, interact with SCN neurons using glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) as the neurotransmitters. In SCN cells, a light signal results in a wide spectrum of kinase responses, which ultimately converge on the cAMP response element binding protein (CREB) pathway, to regulate the expression of a transcriptome of at least 536 genes. Notably, among the genes regulated, Per1/2 genes show a clear earlier onset of expression upon light at dawn (the end of subjective night) and a delayed onset of expression upon light at dusk (the start of subjective night), and are thus thought to be the primary genetic target of photoentrainment of the SCN clock (reviewed in Hughes et al., 2015). Apart from photoentrainment, social activities, food intake and physical exercise are also Zeitgeber that may entrain the internal clock. These external cues are integrated within the thalamic intergeniculate leaflet and brain stem serotonergic raphe magnus nuclei, which then project to and act on the SCN neurons (Mistlberger and Skene, 2005).

Integrating the input from external cues, SCN neurons orchestrate the circadian functional rhythm of peripheral organs (e.g. liver, spleen, lungs) via autonomic neuronal and hormonal outputs (Kalsbeek et al., 2006). In trans-meridian jet lag or social jet lag, oscillators in both SCN neurons and peripheral cells encounter asynchrony (Davidson et al., 2009). It took the SCN 8 days to resynchronize its own circadian rhythm and that of peripheral cells with the environmental change in mice subjected to 6-hour circadian phase advancement (Davidson et al., 2009). We encounter discomfort during the resynchronization process following jet lag, and regular asynchrony of circadian rhythm due to chronic jet lag would cause further pathological effects, as will be discussed in the later sections.

Sleep is controlled by two processes, the sleep homeostat (process S) and the circadian drives (process C) (Saper et al., 2005a, 2005b, 2005c). The sleep homeostat increases sleepiness as the time of activity increases through the day, telling the body to rest, possibly via a rise in adenosine levels in the basal forebrain containing the sleep center, the ventrolateral preoptic nucleus (VLPO) of the hypothalamus (Brown et al., 2012; Huang et al., 2014). The circadian drive is regulated by the SCN projection to the VLPO area via the dorsomedial nucleus of the hypothalamus, signaling the body to sleep in the biological night (Saper et al., 2005a, 2005b, 2005c; Van Erum et al., 2017). SD against the sleeping drive, together with the associated CRD, is involved in the development of Alzheimer's pathology, as discussed in the following sections.

3. Sleep, circadian rhythm and brain waste protein clearance and production

The brain possesses a clearance system for pathological proteins like extracellular Aβ-fibrils and tau-aggregates (Tarasoff-Conway et al., 2015). They may be degraded upon production in cells by pathways like the ubiquitin-proteasome and endosomal-lysosomal pathways, or they may be transported to the interstitium. In the ISF, they are either degraded by processes such as protease degradation or glial phagocytosis, or they may be transported out of the brain via ISF-CSF exchange by the glymphatic pathway or ISF-blood exchange by ApoE facilitated blood-brain barrier transport (for a more detailed description, refer to Review in Tarasoff-Conway et al., 2015). The following sections discuss the role of sleep and circadian rhythms in the brain protein clearance system (see Figs. 1a,b).

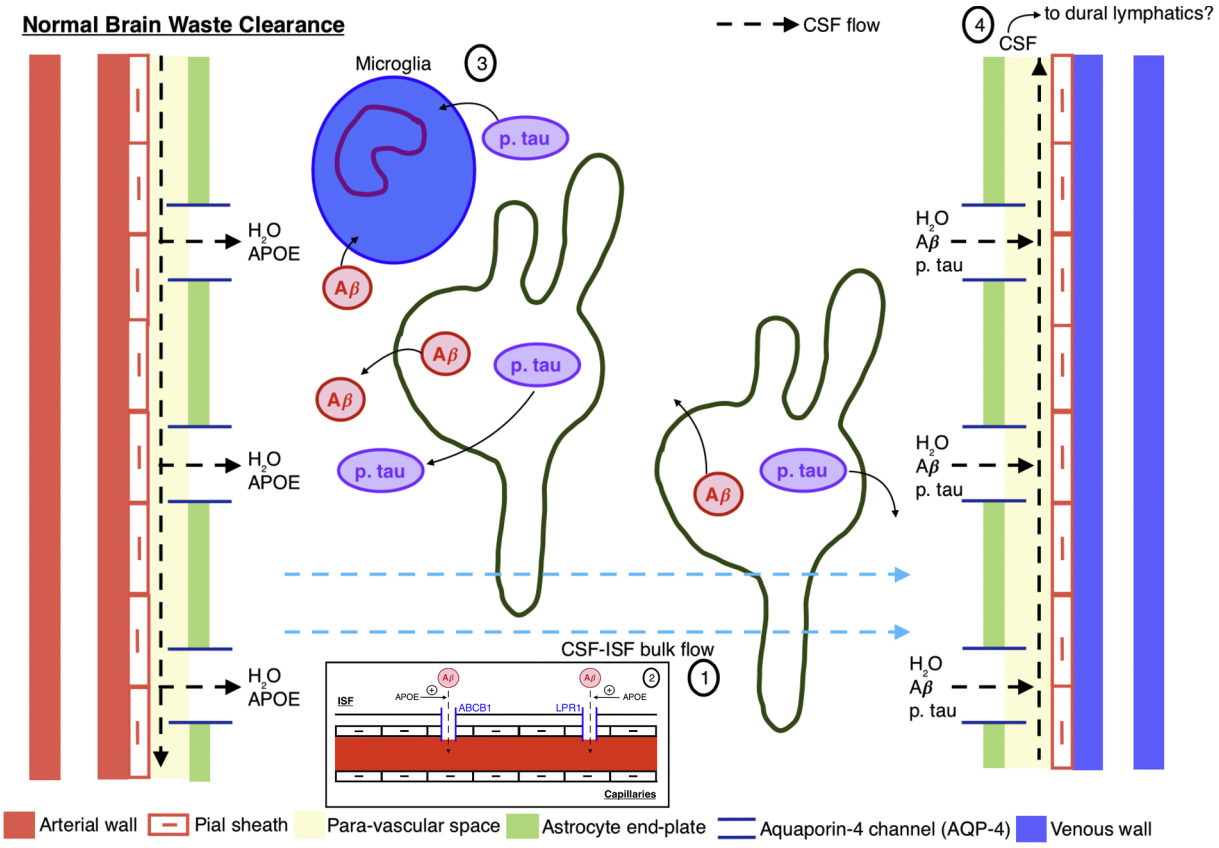

Fig. 1a. *Brain waste clearance.*
1. Arterial pulsation drives CSF-ISF bulk flow from para-arterial space to para-venous space through the brain parenchyma. Extracellular Ab and tau are washed into the para-venous space. 2. APOE is delivered into the brain parenchyma and facilitates Ab binding and clearance by ABCB1 and LPR1 at BBB. 3. Ab and tau are phagocytosed by microglia. 4. The ISF drained into the para-venous space might be further drained by the dural lymphatics. Abbreviations: CSF (cerebrospinal fluid); ISF (interstitial fluid); Ab (b -amyloid); p-tau (phosphorylated tau); ABCB1 (ATP-binding cassette protein B1); LRT1 (Low density lipoprotein receptor-related protein 1); APOE (apolipoprotein E).

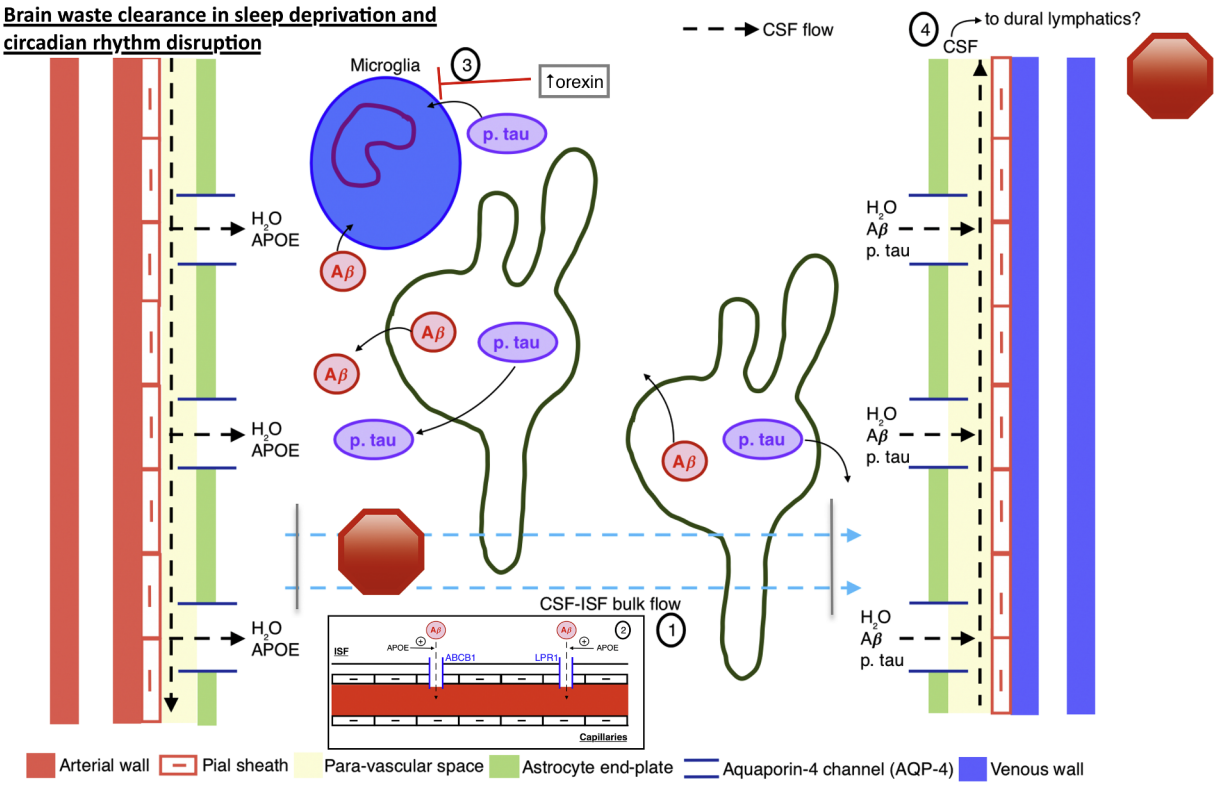

Fig. 1b. Under sleep deprivation, neurons swell up due to increased noradrenaline stimulation. The CSF-ISF bulk flow is impaired as a result of increased resistance, hindering delivery of APOE into and clearance of Ab and tau out of the brain parenchyma. In prolonged waking and circadian rhythm disruption, orexin level keeps elevated and impairs phagocytic clearance of Ab and tau.

3.1. A glimpse of the brain glymphatic clearance system

In 1985, Rennels et al. postulated a paravascular route of CSF circulation across the brain parenchyma, using the infusion of the protein tracer, horseradish peroxidase. The study observed that the tracer injected into CSF in the subarachnoid space entered the paravascular space (also known as the Virchow-Robins Space) along major arteries at early time points, and later appeared in spaces adjacent to microvasculature and venous structures. Rennels et al. (1985) proposed that a new circulation route of CSF exists in such a manner that the arterial pulsation drives the CSF flow via brain interstitium, creating an ISF bulk flow which ultimately exits the brain parenchyma via paravenous space.

Excitingly, this finding was confirmed by Iliff et al in 2012 via the more advanced two-photon imaging. Using mice, Iliff et al. (2012) visualized that the subarachnoid CSF tracer first entered the paravascular space of penetrating arterioles, especially the ventral perforating arteries in the basal ganglion and thalamus regions. The tracer then entered the interstitium and accumulated along capillaries and parenchymal venules, and lastly, exited predominantly along paravenous spaces of medial inferior cerebral veins and ventral-lateral caudal rhinal veins (Iliff et al., 2012). The study named the astrocyte-facilitated paravascular-interstitial route of protein clearance the “glymphatic pathway” (Iliff et al., 2012). The glymphatic paravascular flow and arterial pulsation drive were further confirmed by MRI (Iliff et al., 2013a) and two-photon imaging (Iliff et al., 2013b), respectively. The anatomy of the paravascular space was later delineated such that it is a CSF-containing space surrounding blood vessels, lined by pial sheath internally and basement membrane of astrocyte endfeet (i.e. glia limitans) externally (reviewed in Bacyinski et al., 2017). Subsequent research further demonstrated that the glymphatic pathways are involved in the clearance of various proteins, for example, biomarkers of traumatic brain injury (Plog et al., 2015) and lactate (Lundgaard et al., 2017). This review focuses on discussing the glymphatic clearance of molecules involved in AD, i.e. Aβ and tau, and how they are affected by sleep. More description of the glymphatic system and the metabolites cleared by it can be found in an extensive review by Tarasoff-Conway et al. (2015).

3.2. Sleep and glymphatic clearance of Aβ

Iliff et al. (2012) further demonstrated, using *aquaporin-4 (aqp4)* knockout mice, that the water-transporter, Aquaporin-4 of astrocytes, in the pial-glial interphase in paravascular space is essential for CSF influx and ISF efflux into/out of the brain interstitium, facilitating the ISF bulk flow. *Aqp4* knockout mice showed a 70% reduction in total Aβ clearance compared to wildtype, uncovering that astrocyte water transport is vital for convective clearance, and that the glymphatic pathway plays an essential role in total Aβ clearance in the brain. Lastly, the team demonstrated that a large proportion of soluble, fluorescently-labeled Aβ in the ISF was carried by the bulk flow and cleared away from the brain parenchyma.

Expanding on the findings, Xie et al in 2013 further linked the role of sleep in brain Aβ clearance with the glymphatic pathway. During sleep, the interstitial space in the brains of mice is 60% larger than that of awake mice. This phenomenon is explained by the increased adrenergic signaling by noradrenaline in the awake state that modifies cell volume in the brain, thus diminishing the interstitial space. The increased interstitial space reduced the resistance of convective ISF bulk flow in the brain parenchyma and facilitated glymphatic Aβ clearance (Xie et al., 2013). When repeating the experiment using anaesthetized mice, the interstitial volume in brain tissue was also found to be significantly larger compared to the awake control. This shows that sleeping, but not circadian rhythms (the time of day), is the main contributor to brain Aβ clearance in the glymphatic pathway, as confirmed by Kang et al. in 2009a.

The supine/lateral lying-posture adopted in sleep may also promote the glymphatic clearance of Aβ compared with the mainly upright posture maintained by humans when awake. Lee et al. (2015) demonstrated in mice that the lateral sleeping position is associated with the best glymphatic waste (including Aβ) clearance, followed by the supine position, and is worst in the prone position, i.e. the natural position when mice are awake. The authors deduced that a lateral or supine position increased venous return and cardiac output compared to the prone or upright positions, which resulted in increased arterial pulsation (the driving force of ISF bulk flow) and decreased sympathetic tone, and thus facilitated both glymphatic and lymphatic clearance (Lee et al., 2015).

Combining this finding with the essential role of the glymphatic pathway in Aβ clearance shown previously, SD might be a positive risk factor for AD development in light of Aβ accumulation and aggregation.

3.3. Sleep and glymphatic clearance of tau

The microtubule-associated protein tau is physiologically crucial in the stabilization of neurofilaments in neurons (Shea and Beermann, 1994). In AD conditions, tau is hyperphosphorylated and aggregates to form neurofibrillary tangles intracellularly in cerebral neurons (Binder et al., 2005). Tau is either secreted into the brain interstitium in young healthy individuals (Yamada et al., 2011; 2014) or upon neuronal death (Avila et al., 2014). Compared to Aβ, research on the glymphatic clearance of tau and the corresponding correlation with SD or CRD is limited and discrepant. Two studies demonstrated that sleep-deprived mice showed an increase in phosphorylated tau levels (Qiu et al., 2016; Rothman et al., 2013). Another study showed that phosphorylated tau levels are significantly diminished while insoluble tau levels (the more pathological form) are dramatically increased in sleep-deprived mice compared to controls (Di Meco et al., 2014). Nedergaard's team in 2014 demonstrated that ISF tau clearance is also involved in the same glymphatic pathway as Aβ, and that impairment of the pathway by traumatic brain injury and *aqp4* knockout increased phosphorylated tau levels (Iliff et al., 2014). Since SD would restrict interstitial space and impair glymphatic flow (Xie et al., 2013), we could deduce that SD would thereby hinder ISF tau clearance. Yet, more studies are required to give experimental evidence on this deduction and to clarify whether phosphorylated or insoluble tau protein accumulates after glymphatic pathway impairment.

3.4. SD hinders glymphatic APOE delivery and impairs Aβ clearance at BBB

Apart from the glymphatic pathway, Aβ could also be cleared from the brain interstitium into the bloodstream at the neurovascular unit of the BBB (ElAli and Rivest, 2013). The transport of Aβ from ISF into the bloodstream requires two transporters, namely ATP-binding cassette transporter B1 (ABCB1) and lipoprotein-related protein 1 (LPR1) (Zlokovic, 2008). The binding of Aβ onto the two transporters is facilitated by ApoE, such that ApoE binds Aβ in ISF and modifies its conformation, preventing its aggregation and making Aβ more accessible to ABCB1 and LPR1 (ElAli and Rivest, 2013).

Following the discovery of the glymphatic system, novel findings emerged that the glymphatic flow not only functions as a pathway of clearance, but also as a route of substance delivery from the CSF into the brain parenchyma. A study showed that ApoE is secreted by choroid plexus into the CSF, which in turn is delivered into the brain ISF by glymphatic flow (Achariyar et al., 2016). The delivery of CSF demonstrated by the study is impaired by SD (Achariyar et al., 2016), possibly due to the same manner of interstitial space constriction observed in Xie et al. (2013). It is possible that SD may impair CSF ApoE glymphatic delivery into the brain parenchyma, diminishing ApoE supply to the neurovascular junction, thereby hindering Aβ transport-mediated clearance. In the long term, this might promote Aβ aggregation and increase the risk of AD. Yet, to what extent the ApoE from CSF contributes to total brain ApoE supply, thus impairing total Aβ vascular clearance, still requires further experimentation.

3.5. Role of orexin in sleep modulation, Aβ clearance and tau level

Orexin-1 and orexin-2 (also known as hypocretin-1 and hypocretin-2) are neurotransmitters mainly produced and secreted by a group of neurons in the posterior lateral hypothalamus, discovered in 1998 (Sakurai et al., 1998). Discovered whilst researching the sleep disorder, narcolepsy, orexin is found to be involved in sleep-wake regulation (Saper et al., 2005a,b,c). Studies in rodents (Yoshida et al., 2001), new primates (Zeitzer et al., 2003) and humans (Salomon et al., 2003; Slats et al., 2012) showed that orexin levels in CSF fluctuate in a circadian rhythm, with orexin levels at the nadir in midday, rising throughout the day, peaking at night, and falling as subjects start to sleep. The climbing levels of orexin in the later daytime until sleep is thought to maintain the wakefulness of the subject and to help resist sleep-promoting signals (Zeitzer et al., 2003). In a study on squirrel monkeys (*Saimiri sciureus*), new primates resembling humans that consolidate sleep into one single daily episode, an extension of wakefulness from 7 P.M. to 12 A.M. extended the orexin plateau, in which orexin CSF levels only fell immediately after the monkey went to sleep (Zeitzer et al., 2003). The result suggests that orexin secretion is associated with SD.

It is worth noting that recent studies have shown that CSF orexin levels or orexin expression are positively associated with Aβ load or AD progression. It was demonstrated that Aβ ISF fluctuation in mice and Aβ CSF fluctuation in normal human subjects followed the same diurnal pattern as orexin fluctuation (Kang et al., 2009a). Patients with moderate to severe AD showed increased orexin levels compared to controls, and in global AD patients, orexin levels are positively associated with total tau protein levels (Liguori et al., 2014). Combining the data of normal and AD human subjects, lower mean CSF $A\beta_{42}$ (the clinically more pathogenic type of Aβ) levels are associated with lower CSF orexin levels (Slats et al., 2012). Furthermore, orexin infusion in mice significantly raised ISF Aβ levels, and intracerebroventricular administration of the orexin receptor antagonist, almorexant, for 24 h suppressed ISF Aβ levels in mice (Kang et al., 2009a). Orexin knockout ($OR^{-/-}$) in two different AD models of mice (APP/PS1-21 and APP/PS1δE9) leads to a marked reduction in the development of AD pathology (Roh et al., 2014). Excitingly, An et al. in 2017 established a novel pathogenic pathway supporting the above findings. In the brain protein clearance system, microglial phagocytosis and autophagy play a crucial role in Aβ protein clearance (Thériault et al., 2015). An et al. (2017) demonstrated for the first time that orexin addition to fibrillar Aβ-treated microglial cells impairs actin filament formation around fibrillar Aβ via PI3K, Akt, and p38-MAPK downregulation, thus suppressing Aβ phagocytosis. The study also found that orexin addition to microglial cells inhibits autophagosome-lysosome fusion, thus suppressing autophagy-mediated Aβ clearance (An et al., 2017). In the Roh et al. (2014) study, it was speculated that it was only the secondary effect of orexin, the increased wakefulness, that contributed to increasing Aβ pathology. However, with the new findings by An et al. (2017), orexin should be considered to have an independent role in contributing to Aβ pathology via hindering Aβ clearance, apart from maintaining wakefulness.

Regarding the position of orexinergic neurons in the central nervous system, orexinergic neurons receive direct and indirect input from the sleep center (the VLPO of hypothalamus) and the circadian center (SCN), respectively, in which the SCN (active during light condition) stimulates, while VLPO (active during sleeping condition) suppresses orexin secretion (reviewed in Slats et al., 2013; Van Erum et al., 2017). During extended wakefulness at night, humans are behaviorally exposed to light from light-emitting sources, such as artificial illumination or the screens of electronic devices (Hatori et al., 2017). The human ipRGCs are most sensitive to blue light (wavelength 440–480 nm), the peak wavelength of light emitted by LED light bulbs or electronic

screens (Hatori et al., 2017). Exposure to light at night stimulates the ipRGCs, which further activates the SCN via the RHT as illustrated in the previous section. It is possible that both the activation of the SCN at night by light exposure and the suppression of the VLPO by wakefulness could increase orexin levels in the brain parenchyma in the case of extended wakefulness (or SD), thus impairing Aβ clearance (and potentially aggravating tau pathology), which leads to an increased risk of AD development. A study in the mouse liver also found that autophagy exhibits a prominent circadian rhythm (Ma et al., 2011), and that autophagy in zebrafish is under direct regulation by the circadian clock gene, Rev-erba, and indirect regulation by the circadian clock gene, Cebpb (Huang et al., 2016). CRD in the human brain might also have a direct role in impairing autophagic clearance of waste.

Despite the flow of logic described above, the proposed pathogenesis requires further validation from more *in vivo* experiments and human studies. Some discrepant experimental results in this field also require clarification. It is noted that although orexin knockout in mice reduced Aβ pathology development, overexpression of the orexin gene does not cause an increase in Aβ pathology (Roh et al., 2014). This could plausibly be due to a ceiling effect in Aβ formation. Perhaps repeating the experiments with a mouse model with less prominent initial Aβ pathology could yield a clearer result. Additionally, Slats et al. (2012) interpreted their experiment result, i.e. that lower CSF $A\beta_{42}$ is associated with lower CSF orexin concentrations in humans, differently. The authors argued that in AD, Aβ aggregates and form plaques, which results in reduced soluble Aβ levels in CSF. In this sense, severer AD pathology (signified by lower CSF Aβ levels) is correlated with lower, rather than higher, orexin levels. The subsequent association with lower orexin thus becomes paradoxical to our previous inference. More studies are needed to investigate the role of orexin, SD and CRD, and AD pathogenesis.

3.6. Autonomic nervous tone on brain lymphatics during sleep may have an effect on protein clearance

Despite evidence showing a potential connection of the CSF circulation with peripheral lymphatics (Boulton et al., 1996; Bradbury et al., 1981; Cserr and Knopf, 1992), and the evidence of lymphatic Aβ clearance in an AD mouse model (Pappolla et al., 2014), it has long been thought that the brain is deprived of lymphatic drainage (Louveau et al., 2015). In 2015, it was discovered that novel meningeal lymphatic vessels of initial lymphatic type exist in mice, running parallel to the dural venous sinuses (Aspelund et al., 2015; Louveau et al., 2015). Subsequent research confirmed the presence of meningeal lymphatic vessels in humans by MRI (Absinta et al., 2017; Jani and Sekula Jr, 2018) and histology (Goodman et al., 2018). The new discovery prompted the proposal that the brain lymphatics system may serve as an extension of the brain clearance system, in which Aβ or other waste proteins cleared into the CSF from the brain parenchyma may be further drained into the meningeal lymphatics (Iliff et al., 2015; Louveau et al., 2015, 2016, 2017; Tarasoff-Conway et al., 2015). The proposal was confirmed by Da Mesquita et al. in 2018, who demonstrated that impairment of meningeal lymphatic flow resulted in increased Aβ deposition in the meninges and aggravated parenchyma Aβ deposition in a mouse model (Da Mesquita et al., 2018). The study further demonstrated that ageing would result in a decreased diameter of the meningeal lymphatic vessels, which is associated with decreased drainage of CSF macromolecules (Da Mesquita et al., 2018).

Although to our knowledge there is no direct evidence of an involvement of SD or CRD in the dural lymphatic drainage regulation, it is speculated that long-standing sympathetic tone in extended wakefulness may lead to long-standing lymphatic vessel contraction. A previous study displayed a rich autonomic nervous innervation by both sympathetic and parasympathetic components in human lymphatic vessels, including the initiating type of vessels that the meningeal lymphatics belong to (Mignini et al., 2012). An increase in sympathetic tone is found to result in contraction of lymphatic vessels (Mignini et al., 2012). Since wakefulness is associated with higher sympathetic tones compared to that during sleep (Xie et al., 2013), it is speculated that apart from ageing, chronic SD could also cause decreased meningeal lymphatic vessel diameter via increased sympathetic input, leading to increased lymph flow resistance and impaired CSF waste molecule clearance. The influence of sleep and circadian rhythm on meningeal lymphatic drainage warrants further experimental validation.

3.7. SD may increase ISF Aβ and tau levels by increased synaptic activity

Apart from impairing Aβ and tau ISF clearance, SD may also have a role in increasing Aβ and tau exocytosis, thereby increasing ISF Aβ and tau levels. In recent years, a synaptic homeostasis hypothesis has been proposed regarding the role of sleep on synaptic function. Increasing lines of evidence support the hypothesis that sleep, at least non-rapid eye movement sleep, is associated with the downscaling of synaptic strength in neurons (reviewed in Tononi and Cirelli, 2006, 2012). This is supported by some studies that suggest that ISF Aβ and tau levels are increased with synaptic activity.

In mice, it was demonstrated that brain ISF Aβ levels are directly influenced by levels of synaptic activity. An increase in synaptic stimulation for 1 h augmented the ISF Aβ levels by 130% from baseline via exocytosis (Cirrito et al., 2005). In cell culture (Pooler et al., 2013) and animal (Yamada et al., 2014) studies, ISF tau levels are associated with increased neuronal activities, possibly via glutamatergic excitatory stimulation (Yamada et al., 2014). It should be noted that SD increases Aβ and tau exocytosis at the same time. Also, as mentioned in an earlier section, it causes an increase in brain cell volume due to noradrenergic stimulation (Xie et al., 2013), which increases the resistance of ISF bulk flow and hinders Aβ and tau glymphatic clearance. This would ultimately increase the ISF Aβ and tau concentration, and confer a higher chance of pathological extracellular Aβ and tau aggregation.

3.8. SD potentially promotes neuroinflammation

The extracellular accumulation of pathological Aβ and tau deposits might also trigger chronic neuroinflammation during the development and progression of AD (Reviewed in Akiyama et al., 2000; Heneka et al., 2015; Spangenberg and Green, 2017; Van Eldik et al., 2016). A microglia-mediated chronic neuroinflammatory model was proposed which suggested that accumulated Aβ deposits (Heneka et al., 2015; Spangenberg and Green, 2017) and exocytosed tau (Spangenberg and Green, 2017) bind toll-like receptors (TLR) on microglia in the brain in the developmental phase of AD. The initial activation of microglia in attempt to clear these extracellular aggregates would progress to chronic inflammation due to the persistence of the stimuli, which would result in reduced synaptic remodeling, and neuronal death (Heneka et al., 2015). Further evidence suggested that several pro-inflammatory cytokines e.g. interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), or other immune mediators, e.g. caspases, complements, reactive nitrogen or oxygen species, are also involved in neuroinflammation in AD, and cause neuropathology via the modulation of microglial action, astrocytic atrophy (thus impairing glymphatic clearance) and an increase in oxidative damage (reviewed in Heneka et al., 2015).

Emerging evidence suggests that SD has a role to play in neuroinflammation in AD. A systemic review and meta-analysis (Irwin et al., 2016) and a literature review (Hurtado-Alvarado et al., 2016) both showed that SD results in an alteration of different inflammatory cells (e.g. microglia and astrocyte) and mediators (e.g. C-reactive protein, IL-1 and TNF) in the brain. However, there were discrepancies in the molecules involved, how the levels of each pro-inflammatory molecule is affected, and the precise role of each pro-inflammatory molecule in inducing neuroinflammation. Despite the discrepancies in which pro-inflammatory mediators and effectors are involved, studies showed an

upregulation of key inflammatory pathways by SD. Nuclear factor-κB (NF-κB) gene expression in peripheral blood mononuclear cells, which might migrate across the BBB (Heneka et al., 2015), was significantly upregulated after one night of sleep loss in healthy individuals (Irwin et al., 2008). Signal transducer and activator of transcription (STAT) family proteins, STAT1 and STAT5, which are activated by cytokines and cross-talk with the NF-κB pathway, were also significantly increased in peripheral blood mononuclear cells after partial sleep deprivation in healthy individuals (Irwin et al., 2015). Moreover, four-week-old male C57BL/6J mice, after five days of sleep restriction, showed increased microglial activation in the cerebral cortex (Bellesi et al., 2017), which accords with the microglial neuroinflammatory model aforementioned.

Combining these results with the SD-induced brain waste accumulation discussed in previous sections, it is postulated that SD might induce chronic neuroinflammation via two mechanisms. First, SD impairs brain waste clearance and increases brain waste production. Consequently, the pathological aggregates (extracellular Aβ and tau) may persist in the ISF and constantly stimulate the immune response of microglia, turning an acute microglial inflammatory response to chronic inflammation. The over-activated microglial might subsequently injure the surrounding neurons, as in the sequelae of chronic inflammation in other parts of the body such as pulmonary tuberculosis. Second, SD might induce a systemic inflammatory response via a yet unknown process (Hurtado-Alvarado et al., 2016), which upregulates the core inflammatory pathways such as NF-κB and STAT, and further alters the cytokines and other pro-inflammatory mediators profiles systemically. The overall pro-inflammatory status stimulates microglia and alters the behavior of other cell populations, e.g. astrocytes, which might secrete more cytokines and sustain the neuroinflammation, forming a vicious cycle. Future experimentations should be directed to elucidate the precise alteration of inflammatory mediator's profile in SD-induced neuroinflammation. Kincheski et al. (2017) recently demonstrated that the TNF-α neutralizing monoclonal antibody, infliximab, could prevent memory impairment in sleep-restricted mice with Aβ-oligomer CSF infusion. This signified the possibility that current immunosuppressants or biologics might be applied in the future treatment of AD, by targeting the neuroinflammatory pathway. However, this could only be feasible after the establishment of a complete SD-induced pro-inflammatory mediator profile.

4. SD and CRD may lead to aberrant redox chemistry

Owing to the unique features of high energy metabolism and abundance of polyunsaturated fatty acid (Khadrawy et al., 2011), and the inability to divide in a differentiated state (Kondratova and Kondratov, 2012), neurons are particularly sensitive to oxidative stress, which is one of the major causes of neuronal death in the brain (Kondratova and Kondratov, 2012). Increased oxidative stress, resulting in lipid peroxidation, protein and nucleic acid oxidation in brain cells, is involved in the early pathogenesis of AD (Reviewed in Markesbery, 1997; Wang et al., 2014). The following sections review the potential roles of circadian oscillators, sleep duration and melatonin levels in modulating the brain redox homeostasis, and the association with AD development (see Fig. 2).

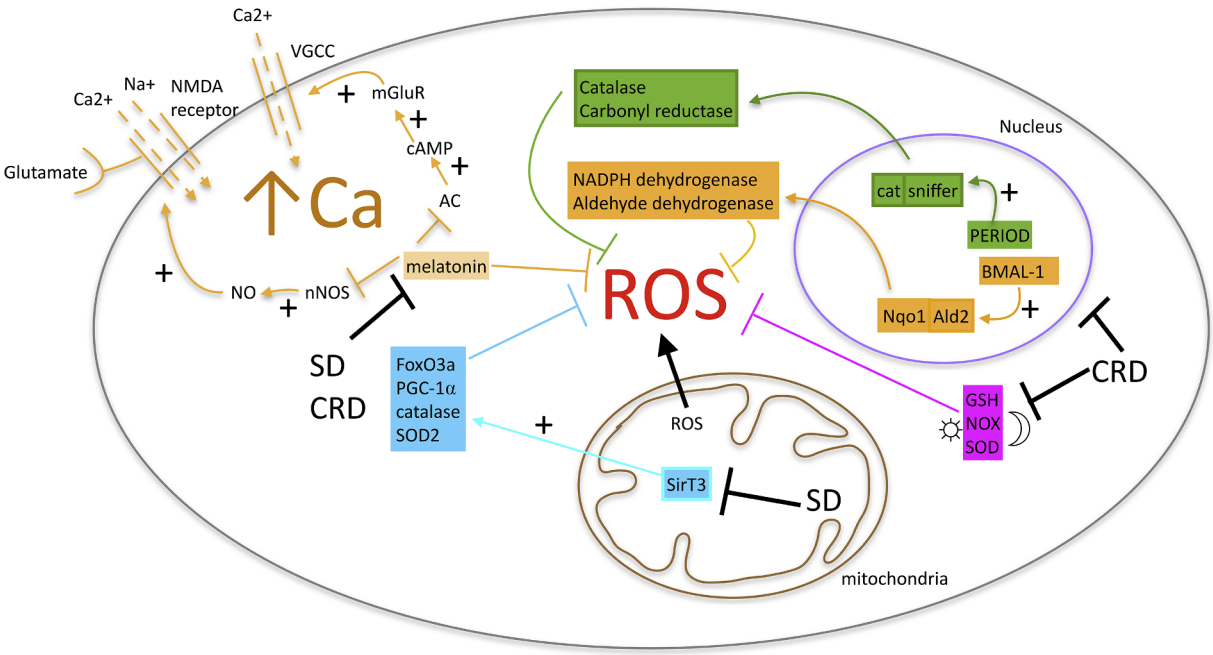

Fig. 2. *Neuronal redox and calcium dyshomeostasis.*
Circadian proteins (PERIOD and BMAL-1) are transcriptional activators of various anti-oxidant genes (*Nqo1*, *Ald2*, *cat* and *sniffer*), which codes for NADPH dehydrogenase, aldehyde dehydrogenase, catalase and carbonyl reductase respectively. Several anti-oxidant processes show circadian oscillation, involving SOD, GSH and NOX. Circadian rhythm disruption may impair these processes and cellular anti-oxidant defense. The mitochondrial protein SirT3 stimulates anti-oxidant machinery such as FoxO3a, FGC-1a and SOD2. SirT3 level is reduced in sleep deprivation. Melatonin is essential antioxidants in neurons. It also inhibits glutamate NMDA receptor and VGCC, preventing glutamate excitotoxicity and calcium overload. Sleep deprivation and circadian rhythm disruption together cause abrupt drop of melatonin level in the body, rendering neurons to be more prone to oxidative stress and calcium overload. Abbreviation: ROS (reactive oxygen species); SD (sleep deprivation); CRD (circadian rhythm disruption); GSH (reduced glutathione); NOX (reduced nicotinamide adenine dinucleotide phosphate oxidase); SOD (superoxide dismutase); BMAL-1 (brain and muscle Arnt-like protein-1); SirT3 (nicotinamide adenine dinucleotide-dependent deacetylase sirtuin type 3); FoxO3a (forkhead Box O3a); PGC-1a (peroxisome proliferator-activated receptor gamma coactivator 1-a); AC (adenylyl cyclase); cAMP (cyclic adenosine monophosate); mGluR (group III metabotropic glutamate receptors); VGCC (voltage-gated calcium channel); NO (nitrogen oxide); nNOS (neuronal nitrogen oxide synthase); NMDA receptor (N-methyl-D-aspartate receptor).

4.1. Direct involvement of TTFL circadian oscillators in antioxidant defense

Both reactive oxygen species (ROS) and antioxidant gene/product levels in brain cells affect circadian oscillation (reviewed in Hardeland et al., 2003). For instance, the nucleic acids in mammalian neurons are constantly under oxidative challenge, necessitating moment-to-moment DNA repair (Kang and Sancar, 2009b; Kang et al., 2009c). It was found that the DNA excision repair activity in the mouse cerebrum followed a circadian rhythm (Kang and Sancar, 2009b; Kang et al., 2009c). CRD was shown to increase oxidative stress in the mouse brain (Varadinova et al., 2016). Though the exact molecular pathway of clock gene's modulation on ROS and antioxidant production are not fully understood, several core clock genes e.g. *bmal1* and *period* are shown to be highly related to antioxidant defense in cells.

A series of studies by Natraj Krishnan et al. on *Drosophila melanogaster* (fruit flies) showed an involvement of the *period* genes in oxidative responses. Fruit flies exposed to a constant light condition, which disrupts circadian molecular oscillation by preventing the accumulation of the clock proteins TIMELESS and PERIOD, are more susceptible to oxidative challenge by H_2O_2 compared to the control group exposed to a normal light-dark pattern (Krishnan et al., 2008). Studies using the null-mutation per^{01} fruit fly model show that the *period* gene has a protective effect over protein carbonylation and lipid peroxidation (Krishnan et al., 2009), possibly via an interaction with genes *cat* (coding catalase) (Krishnan et al., 2008) and *sniffer* (coding carbonyl reductase) (Krishnan et al., 2012), and some other unidentified pathways. The increase in oxidative stress in the per^{01}-mutant strain was associated with increased neurodegeneration compared to controls (Krishnan et al., 2012). Despite the promising results in studies of fruit flies, a *period* gene mutation in mice only show disrupted circadian rhythm, but no AD-associated pathologies (Musiek et al., 2013). The protective effect of the gene *period* in human brain cells remains to be verified.

Compared to *period,* the study of the role of another clock gene, *bmal1*, which acts upstream in activating the transcription of *period* in the TTFL, on redox chemistry is more available in mammals. *Bmal1*-deficient animals showed increased ROS levels in the heart, kidney and spleen compared to wildtype (Kondratov et al., 2006), while the feeding of water-dissolved antioxidant N-acetyl-L-cysteine in BMAL1 protein-deficient mice alleviated symptoms of premature aging compared to control (Kondratov et al., 2009), establishing a potential role of *bmal1* in regulating redox chemistry. It was later confirmed that *bmal1* directly regulates the expression of two critical antioxidant genes, namely *Nqo1* (coding NADPH dehydrogenase that reduces toxic quinones and suppresses oxidative injury) and *Aldh2* (coding aldehyde dehydrogenase 2 that reduces reactive aldehyde in mitochondria), via BMAL1-binding to the noncanonical E-box motif promotor of *Nqo1* and the canonical E-box promotor of *Aldh2* respectively (Musiek et al., 2013). Bmal1 knockout mice showed reduced transcription for *Aldh2* and *Nqo1*, increased neuronal oxidative injury and lipid peroxidation markers, and other signs of neurodegeneration, such as astrocytosis and microgliosis, degeneration of presynaptic axonal terminals as well as a loss of functional cortical connectivity (Musiek et al., 2013). The same study also illustrated that double deletion of another two circadian genes, *Clock* and *Npas2*, in mice mimics the effect of oxidative injury and features of neuropathology in *Bmal1* deletion (Musiek et al., 2013), suggesting that a wider spectrum of circadian genes is involved in brain redox regulation. Interestingly, SD is shown to decrease the binding of BMAL1, CLOCK and NPAS2 proteins on downstream target genes in the circadian oscillation pathways (Mongrain et al., 2011). In fact, SD affects the blood transcriptome of at least 500 genes (including genes involved in DNA repair and oxidative stress response), as demonstrated in various animal and human studies (reviewed in Archer and Oster, 2015). This again suggests the interactive feature of SD and CRD in AD development, in the sense of redox dyshomeostasis.

4.2. Future direction: Potential role of non-transcriptional redox clock in AD redox homeostasis

Apart from the conventional clock genes/proteins involved in the TTFL, some novel metabolic and non-transcriptional circadian clocks have been identified, interacting with or independent of the TTFL (reviewed comprehensively in Reddy and Rey, 2014). Some of these newly identified clocks are involved in the control of cellular redox status. For example, the circadian rhythm of NAD^+ biosynthesis is regulated by the effects of CLOCK/BMAL1 on transcription of nicotinamide phosphoribosyltransferase (NAMPT) (Nakahata et al., 2009; Ramsey et al., 2009), while NADH or NADPH circadian oscillation could occur independently of a transcriptional oscillator in human red blood cells (O'Neill and Reddy, 2011). It is worth noting that the redox circadian clock peroxiredoxins are co-compartmentalized with various redox-determining molecules in eukaryotes, e.g. reduced or oxidized glutathione (GSH/GSSG), NADPH oxidase (NOX) and superoxide dismutase (SOD) (Reddy and Rey, 2014). These pathways are new areas of research in recent years. Whether they are disrupted in SD and social or trans-meridian jet lags, and thereby contribute to AD development via cellular redox disturbance, awaits future studies.

4.3. Independent effect of sleep on brain redox chemistry

SD alone could induce oxidative stress on brain cells. Vitamin E (as an antioxidant) was found to reverse memory impairment caused by SD in rats (Alzoubi et al., 2012). SD was also shown to increase the total oxidized/reduced glutathione ratio (Alzoubi et al., 2012; Khadrawy et al., 2011; Silva et al., 2004), increase lipid peroxidation (Khadrawy et al., 2011; Silva et al., 2004), and reduce catalase and SOD activity (Alzoubi et al., 2012) in the rodent hippocampus.

Zhang et al. (2014) have demonstrated the relationship between SD and an increase in oxidative stress with cellular levels of nicotinamide adenine dinucleotide-dependent deacetylase sirtuin type 3 (SirT3) in mouse locus coeruleus neurons. SirT3 is a mitochondrial molecule responsible for upregulating antioxidant machinery e.g. forkhead Box O3a (FoxO3a), peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), catalase and superoxide dismutase 2 (SOD2) via unclear mechanisms, and SD is associated with decreased SirT3 levels in mice, observed together with an increase in ROS levels and neurodegeneration e.g. increased neuronal apoptosis (Zhang et al., 2014). Mitochondria are thought to be the major source (90%) of endogenous ROS in cells due to the inevitable production of superoxide anions in electron transport processes (Wang et al., 2014). It is possible that the interaction of SD and SirT3 expression in mitochondria may have an important role in neuronal redox dyshomeostasis, along the causal pathway to AD.

One piece of contradictory experimental results exists, which found that SD had no correlation with oxidant production, SOD activity, lipid peroxidation, and protein oxidation in the rodent brain (Gopalakrishnan et al., 2004). Yet, the results of the experiments were mostly statistically insignificant ($p > 0.05$), probably due to the small numbers of rats used, as admitted by the author, that valid conclusion could hardly be drawn. However, more studies are still required to fully demonstrate the role of SD in redox homeostasis at a whole cortical level in the human brain, since most current studies are performed on rodent hippocampus or locus coeruleus regions only.

4.4. Role of melatonin: Redox modulation and beyond

Melatonin (N-acetyl-5-methoxytryptamine) is a molecule locally synthesized and secreted in numerous organs in the body, e.g. intestines, skin, retina, bone marrow, and the pineal gland in the epithalamus region (reviewed in Tan et al., 2007). Melatonin in most tissues is consumed locally as a potent antioxidant and anti-inflammatory agent, while only melatonin of pineal origin contributes to the

circulatory melatonin levels and follows a distinct circadian rhythm (Tan et al., 2007). Production of melatonin in the pineal gland is tightly regulated by the SCN (Touitou et al., 2017), in which the pineal synthesis of melatonin in daytime is inhibited by γ-aminobutyric acid (GABA) signaling from the SCN to the paraventricular nucleus (PVN) of the thalamus (Kalsbeek et al., 2000). In contrast, pineal melatonin synthesis at night is elevated due to the switch of SCN GABAergic signaling to glutamatergic on the PVN (Perreau-Lenz et al., 2004).

Many neuroprotective roles of melatonin have been established. As a potent antioxidant, melatonin scavenges ROS in neurons and upregulates SOD catalase activity, and reverses cognitive impairment caused by SD (Kwon et al., 2015; Zhang et al., 2013). Melatonin interacts with brain-derived neurotrophic factor (BDNF) (Zhang et al., 2013), and promotes neurogenesis and inhibits apoptosis (Fredrich et al., 2015; 2017). In mice exposed to chronic intermittent hypoxia, melatonin ameliorated brain Aβ pathologies (Ng et al., 2010). In neuroblastoma cells treated with calyculin-A, melatonin reduced tau hyperphosphorylation (Li et al., 2005).

More importantly, melatonin exhibits inhibitory effects on N-methyl-D-aspartate (NMDA) glutamate receptors (Bavithra et al., 2015; Escames et al., 2004; Yamamoto and Tang, 1998) and voltage-gated calcium channels (Ayar et al., 2001; Prada and Udin, 2005). Glutamate excitotoxicity (Ong et al., 2013) and calcium dyshomeostasis (LaFerla, 2002) are early events in the development of AD. The non-competitive NMDA receptor antagonist, memantine, is now used to treat moderate to severe AD patients, to alleviate clinical conditions caused by glutamate excitotoxicity (Esposito et al., 2013), while calcium-channel blockers are gaining clinical interest in the treatment repertoire of AD (Saravanaraman et al., 2014). Melatonin inhibits the NMDA receptor by two mechanisms (Escames et al., 2004). First, it inhibits nitric oxide (NO) production by neuronal NO synthase (nNOS), modulating the intra-receptor. Second, it modulates the intra-receptor redox site. For voltage-gated calcium channel inhibition, melatonin initiates an intracellular signaling cascade, inhibiting adenylyl cyclase and decreasing cAMP levels, in turn diminishing the inhibitory effect of cAMP on group III metabotropic glutamate receptors (mGluRs). Increased activity of group III mGluRs would thereby pose inhibition on voltage-gated calcium channels, limiting calcium influx and overload (Prada and Udin, 2005). Physiological melatonin exhibits neuroprotective effects by limiting glutamate excitatory activity and calcium influx in neurons, thereby preventing the progression to excitotoxicity and calcium overload.

Considering the above mentioned neuroprotective effects of melatonin against events leading to AD development (e.g. Aβ pathology, tau hyperphosphorylation, oxidative stress, glutamate excitotoxicity and calcium dyshomeostasis), it is sensible to infer that events leading to decreased melatonin levels might increase the risk of AD. SD alone was linked with a rapid decline in circulatory melatonin levels, caused by rapid consumption of melatonin as a first-line defense against the associated rise in oxidative stress (Tan et al., 2007). Exposure to light emitted from electronic screens markedly suppressed evening melatonin levels in humans (Chang et al., 2015), probably due to circadian phase delay in the SCN in response to the light condition (Touitou et al., 2016). Moreover, melatonin itself is a sleep-promoting signal, inducing sleepiness via ecto-5-nucleotidase mRNA transcription in VLPO neurons, which in turn increases adenosine levels (Pfeffer et al., 2017). Diminishing levels of melatonin at night due to light exposure would cause poorer sleeping quality, forming a vicious cycle in melatonin physiology impairment. In this sense, SD and CRD are associated with an increased risk of AD development due to their detrimental effects on pineal melatonin secretion.

5. Stress granules, SD and CRD: A new perspective of AD pathogenesis?

In 2006, a study on frontotemporal lobar degeneration and amyotrophic lateral sclerosis identified a novel protein in neurons that sequesters RNA (Neumann et al., 2006). This new form of protein was later named RNA-binding proteins (RBP), and in fact, there are currently more than 800 different RBPs identified. RBPs commonly contain two domains, one glycine-rich domain facilitating self-aggregation, and another RNA binding motif facilitating RNA sequestration. Some RBPs are involved in cellular stress response. Upon cellular stress, these RBPs aggregate and triage mRNA transcripts in the cytoplasm, sequestering mRNAs and some proteins to form stress granules. The remaining, unsequestered mRNAs to be translated in the cytoplasm are mainly those involved in stress responses so that the cellular machinery could be more focused on counteracting the stress. Benjamin Wolozin and his team provide a series of comprehensive reviews on this topic (Ash et al., 2014; Vanderweyde et al., 2013; Wolozin, 2012; 2014). Normally, within hours of stress removal, the stress granules would dissociate (Wolozin, 2012), probably via mechanisms of autophagy (Buchan et al., 2013). Stress granules gained interest in AD pathogenesis as a group of core RBPs, namely T-cell-restricted intracellular antigen-1 (TIA-1), TIA-like-1 (TIAR), Tristetraprolin (TTP) and GTPase Activating Protein (SH3 Domain) Binding Protein 1 (G3BP1), which were demonstrated to form pathological stress granule aggregates in neurodegeneration (Ash et al., 2014). It is suggested that when the stress cannot be acutely removed after stress granule formation (as in the situation of Aβ and tau aggregation), the chronic persistence of cellular stress would induce pathological stress granule formation, in which the reversible property of protein aggregation is lost, and the aggregate itself becomes pathological to the neurons (Ash et al., 2014).

Experimentally, stress granules are found to be specifically correlated with tauopathy. It was found that microtubule instability, as demonstrated in tauopathy in AD, facilitate stress granule formation (Chernov et al., 2009). Conversely, stress granules may bind phosphorylated-tau, thereby bringing phosphorylated-tau within close vicinity, and in high concentrations, which may facilitate tau aggregation (Vanderweyde et al., 2012). This relationship was demonstrated in both mice and post-mortem human brain tissues, and the co-localization of stress granules and tau increases with disease severity (Vanderweyde et al., 2012). Apart from tauopathy, stress granule formation in microglia was found to impair microglial phagocytosis, a process involved in brain waste protein clearance, mentioned in previous sections, due to the sequestration of SYK tyrosine kinase, a molecule that is vital to normal microglial phagocytosis activation (Ghosh and Geahlen, 2015). Another study demonstrated that autophagy impairment (also involved in AD protein clearance) might also contribute to pathological stress granule aggregation (Ryu et al., 2014). These experimental results indicate that pathological stress granules may open a new pathway in the model of AD pathogenesis.

In relation to stress granules, we are prompted to think that SD and CRD may cause cellular stress via depleted brain waste clearance (and subsequent Aβ and tau aggregation), increase in ROS production/reduced clearance and calcium dyshomeostasis, which may in turn chronically stimulate pathological stress granule formation (see Figs. 3a,b). The dramatic change in blood transcriptome observed after SD (Archer and Oster, 2015) also seems to coincide with RNA-sequestration events during stress granule formation. To our best knowledge, no research has been performed on the correlation between stress granule formation, sleep and circadian rhythm. This might be a new land of research into the role of SD and circadian rhythm in contributing to AD development.

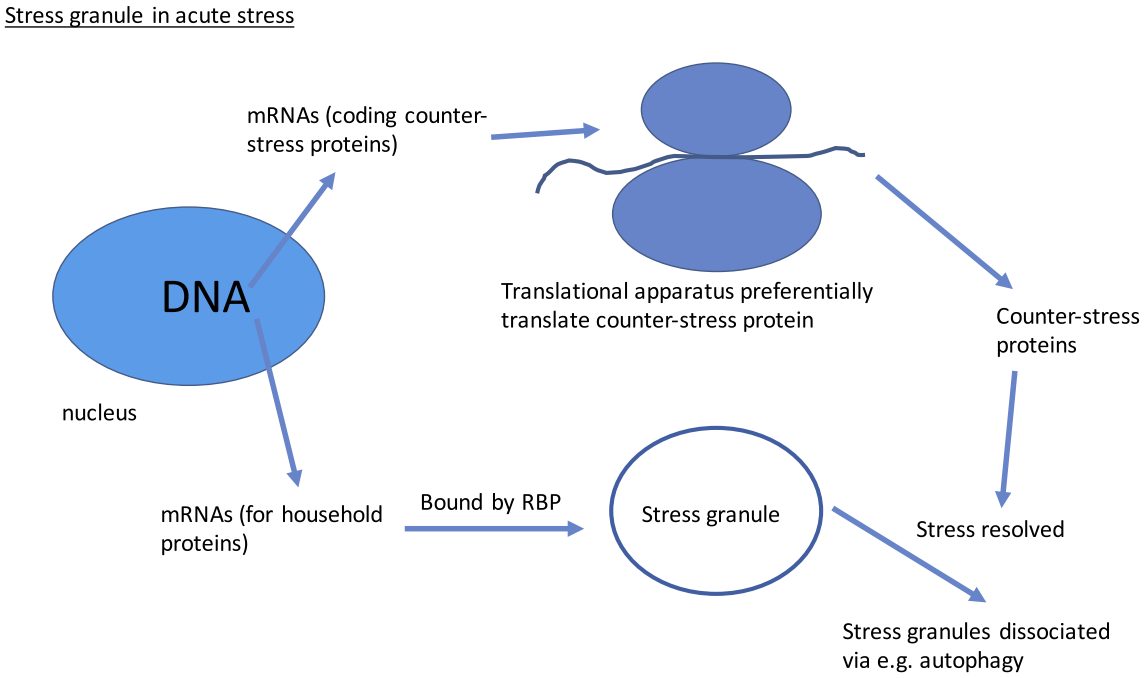

Fig. 3a. *Stress granules in acute and chronic stress.*
Responding to acute stress, neurons triages mRNAs by forming stress granules. RBP binds household mRNAs and form stress granules, sparing translational apparatus to focus on translating proteins responsible for counteracting cellular stress. When stress resolved, stress granules dissociated by processes such as autophagy. Abbreviation: mRNA (messenger ribonucleic acid); RBP (RNA-binding protein); p-tau (phosphorylated tau).

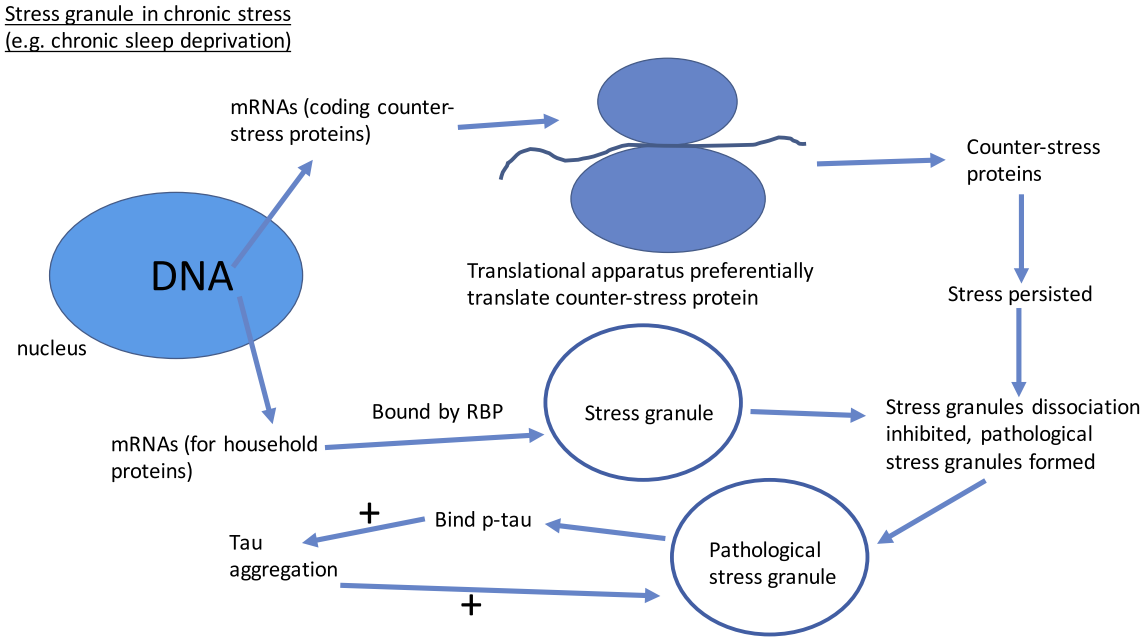

Fig. 3b. Upon chronic stress (for example sleep deprivation or oxidative stress), stress granules may develop into pathological aggregates, which is resistant to dissociation and may interact with and bind p-tau, stimulating its aggregation. Tau aggregate may in reverse stimulate further pathological stress granule formation.

6. Conclusion and future perspectives

Experimental evidence, in general, accords with the epidemiological studies in terms of the association between SD, CRD and AD. Both SD and CRD are likely involved in the brain waste clearance system. SD may impede the glymphatic pathway for extracellular Aβ and tau clearance, and may potentially further impact the glymphatic-vascular-lymphatic line of clearance system. However, CRD may not be directly involved in glymphatic clearance infringement, and may interact with SD and impair Aβ microglial phagocytosis and autophagy clearance via the orexinergic surge. While impairing Aβ and tau clearance, SD and CRD might also increase Aβ and tau exocytosis, further adding to the ISF load of Aβ and tau, precipitating Aβ and tau aggregation and subsequent pathology. SD may potentially induce neuroinflammation via chronic microglial activation and systemic inflammatory response, aggravating AD progression. Apart from amyloidopathy and tauopathy, SD and CRD may also alter the redox chemistry status in neurons and glia. The deranged clock function and SD may both independently

increase the intracellular oxidative state. Clock genes and non-transcriptional/translational oscillatory processes may act upstream of antioxidant defense, while sleep may also modulate antioxidant production in brain cells. Moreover, SD and behavioral exposure to light in CRD may interact and reduce melatonin levels, further hindering the antioxidant defense, and inducing calcium dyshomeostasis and excitotoxicity. Pathological stress granule aggregates may be the third form of pathological aggregates in AD, after amyloid plaques and neurofibrillary tangles. Chronic SD may impose sustaining stress on neurons and glia, inducing pathological stress granule response and interactions with phosphorylated tau or other pathogenic pathways.

Despite the distinct pathways SD and CRD can impact AD development, it should be noted that in reality, these pathways are likely inter-mingled, and that the detrimental effects of SD and CRD may be secondary to each other. Behavioral SD at night due to social or occupational reasons inevitably causes CRD and its downstream effects on AD. In addition, the circadian drive (Process C) is part of the control of sleep in humans. Sleeping at daytime might cause individuals to receive less SCN input to the VLPO area, resulting in poorer sleep quality. Additionally, the downstream effects of SD and CRD may cross-talk at the orexin, melatonin and stress granule pathways, mutually augmenting the impact on AD. Therefore, to avoid the risk of AD derived from SD and CRD, the most appropriate way is to sleep at the appropriate quality and quantity, at the appropriate time of day.

Integrating the existing epidemiological and biochemical evidence, it is likely that both SD and CRD are positive risk factors for AD. While quite a few studies demonstrated that AD pathology may be a cause of SD and CRD, this review goes along with the idea that the relationship is more likely bidirectional (Ju et al., 2014). However, it should be noted that most studies are performed on nocturnal animals such as rodents, even though humans are diurnal. The sleep and circadian rhythm regulation in nocturnal animals might be different from that in humans, and caution should be taken when interpreting and extrapolating results from animal studies to human physiology. Recently, research succeeded in harvesting human microglia-like cells from induced pluripotent stem cells (iPSCs), which were validated to resemble human fetal and adult microglia, providing a new model for studying neurodegeneration (Abud et al., 2017). This opens up a new direction of experimental model development in the study of AD, and in the future, it may be possible to harvest human glia or even neurons from iPSCs, to obtain results that could better reflect the actual pathophysiological condition in the human brain.

The global cost of dementia could reach 250 billion euros by 2030 (Duthey, 2013). Considering the large urban population undergoing increasing SD and CRD, it would be a cost-effective way to prevent the AD epidemic by launching public health campaigns to promote lifestyle changes, such as acquiring adequate sleep, maintaining good sleep hygiene and sustaining a life of normal circadian rhythm. Of course, these campaigns should be backed up by improved urban infrastructure, for instance, more convenient public transport systems that can shuttle people to the workplace from home. The wider application of light sources which emit minimal blue light would also likely improve the long-term outcome of urban nightlife. On the other hand, research may reveal molecules that are suitable candidate targets for the development of future pharmaceuticals in the management of AD patients. Central-acting noradrenergic receptor antagonists may reduce neuronal swelling and facilitate glymphatic clearance. Orexin receptor antagonists and melatonin analogues may improve the sleep quality of AD patients. Molecules along the clock genes and non-genetic clock pathways may also be targeted in the future development of drugs protecting against AD.

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