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Review Article

Impact of Sleep on Autophagy and Neurodegenerative Disease: Sleeping Your Mind Clear

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Abstract

Sleep is an evolutionarily conserved phenomenon which has survived tremendous evolutionary pressures. Its disruption has deleterious implications for human health. The importance of sleep is illustrated by the fact that sleep deprivation in many animals leads to death. While sleep is tightly regulated by a combination of intrinsic and extrinsic factors it becomes progressively disrupted in old age and in neurodegenerative diseases including Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD) and Huntington's disease (HD). One of the key effects of sleep disruption is increased levels of reactive oxygen/nitrogen species (ROS/RNS) and accumulation of protein aggregates, such as Amyloid β and alpha-Synuclein. A possible mechanism of protein plaque clearance is its autophagic degradation through endo-lysosomal pathways. In this review, we will discuss how sleep disruption is intimately linked with neurodegenerative diseases. We will also discuss the evidence that cellular autophagy and antioxidant defense are regulated by sleep, making it a target for future intervention strategies to tackle neurodegenerative diseases.

Keywords: ROS, RNS, REM, NREM, Autophagy, Glia

Introduction

Sleep is a state of behavioral quiescence when animals show reduced responsiveness to all kinds of sensory stimulation. The effects of sleep on our body are understood from studies on sleep deprivation in human and animal models. Lack of sleep leads to several detrimental effects on our health including increased risk to diabetes, forgetfulness, high blood pressure, weakening of immune system, cardiac problems, hallucinations and paranoia [1-7]. Recently, sleep has been identified as a risk factor for several neurodegenerative diseases including AD, PD, and FTD [8-10].

In 1894, Marie de Manacéine, a Russian physician and scientist, reported that sleep deprived puppies kept in constant activity die after a few days [11]. In 1898, a similar outcome was reported by Italian physiologists Lamberto Daddi and in 1989 Giulio Tarozzi in dogs. When they subjected dogs to constant sleep deprivation, the dogs died within 10 days [12a, 12b]. Marie de Manacéine further showed that the need for sleep was greater than for food since dogs could be rescued after 20-25 days of starvation, but they were 'irreparably lost' after 4-5 days of sleep deprivation. Daddi and Tarozzi also reported degeneration of spinal ganglia, Purkinje cells of the cerebellum, and neurons of the frontal cortex. They would base these changes on 'autointoxication' due to sleep deprivation. While the toxicity of sleep deprivation and disorder have long been known to scientists and lay-people alike, research into the mechanisms of this damage has formed a perplexing web of biochemical processes which extend into the pathways of many prevalent diseases today. Furthermore, anatomical evidence has shown that sleep fragmentation is directly linked with neuron loss in the brain [13] demonstrating that sleep loss and loss of neurons have a direct relationship.

To understand the current evidence linking sleep to

cellular metabolism and neurodegeneration, it is important to consider the role and origins of sleep. Sleep is a state of behavioral quiescence and reduced responsiveness to sensory stimulation, when most but vital motor movements cease and all active experiences, such as learning, stop [14]. Sleep has been observed in animals across different orders from jellyfish to humans emphasizing its evolutionary importance [15-18] . While sleep prevents most animals from beneficial activities such as foraging and gathering knowledge and experience, it must have a more important role to play in their survival that has allowed sleep to overcome such selective pressures. The characteristics of sleep including cessation of movement and behavioral quiescence are highly conserved between organisms such as *C. elegans*, *Drosophila* and humans indicating that similar molecular mechanisms govern the need and physiological effects of sleep [19,16]. This has allowed investigation of mechanisms of sleep, in simple model animals such as *Drosophila* where the complexity of biochemical and behavioral pathways is comparatively reduced. Sleep is yet to be found in organisms lacking a nervous system [20] suggesting a possibly fundamental role in the maintenance of neural tissue in particular.

Sleep deprivation has been shown to have profound detrimental effects on cognitive and physiological processes in many organisms. In mice, chronic sleep deprivation can lead to several homeostatic abnormalities eventually leading to death [21,22]. In *Drosophila* and *C. elegans* sleep deprivation has been shown to shorten lifespan [19,23]. However, some other reports showed little effect of sleep disruption on Drosophila and *C. elegans* [24,25]. In both examples, however, the authors acknowledge that residual sleep may fulfil the necessity of sleep, sufficient for survival in the absence of consolidated sleep. An important consideration that these studies may thus highlight is that while sleep is highly conserved, behavioral measures of sleep may not be sufficient to conclusively highlight the effects of sleep deprivation. For example, while sleep bouts are not essential for *C. elegans* survival, DAF-16/FOXO activation, a critical stress resistance pathway, is still essential to compensate for sleep loss [24]. This suggests that behavioral features of sleep may be of secondary importance to physiological functions.

Mammalian sleep has long been distinguished from invertebrate sleep in that in vertebrates sleep can be divided into different phases: rapid eye movement (REM) sleep and the more conserved non-REM (NREM) sleep [20]. NREM can be further subdivided into 4 stages - the deepest of which, stage 3 and 4, are also called slow-wave sleep (SWS) and seen outside the animal kingdom. REM sleep involves a more "active" stage of sleep, sometimes referred to as paradoxical sleep, due to wake-like neural function and rapid eye movements. REM sleep is differentiated from NREM sleep in mammals through delta wave frequency oscillations between 0.5 and 3.5 Hz [26] and many of the regenerative functions of sleep are associated with REM sleep in particular [27]. Others functions of sleep such as the Hippocampus dependent memory benefit more from the SWS and not from late REM sleep.

Determining sleep in *Drosophila* relies largely on inference and behavioral observations. In the currently used sleep assays, more than 5 minutes of continuous inactivity is considered as sleep in Drosophila [28-30]. Recently, developments in the study of *Drosophila* sleep have provided some new perspectives on the distinction between mammalian and invertebrate sleep. REM-like sleep has been shown to exist in *Drosophila* where activation of the dorsal fan-shaped body (dFB) induces a state of wake-like neuronal function but no response to mechanical stimulation. This paradoxical-like sleep state cycles between the more and less active stages, reminiscent of mammalian sleep [31]. Similarly, a form of deep sleep is shown to exist in *Drosophila* characterized by proboscis extension (PE). Inhibition of PE doubled the rate of mortality of full-body injured flies compared to controls highlighting an important role in recovery [32]. Of particular interest however is the finding in this report that PEs facilitated waste clearance in *Drosophila*: using a luciferin feed protocol they demonstrated that metabolites were excreted more slowly in PE-immobilized flies than controls and that sleep deprivation yielded a similar result. Stress-induced sleep peptides *flp-13* and *nlp-8* in *C. elegans* are also known to be important in inhibiting defecation during sleep [18] but whether these or other peptides play a role in promoting metabolism is yet to be seen. Furthermore, some preliminary evidence suggests that *flp* family genes may be orthologous to NPF/NPY in *Drosophila* and humans [33,34]. However, the relationship between *flp-13, nlp-8* and possible orthologs in other species warrant further investigation. These data suggest that deep sleep is an evolutionarily conserved promoter of waste clearance and the mechanisms through which this process operates are a subject of interest in determining the therapeutic significance of sleep in neurodegenerative disease. Additionally, emerging evidence of more complex sleep in *Drosophila* warrants further investigation to determine whether new, more applicable sleep models can be designed for studying human sleep.

Loss of sleep or sleep deprivation has many physiological and behavioural consequences such as neuronal oxidative stress [35,36,37], endoplasmic reticulum stress, mitochondrial dysfunction [38] and amyloid beta and tau accumulation [39-42,38], chromatolysis and vacuolization [43], abnormal spine homeostasis [44], disrupted synaptic AMPA channel [45] function neuronal loss [46] and impaired learning [44,47]. Discussion of all of these is beyond the scope of this review. The theme of autophagy is embedded throughout this article without dedicating a large section to describing autophagy on its own.

Autophagy and Sleep in Neurodegenerative Disease

While we do not intend to give an in-depth review of autophagy (for this, see Boland et al., 2018), a comprehensive

knowledge of autophagy and its role in cellular homeostasis is important in understanding the scope of this review. Autophagy is a multistage process that involves the identification of undesirable substrates in the cell and their degradation by lysosomal enzymes [48]. Each of these stages depends on activation of several, already identified genes. Mutations in these genes have been found in neurodegenerative disease patients [49]. The common hallmarks of autophagy disruption include oxidative stress, accumulation of amyloid beta, alpha-synuclein and mitochondrial stress [48,50]. While the contribution of autophagy defects to neurodegenerative disease has been long known, recent studies have suggested the role of sleep both as a cause and effect of autophagy disruption [51,52]. It is likely that autophagy sits at an interface between sleep and neurodegeneration, where sleep and autophagy could be connected through a feedback loop (Figure 1). The idea of a tripartite model of sleep, neurodegeneration and autophagy has not been well explored and given the importance of this model in understanding the mechanisms of neurodegeneration it warrants further investigation.

Sleep and Oxidative Stress

Recent evidence suggests that ROS accumulation may be a fundamental mechanism of sleep deprivation-related

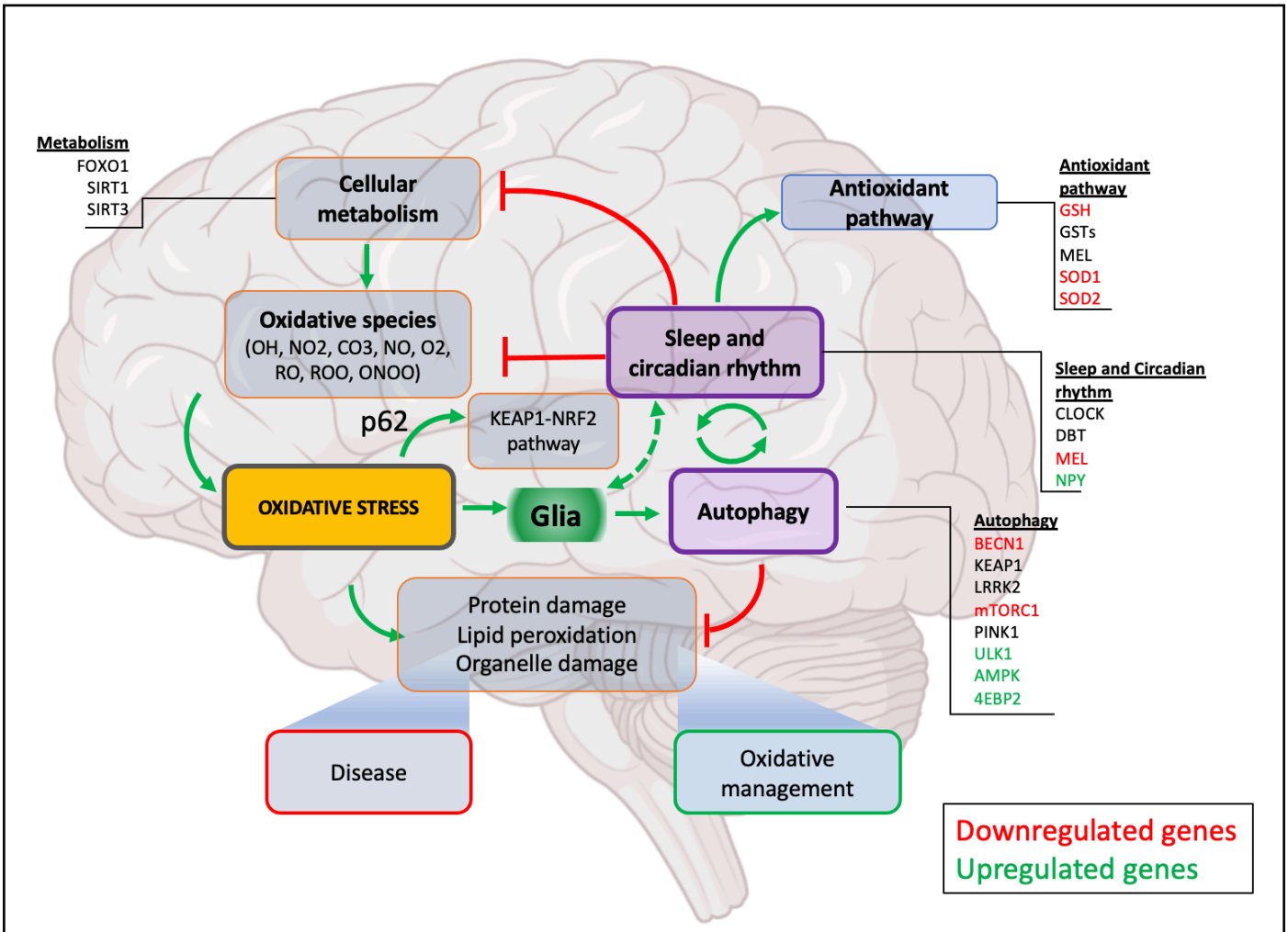

Figure 1: Sleep regulated autophagy. Sleep intervenes to alleviate oxidative stress and its effects at multiple levels. Firstly, in addition to sleep reducing overall metabolic rate, potential interactions exist between key sleep and metabolism genes. Secondly, several sleep-promoting genes are also important in the function of key antioxidant pathway (SODs, GSTs, MEL). Sleep is also associated with autophagy highlighting one of the mechanisms through which sleep regulates oxidative stress. Through both sleep's inhibitory actions on the oxidative pathway and promotion of the antioxidative pathway, it plays an important role in the maintenance of healthy cellular metabolism and response to both oxidative processes and the products of oxidative damage. Glia act as a moderator of neuronal activity by providing additional support for the removal of waste materials and debri produced by stressed neurons. Glial activation is known to be tightly associated with sleep both microglia and astrocyte regulating sleep pressure and intensity. Sleep promotes autophagy by yet poorly understood mechanisms preventing accumulation of proteinaceous and lipid waste thus. Disruption of autophagy or sleep deprivation both lead to defective oxidative stress management, accumulation of cellular waste eventually leading to disease.

death. In both *Drosophila melanogaster* and mice, sleep loss has been shown to increase ROS levels in the gut which contribute to premature death [53]. However, both exogenous and transgenic antioxidants can rescue animals from sleep deprivation and allow them to live normal lifespans with little to no sleep [54]. While the rescue of ROS-damaged tissue in the gut may not be transferable to the CNS due to the gut's high regenerative capacity compared to neural tissue [54-57], this does indicate ROS as a possible candidate for the physiological purpose of sleep. Moreover, it implicates sleep as a fundamental process in oxidative resistance. This notion of sleep as a promoter of oxidative resistance is supported by the contribution sleep makes to two key strategies which cells employ to combat oxidative stress: antioxidant production and autophagy.

The central nervous system is at particular risk of oxidative stress due to the lower expression of antioxidants and their heavy dependence on polyunsaturated fatty acids (e.g. arachidonic acid) and catecholamines whose degradation releases abundant free radicals (Figure 1) [58]. Furthermore, the structural and high-energy demand leads to relatively higher levels of lipid consumption in the brain which leads to many other fatty acids finding their way into neural tissue. The degradation of these molecules has been shown to increase the production of ROS through a cyclic activation of NMDA receptors driving calcium influx into the neurons followed by activation of PKCs leading to proliferative peroxide production even after the reactant has degraded [59,60]. Other processes that trigger NMDA-PKC chain activation (e.g. traumatic brain injury) show a similar increased production of ROS which are thought to contribute to secondary neuronal damage following injury [36]. Different neuronal populations also appear to show different selective neuronal vulnerability to oxidative stress depending on several factors such as high intrinsic ROS production [61,62], differential requirements for ROS in cellular signaling [63] and astrocytic inflammatory response [64]. These differences may underlie localization of pathological processes in neurodegenerative diseases.

Sleep and Cellular Antioxidants

Due to their high metabolic demand, neurons produce a variety of oxidants which, if not metabolized, can lead to intracellular damage. Neurons thus produce a variety of oxidant scavengers (Figure 1) to counter-metabolize the oxidative species it produces. Melatonin (MT) is an important hormone produced by the pineal gland that helps regulate circadian rhythm and is widely prescribed to patients suffering from insomnia [65,66]. In mice, melatonin has been shown to have a specific role depending on which receptor is bound: MT1 receptor knockout leads to disrupted REM sleep while MT2 receptor knockout leads to NREM sleep disruption [67] suggesting a differential role of MT which perhaps can adapt to need for sleep. Melatonin has also been shown to promote sleep and reduce sleep latency in both humans and *C. elegans* through activation of the BK channel and reducing neurotransmitter release [68] showing that its function in sleep is highly conserved. Beyond being a sleep promoting factor, melatonin is a low molecular weight antioxidant that has been shown to be not just linked with sleep, but also autophagy. Cyclosporine-induced oxidative stress can raise levels of autophagy, but subsequent co-administration of melatonin with Cyclosporin suppressed autophagy through direct suppression of LC3-II expression and increased expression of catalase [69]. This evidence suggests melatonin acts as a "peacekeeping" molecule, reducing ROS and inhibiting autophagy at the same time during asleep. In sleep deprived rats, decreased levels of superoxide dismutase (SOD) in the liver were accompanied by decreased expression of autophagy receptor *p62* and increased expression of LC3-II and *Beclin-1*, the latter two signaling an upregulation of autophagy [37], suggesting that increased autophagy may compensate for reduced antioxidant expression. A decrease in the expression of melatonin receptor 1 (MT1) in old age and AD brains when oxidative stress is higher and autophagy levels are lower further suggests a link between sleep and autophagy through MT receptor pathway [70-73]. Also, in preclinical cases of dementia, a decrease in melatonin release at night time has been reported with accompanying daytime sleepiness [71,74,75]. Administration of melatonin provides neuroprotection in genetic models of HD, perhaps suggesting a central position of melatonin in neurodegenerative disease [76]. A recent study has found that melatonin directly inhibits mTOR, which is accompanied by increased levels of phosphorylated AMPK (p-AMPK) and ULK1, promoting autophagy [77]. Sleep has similar effects on the levels of p-AMPK which then suppresses TORC1 complex and phosphorylation of 4EBP2 consequently influencing transcription of the 4EBP2 target genes [78]. This dual action of melatonin to inhibit autophagy in some contexts but promote it in others is curious as typically oxidant production signals an increase in *p62*-mediated autophagy through positive feedback from the KEAP1-NRF2 system to remove faulty organelles [79].

Superoxide dismutase (SOD) and glutathione S-transferases (GSTs) are fundamental in the regulation of ROS and antioxidative processes. Ubiquitous decrease in SOD1 expression has been shown to decrease lifespan and accelerate age-related locomotive impairment in *Drosophila* [80]. Furthermore, a bidirectional relationship between these antioxidant enzymes and sleep has been proposed: upregulation GSTs and SOD1 expression has been demonstrated to be both a result of oxidative stress as well as a mechanism for promoting sleep in *Drosophila* [35]. This relationship, which merits further study in mammals, highlights the intimate relationship between antioxidants and sleep.

Nicotinamide adenine dinucleotide (NAD^+) is a critical molecule in cellular metabolism [81]. Its role as an important

oxidizing agent and electron transporter in processes such as the citric acid cycle and electron transport chain are well understood, and it is therefore no surprise that NAD^+ should be implicated in cellular pathology. NAD^+ exists in its oxidized state NAD^+ and its reduced state NADH, which it cycles between to deliver electrons from the TCA to mitochondrial membrane complexes I through IV to drive ATP synthesis. Decreased NAD^+ levels as a result of age have been suggested as a critical underlying mechanism of pathological aging [82]. While there is extensive research into NAD^+, due to its ubiquity in cells and in particular its involvement in mitochondrial function, it is especially difficult to identify NAD^+ as being a molecule causative of pathology or whether its disruption is a result of other pathological processes acting within the cell. Despite this, there has been evidence that administration of nicotinamide mononucleotide (NMN), a precursor molecule to NAD^+, is capable of producing beneficial effects on cells *in vitro* and *in vivo*: NMN injections in transgenic AD (tg-AD) mice has been found to reverse oxygen consumption rate deficiencies to levels of control and a significant decrease in full length amyloid beta. Interestingly, administration of NAD^+ also reduced SIRT1 immunoreactivity in the brain of tg-AD mice [83] which, as we will discuss, is a candidate gene for linking autophagy and oxidative management. A possible mechanism for the beneficial impacts of NMN on cellular health in AD is that NMN increases mitochondrial NAD^+ stores as well as decreases SIRT3-mediated protein deacetylation [46]. NMN has also been shown to improve spatial learning and contextual memory in tg-AD rats when compared to untreated controls through inhibition of c-Jun N-terminal kinase (JNK) proteins: inhibition of JNK, which is especially prevalent in the hippocampus and cerebral cortex, leads to increased cleavage of amyloid-β precursor protein (APP) by non-oligomeric α-secretase and decreased cleavage by oligomeric β-secretase, suggesting that JNK inhibition by NMN can promote cleavage of APP into non-pathological Aβ [46]. This evidence implicates the NMN-JNK interaction in preventing localized Aβ oligomers and the behavioral manifestations of AD, and thus the importance of NMN in AD.

While NAD^+ has been studied extensively in the context of aging, links between NAD^+ and sleep are less well covered in literature. There are still clues that point to further lines of research into the impact sleep may have on NAD^+ activity. Firstly, intracellular nicotinamide phosphoribosyl transferase (iNAMPT) is an enzyme that converts nicotinamide into NMN through the NAD salvage pathway and is encoded by the *Nampt* gene, whose expression is mediated by the fundamental circadian transcription factors CLOCK and BMAL1 [84]. The inhibition of CLOCK/BMAL1 by cytokines in chronic inflammation is believed to have a role in age-related circadian disturbances [85] but this may demonstrate that circadian disturbances through the CLOCK/BMAL1 pathway end up disrupting the salvage of cellular NAD^+ through inhibition of *Nampt*. Secondly, recent evidence has suggested that NMN and SIRT1 may together play a role in both sleep- and age-related NAD^+ depletion. NMN administration differentially influences gene expression in the presence of SIRT1 with a large subset of genes not differentially regulated in SIRT1 knockout mice presumably due to loss of BMAL1 binding to chromatin indicating that NAD^+ transcription operates through a SIRT1/BMAL1 pathway [86]. BMAL1 and CLOCK are inhibited by clock suppressing proteins cryptochrome (CRY) and period-2 (PER2), which are sequestered in the cytoplasm during day but at night are present in the nucleus, inhibiting CLOCK/BMAL1 expression. In *Drosophila* SIRT1 knockout led to increased PER2 in the nucleus during the day which was more stable in response to NAD^+ depletion, as well as impacting PER2 phosphorylation and acetylation [87]. Conversely, pharmacological inhibition of SIRT1 deacetylase activity has been shown to increase the cytoplasmic localisation of PER2 thereby inhibiting the PER/BMAL1 promoter driven circadian oscillation [88]. This evidence together suggests that SIRT1 is important for maintenance of circadian rhythms and in modulating the impact of NMN administration by regulating expression of several genes. Furthermore, PER2 is known to be upregulated in elderly mice [89] and 6 months of NR supplementation has been shown to both dramatically reduce PER2 levels and to inhibit PER2 binding at BMAL1 [86] suggesting that PER2 levels may be both up- and down-regulated by NAD under the control of SIRT1. The impact of NAD and other reduced coenzymes on sleep (or vice versa) is still largely unexplored. Similarly, further studies are required to establish a link between NMN and SIRT1 in the regulation of mitochondrial health and oxidative stress linked with sleep deprivation.

SIRT1 is the focal member of the Sirtuin family of seven histone deacetylase proteins, responsible for the regulation of post-translation protein acetylation [90]. SIRT1 has been shown to have neuroprotective qualities which are reduced as its expression decreases with age, demonstrated through the reduction in neurotransmitter enzymes, dendrites, axons and increased accumulation of lipofuscin proteins [91]. However, the increase in protein aggregation in the absence of SIRT1 identifies it as a possibly important gene in oxidative management and autophagy. As previously discussed, SIRT1 is understood to be highly dependent on NAD^+ in performing its functions. SIRT3 is also expressed in the mitochondria and plays an essential role in regulating ROS by deacetylating the enzymes SOD2, Cytochrome C, Complex I and II [92] with SIRT3 knockout mice shown to be immune to the calorie restriction benefits of antioxidative protection [93]. SIRT1 has been found to activate AMPK and inhibit mTOR [94] indicating it is a prime candidate for regulation of autophagy. Indeed, SIRT1 knockout leads to increased damage resulting from peroxide infusion through downregulation of Beclin-1 and LC3-I to LC3-II conversion [95]. SIRT1 upregulation through resveratrol was also shown to have a protective effect against fluoride-induced cell-stress through upregulation of ATGs [46,96].

Mitophagy is a particularly relevant form of autophagy in the context of oxidative stress, given the role of damaged and faulty mitochondria in ROS production [97]. The impact of SIRT1 on mitophagy however remains far less clear. SIRT1 knockout promotes mitophagy by promoting ROS production through increased SOD2 acetylation, resulting in increased Parkin2 recruitment to mitochondrial membranes in prostate cancer cells in mice [98]. Whether SIRT1 bears the same impact on mitophagy in the brain is yet to be shown.

Neuropeptide Y (NPY) is one of the most abundant peptides in the mammalian brain [99]. It has several important roles in maintaining homeostasis in both the CNS and PNS, however in the CNS it is especially important for regulating food intake [100] and fat storage, blood pressure [101] and circadian rhythm [102,103] as well as being a molecule of interest in epilepsy [104,105]. NPY is also highly conserved, with the *C. elegans* homolog NPR1 being essential in maintaining homeostasis in response to sleep deprivation. NPR1 seems to be specifically associated with minor sleep disturbances (such as light exposure or vibrations) whereby it extends the duration of individual sleep bouts and this role seems to be separate from the DAF-16/FOXO pathway (which compensates for major sleep disturbances (such as vigorous agitation) by extending the overall duration of lethargus) [106]. In *Drosophila*, NPY homolog NPF has been shown to impact sleep quality but not duration and to mitigate some of the consequences of sleep deprivation [107]. While such mechanisms in mammals have yet to be shown, there is some evidence that NPY may be involved in regulating the structure of sleep without necessarily affecting the overall duration. Lateral hypothalamus and intracerebroventricular infusions of NPY in mice were shown to suppress REM and NREM sleep with higher doses eliminating REM sleep and suppressing the number but not the duration of NREM episodes [108]. Together these studies show a divergence in the role of NPY: in some mammalian studies such as in rodents [109] and humans [110] it promotes sleep, but it has equally been shown to promote waking [108,111]. Indeed, it has been shown that NPY overexpression and injection promotes sleep in zebrafish by inhibiting noradrenergic wake-promoting pathways, suggesting that NPY's sleep promoting function is localised to specific neuronal populations [112]. How exactly this data could map onto mammalian models has yet to be seen, but NPY's impact in reducing the arousal threshold during sleep could represent a conserved mechanism of NPY linking its role in minor sleep disturbance in *C. elegans* to its sleep promoting actions.

NPY has been shown to have neuroprotective effects in both PD [113] and AD [114]. In PD, one possible mechanism is NPY's ability to inhibit microglia-mediated inflammatory markers which are responsible for the majority of dopaminergic neuron loss in PD [115]. Neprilysin (NEP) is a metalloprotease whose levels in the brain inversely correlate with deposition of Aβ plaques AD [116,117]. As well as its role in degradation of Aβ, NEP is involved in cleaving NPY producing NPY C-terminal fragments which show a protective function against the neurotoxic effects of Aβ in a transgenic mouse model [114]. Interestingly, NPY is also an autophagy promoting factor in hypothalamic neurons in rodents through activation of NPY Y1 and Y5 receptors associated with activation of PI3K, MEK/ERK and PKA pathways. As such NPY could provide a useful target in determining the efficacy of autophagy-promoting sleep treatments and strategies [118].

The Glial System

The glial system is a support system which neurons heavily rely upon for protection against toxins and for providing the necessary neurotrophic support for maintenance. There are three main cell types in the glial system: Astrocytes, microglia, and oligodendrocytes [119]. Activation of astrocytes and microglia is an indication of neuronal stress and is reported to increase with age and in various neurological diseases [120]. Glia in particular plays an important role during development, synapse formation, pruning and maintenance [121,122]. Similarly, dysfunction of astrocytes and microglia has also been associated with various neurodegenerative diseases [123]. Recently, progress has been made in the identification of glial genes which have been associated with neurodegenerative disease, highlighting molecular pathways required for microglial function [124-126].

Glia play a crucial role in maintaining the ionic balance and clearance of waste materials from the brain through the glymphatic system [127]. Astrocytic function is necessary for maintaining the fluid volume during sleep-wake cycles which are essential for metabolic waste clearance from the brain dependent on aquaporin pump (AQP4) [128,129]. Interestingly sleep deprivation has been suggested to regulate the clearance of waste materials including neurotoxic proteins Tau and Aβ (Figure 2) [130,41]. Interestingly, AQP4 knockout mice show a compromised clearance of Aβ [129] suggesting that it is indeed through this mechanism that Aβ is cleared. In humans and rodents, sleep loss has been shown to increase inflammation markers [131]. It is now known that sleep deprivation leads to the activation of astrocytes and glia in mouse models, a phenomenon shared with aging and neurodegenerative disease [132]. The relevance of astrocytes in disease is demonstrated by the fact that they actively take up misfolded alpha-synuclein secreted by neurons in the brain of PD patients acting like a 'sponge' protecting from secreted alpha-synuclein [133]. In normal homeostatic state they are a partner of the tripartite structure including pre- and post- synaptic terminals where they take up some of the glutamate secreting into the synaptic cleft which they change into reusable Glutamine [134]. It is suggested that microglia and astrocytes activation shift between two different stages. In the case of microglia, these stages are termed 'M1' and 'M2'

Figure2

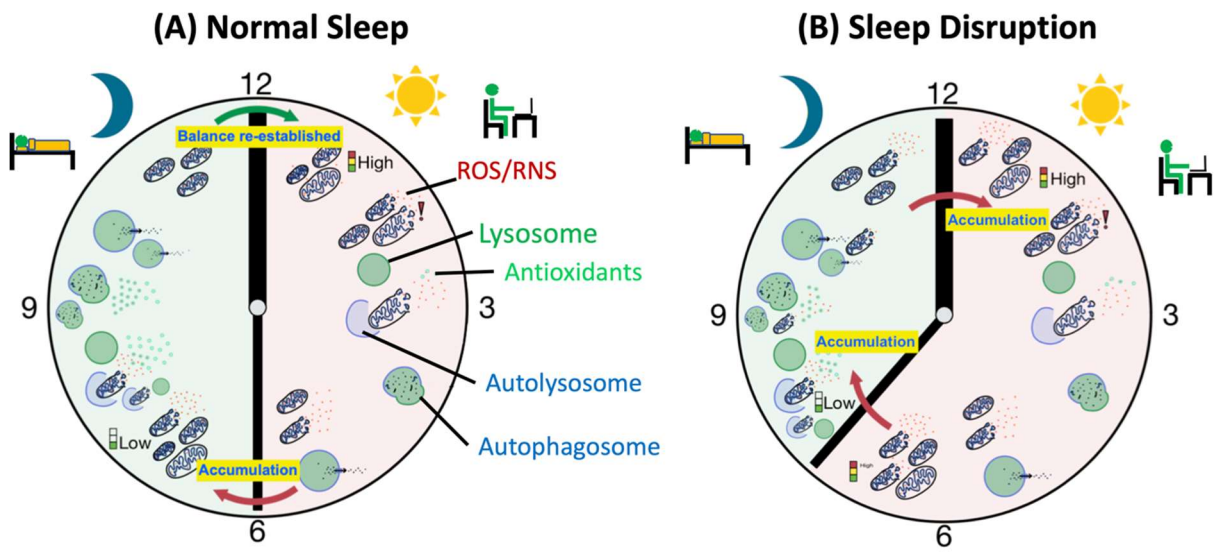

Figure 2: Sleep Disruption leads to metabolic waste build-up. (**A)** Metabolic activity during the day leads to accumulation of metabolic waste and the balance, between waste production and waste clearance, is tipped towards waste production leading to a build-up of metabolic waste. During the night when autophagy is higher waste clearance is high leading to cleanup of the cellular debris. (**B)** Sleep deprivation or loss of sleep tips the balance towards waste production and build-up which overpowers the autophagic waste clearance. Continuous imbalance in waste clearance leads to further accumulation of metabolic waste to toxic levels eventually leading to cell death.

and in M2 state microglia release a host of anti-inflammatory cytokines including BDNF, TGFβ and IGF-1 which help neurons deal with stress factors. The effect of sleep deprivation on this shift is yet unknown but is thought to be a potential treatment for neurodegenerative diseases [135-137]. In fact, mice lacking the M2 macrophages show an impairment in restorative slow wave sleep (SWS) after sleep deprivation [138]. On the other hand, proinflammatory signals such as bacterial infections shift macrophages towards the proinflammatory state M1 releasing proinflammatory cytokines such as IL-1β and TNFα and Nitric oxide (NO). These cytokines stimulate non-restorative NREM sleep indicating a relationship between sleep and proinflammatory response together [139,140]. Recently, sleep deprivation in rats was demonstrated to directly cause neuroinflammation [141]. Interestingly, this study also showed an increase in AQP4 in sleep deprived rats. Together these data suggest that normal Glial function is regulated by sleep and its function is important for neuronal homeostasis and removal of waste materials from the brain.

Discussion

Sleep is one of those things that we all know we need to function at our prime, and yet we aren't entirely sure why. It is often taken for granted in modern society where, through light/noise pollution, demanding work expectations or through general distractions, it can be tempting to push sleep aside despite an abundance of evidence citing the physiological, cognitive and behavioral effects of sleep deprivation as well as emerging evidence of an intimate relationship between sleep and neurodegenerative disease. Yet the biological mechanisms underlying these relationships are poorly understood. Here, we propose the idea that sleep plays a fundamental role as an evolutionarily conserved self-preservation mechanism of highly metabolically active neural tissue, inducing a pro-antioxidant and -autophagy environment to counteract the accumulation of cellular damage throughout waking. The abundance of mitochondria and charged molecules in neural tissue creates a hostile environment, vulnerable to oxidative damage, and disruptions to cellular maintenance processes (in part mediated by sleep) may underlie the profound effects of sleep disruption over time in humans and other organisms. Recent findings have shown that autophagosome production is decreased in sleep and that sustained upregulated autophagosome levels increase sleep duration [52]. While this hints at a regulatory role of autophagy in sleep it is uncertain whether this reduction of autophagosomes in sleep is, rather than being paradoxical, through the procession of autophagy to clear cellular debris. This highlights the need for further research in the genetic relationship between autophagy and sleep. Of particular interest are the SIRT family of genes. SIRTs are some of several exciting genes in aging research, with current evidence implicating them in mediating the longevity-promoting effects of calorie restrictive diets

[142,143] though the exact contributions of SIRTs are still unknown. The relationship between SIRTs and sleep has been discussed above, however, the links between SIRTs and autophagy are not clear. For instance, the impact of SIRT1 on autophagy-mediated clearance of cellular debris is yet to be established. NPY, yet another protein implicated in longevity-promoting effects of calorie restriction [144] requires further investigation to determine its role in autophagy.

Sleep plays an important role in regulating various homeostatic functions of the brain which deteriorate with age and in neurodegenerative disease partly due to decreases in the expression of Melatonin. The role of sleep in regulating autophagy is of particular interest to neurodegenerative disease because of its potential to be used as an intervention strategy to treat neurodegenerative disease. Because of a direct relationship of sleep with autophagy it is important to consider sleep together with autophagy in this picture. Although melatonin is already in clinical use to treat various sleep disruption conditions, its impact on neurodegenerative disease has not yet been exploited. Furthermore, finding alternative targets and ways to boost autophagy as an intervention mechanism needs to be exploited.

Establishing a clearer picture of the links between metabolism, age-related genes (such as SIRTs) and sleep has strong implications for society. Sleep disruption is seen as part of natural aging [145]. Approximately 40-70% of older adults experience some degree of chronic sleep problems [146]. In the context of an aging population where neurodegenerative diseases are more common, such as in the Western world, a better understanding of mechanisms of sleep and finding possible intervention strategies can be immensely useful. Sleep disruption is not however an issue specific only to the elderly, with increasing numbers of younger individuals reporting chronic sleep disturbances, especially relating to distractions such as smartphone use at night [147]. While younger people may feel immune to the effects of sleep deprivation, there is evidence that even in otherwise healthy young adults sleep deprivation leads to a significant increase in Aβ40 and reduction in Aβ42/40 ratio as a result of increased oxidative stress and reduced cellular clearance [42]. Whether this may impact long-term risk of AD or AD epidemiology in the future is yet to be seen, however some known impacts of sleep deprivation in young people (such as increased risk of depression) have been linked to significantly higher Aβ40 and lower Aβ42/40 ratios [148] suggesting that young people may not be immune from short-term pathological impacts of protein aggregation. It should be noted that this evidence does not imply a directional relationship and further research is needed into the implications of oxidized protein oligomerization in young people.

Recently, a direct relationship between sleep, autophagy and obesity was shown. Obesity is increasing in prevalence across both the developed and developing world and has been identified as a significant risk factor for neurodegenerative diseases such as AD and PD [149-151]. While obesity alters cellular metabolic health in a broad spectrum of ways, pathways of particular note are firstly the influence that a sustained positive energy balance induced by overnutrition has on promoting anabolic mTORC1 activity and inhibiting catabolism by autophagy [152]. Secondly, either independently or as a result of downregulation of autophagy, obesity results in increased ROS production which can then contribute to oxidative stress [153]. Sleep and obesity are directly linked, with obesity being associated with poorer sleep quality across age groups [154,155]. It thus appears that obesity and sleep may operate through similar mechanisms to increase neurodegenerative disease risk, providing possible biomolecular interaction between the two. It is therefore important to consider the possible interactions between both increasing chronic sleep disruption and obesity on neurodegenerative disease in the future.

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Author contribution

BM conceptualized the idea and both BM and SD wrote the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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