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Review

The wrinkling of time: Aging, inflammation, oxidative stress, and the circadian clock in neurodegeneration

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ABSTRACT

A substantial body of research now implicates the circadian clock in the regulation of an array of diverse biological processes including glial function, metabolism, peripheral immune responses, and redox homeostasis. Sleep abnormalities and other forms of circadian disruption are common symptoms of aging and neurodegeneration. Circadian clock disruption may also influence the aging processes and the pathogenesis of neurodegenerative diseases. The specific mechanisms governing the interaction between circadian systems, aging, and the immune system are still being uncovered. Here, we review the evidence supporting a bidirectional relationship between aging and the circadian system. Further, we explore the hypothesis that age-related circadian deterioration may exacerbate multiple pathogenic processes, priming the brain for neurodegeneration.

1. Introduction

The myriad correlations between aging, aging-related disease, and circadian rhythms (Hood and Amir, 2017; Kondratova and Kondratov, 2012; Leng et al., 2019) provide ample justification for investigation into potential causative relationships between these phenomena. The progressively increasing prevalence of circadian dysfunction with increasing age suggests that aging drives circadian dysfunction. However, disruption of the circadian clock – either behaviorally or through genetic manipulation - can also drive aging-like phenotypes, suggesting that the relationship between aging and circadian rhythm dysfunction is bi-directional (Hood and Amir, 2017). More recently, evidence has accumulated documenting changes in circadian systems preceding or being predictive of the development of neurodegenerative diseases, suggesting that circadian dysfunction could increase dementia risk (Leng et al., 2019). However, this possibility as well as the implication that aging and circadian dysfunction could represent concomitant, positively reinforcing cycles of deterioration remain active areas of investigation. Additionally, while the mechanisms by which these cycles may lead to increased risk for dementia remain unknown, immune dysregulation and oxidative stress have been identified as prime candidates (Leng et al., 2019). Initial studies suggest the circadian clock as a potentially viable therapeutic target for the treatment of both neurodegeneration and other age-related diseases. In connecting these concepts, it is helpful to contextualize newer investigations exploring circadian clock regulation of the immune system by considering what is known linking circadian dysfunction with aging (Also see (Hood and Amir, 2017)).

2. Overview of the mammalian circadian system

Circadian rhythms are a fundamental part of biology, as most organisms have a circadian clock that allows behavioral and physiological adaptation to the 24-hour light-dark cycle of earth. In mammals, the "master clock" of the body resides in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN receives synaptic input from the retina and the cellular clocks within neurons of the SCN are thus entrained to the external light-dark cycle. These cellular clocks then keep 24-hour time and the SCN has specific neural circuitry to ensure timekeeping that is both robust and flexible (Weaver, 1998). The SCN provides synchronizing cues through regulation of endocrine and autonomic nervous system function to cellular clocks throughout the body, including in neurons and glia in the brain (Mohawk et al., 2012; Prolo et al., 2005). The core molecular clock found in each cell is comprised of a positive transcriptional limb and negative feedback limb. The positive limb is composed of the bHLH-PAS transcription factor BMAL1 (aka *Arntl*), which forms hetereodimers with CLOCK or NPAS to drive circadian transcription via binding to E-box motifs. The negative limb consists of the PERIOD and CRYPTOMCHROME families of proteins, which are direct transcriptional targets of BMAL1 and which in turn

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inhibit BMAL1 function (Mohawk et al., 2012). The ROR and REV-ERB proteins, positive and negative regulators of *Bmal1* transcription, respectively, are also transcriptional targets of BMAL1 and further modulate clock timing. This core clock is tuned to a 24-hour period through the concerted actions of numerous post-translational mechanisms carried out by a network of secondary clock proteins (Wang et al., 2019). These core clock genes are expressed in nearly every cell in the body and can generate circadian rhythms in transcription and cellular function in the absence of any external cues. The circadian clock regulates between 10-50% of all transcripts in a cell, depending on tissue type, and influences critical processes such as cell cycle, redox homeostasis, inflammation, and metabolism (Zhang et al., 2014a). This breadth of clock-controlled genes may partially explain the wide ranging consequences of circadian clock disruption for aging as well as in the pathogenesis of many chronic diseases (Evans and Davidson, 2013).

3. Behavioral circadian disruptions in aging

On a behavioral level, circadian disruption is a widely-studied characteristic of both aging (Carskadon et al., 1982; Hayashi and Endo, 1982; Foley et al., 1995; Van Someren, 2000) and neurodegeneration (Okawa et al., 1991; Hatfield et al., 2004; Morton et al., 2005; Musiek et al., 2018; Musiek and Holtzman, 2016; Breen et al., 2014). Specifically, age-associated sleep changes, including sleep fragmentation, represent perhaps the most consistent and clear evidence linking behavioral circadian disruption to aging (Hood and Amir, 2017). Sleep disturbances such as difficulties with falling and staying asleep (Foley et al., 1995), increased sleep to wake transitions (sleep fragmentation) (Carskadon et al., 1982; Musiek et al., 2018), and increased daytime drowsiness and napping (Carskadon et al., 1982; Foley et al., 1995) are all characteristic of elderly populations. Sleep structure is also altered (Carrier et al., 2001) with a particularly prominent age-associated decrease in slow wave sleep (Hayashi and Endo, 1982; Dijk et al., 2000; Dijk and Czeisler, 1995; Ohayon et al., 2004; Landolt et al., 1996), which is deemed important for protein clearance (Holth et al., 2019; Iliff et al., 2012; Shokri-Kojori et al., 2018; Ju et al., 2017), maintaining metabolic health (Tasali et al., 2008), and potentially in memory consolidation (Rasch and Born, 2013). Interestingly, a recent report details dampening of rhythms in cortical excitability with age, which correlates with sleep changes and potentially contributes to age-related cognitive decline (Gaggioni et al., 2019). Older populations tend to display earlier chronotypes (Carrier et al., 2001; Duffy et al., 1998; Roenneberg et al., 2007; Zhdanova et al., 2011) while, at least in men, an individual's chronotype shifts earlier as age increases (Broms et al., 2014). Somewhat paradoxically, in a Dutch population aged 18-65, a later sleep onset was correlated with shorter telomere length (Wynchank et al., 2019), a feature associated with cellular aging and senescence (Blackburn et al., 2015). While the robustness of an individual's sleep rhythm declines with age, their ability to adapt to an environmentally imposed phase shift, as with jet lag, also declines with age in humans (Sellix et al., 2012; Monk et al., 2000) and in mice (Davidson et al., 2006; Valentinuzzi et al., 1997). Increasing fragmentation of circadian activity rhythms is also specifically noted in aging men and is independent of preclinical Alzheimer Disease pathology (Musiek et al., 2018). However, further research is required to disentangle whether these changes reflect alterations to the circadian system itself, independent from aberrant regulation of sleep homeostasis. The incorporation of other circadian readouts in addition to sleep may help facilitate this endeavor.

4. Other systemic circadian changes with aging

Outside of sleep, alterations in several other systemic circadian processes have been shown with age. For instance, body temperature normally peaks in the evening while the trough occurs in the early morning before waking (Refinetti and Menaker, 1992). In aged humans there is a phase advance in body temperature rhythm such that the nadir occurs earlier. The relationship between sleep and body temperature rhythms may also be altered, with age being associated with a later body temperature nadir relative to time of awakening (Duffy et al., 1998; Czeisler et al., 1992). At least in men (Monk et al., 1995; Vitiello et al., 1986), there may also be a reduction in amplitude (Czeisler et al., 1992) and increased variability (Gubin et al., 2006) of the temperature rhythm in aged adults (60s or older).

Melatonin, a hormone regulated by the SCN and secreted by the pineal gland, normally induces sleep, possibly by acting on BMAL1 (Beker et al., 2019) and regulates body temperature (Brzezinski, 1997). A potential decrease in melatonin secretion with age (Skene et al., 1990; Kin et al., 2004; Zhao et al., 2002) has been inconsistently documented (Duffy et al., 2002; Zeitzer et al., 1999) and may be specific to women (Kin et al., 2004). Additionally, it is possible that a decrease in melatonin secretion could be indicative of pathological instead of healthy aging (Zeitzer et al., 1999; Waller et al., 2016). In the SCN, the expression of melatonin receptor declines with age, which may contribute to the dispersion of behavioral rhythms (von Gall and Weaver, 2008; Wu et al., 2007). This decrease may be at least partially responsible for the loss of both sleep and body temperature rhythm robustness in advanced age.

Glucocorticoids, steroid hormones of which cortisol is the primary form in humans, have a complex relationship to stress, the immune system, and the regulation of plasma glucose homeostasis (Oster et al., 2017). Glucocorticoids are regulated by the SCN, follow a circadian pattern of secretion, and are potent synchronizers of a number of peripheral molecular clocks (Oster et al., 2017; Balsalobre et al., 2000; Oster et al., 2006). Van Cauter et al. as well as several others (Van Cauter et al., 2000; Vgontzas et al., 2003; Kumari et al., 2010) found that the rhythm in circulating cortisol is dampened in aging, enabled by a progressive rising of the nadir and accompanied by an overall increase in levels (Van Cauter et al., 1996). However, others found a phase shift in elderly subjects, but no change in amplitude (Sherman et al., 1985), while still others found no major changes in cortisol with age (Touitou et al., 1982). In mice, an age-related decline in glucocorticoid signaling in the hippocampus, potentially due to a decrease in glucocorticoid receptor expression, may play a role in the depletion of the neural stem cell pool (Schouten et al., 2019). Despite disagreement on specific cortisol rhythm abnormalities (possibly due to high variability or vastly different sample sizes), a remaining diurnal rhythm in circulating cortisol in aged humans is consistent between studies (Van Cauter et al., 2000; Vgontzas et al., 2003; Kumari et al., 2010; Van Cauter et al., 1996; Sherman et al., 1985; Touitou et al., 1982). This persistence of a cortisol rhythm in aging, which in contrast to the case of melatonin is retained during pathological aging (Hatfield et al., 2004; Waller et al., 2016), adds another level of complexity to the series of interconnected feedback loops that experience age-associated alterations or losses in robustness.

5. Age-related changes in the SCN

In addition to the impairments and alterations observed in SCN-regulated rhythms, age-associated changes in the SCN itself have been documented. An impairment in the rhythm of neuronal firing in mice (Nakamura et al., 2011; Farajnia et al., 2012) and flies (Curran et al., 2019), as well as decreases or altered rhythms (Hofman and Swaab, 1994) in the expression of neuropeptides arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) in the SCN have been observed in humans, especially in men (Zhou et al., 1995), and in rodents (Chee et al., 1988; Roozendaal et al., 1987) with advanced age. A loss in GABAergic synapses in the SCN has also been reported in aged mice (Palomba et al., 2008). GABA-mediated neuronal activity, as well as the expression of VIP are critically important for the cohesiveness of SCN neuronal firing rhythms (Aton et al., 2005; Aton et al., 2006) and the maintenance of behavioral rhythms depends on the coordination of

SCN neuron firing (Herzog et al., 2004; Vasalou et al., 2009). In a small sample of elderly people and Alzheimer patients, fragmented sleep-wake rhythms during life were associated with loss of VIP-ergic neurons in the SCN on post-mortem examination (Wang et al., 2015). Thus, current data support the hypothesis that changes in SCN neurons could contribute to age-associated behavioral rhythm desynchrony. However, this possibility requires more thorough evaluation to show that these changes in neuronal populations directly influence organismal rhythms.

6. Aging and circadian clock gene expression

Reports documenting age-induced alterations in the molecular clock have been more controversial. Some have shown dampening or dispersion in the SCN expression rhythms of *Bmal1*, *Clock* (Wyse and Coogan, 2010; Kolker et al., *2003*), and *Per2* (Nakamura et al., *2015*; Chang and Guarente, 2013) while others report normal *Per1* and *Per2* rhythms (Yamazaki et al., 2002; Asai et al., 2001) with advanced age. Altered molecular rhythms, including an impaired ability to phase reset, have also been observed in the mouse liver (Davidson et al., 2008) (although to a lesser extent in some reports (Sato et al., 2017; Novosadova et al., 2018)), heart (Bonaconsa et al., 2014), kidney, lung (Yamazaki et al., 2002), thymus (Sellix et al., 2012), and pancreas (Novosadova et al., 2018) among others. However, intact molecular rhythms have been observed in muscle and epidermal stem cells of aged mice (Solanas et al., 2017). Interestingly, the induction of replicative cellular senescence has been found to impair entrainment of the molecular clock (Kunieda et al., 2006), suggesting that perhaps the accumulation of senescent cells in a given tissue with age could play a role in the dispersion of circadian phases between cells. Outside of genes directly involved in the core molecular clock, a large number (more than 1000) of clock-controlled genes display altered rhythmicity, some even gaining rhythms with age in the human prefrontal cortex (Chen et al., 2016). The liver (Sato et al., 2017) as well as muscle and epidermal stem cells (Solanas et al., 2017) also undergo substantial circadian reprogramming in aged mice. However, more data is needed to solidify the physiological relevance of altered molecular rhythms, especially in the aged brain.

7. The circadian system, healthspan, and lifespan

Changes in the circadian system can be predictive of, while inducing circadian disruption can reduce, healthspan and lifespan. For instance, the degree of deviation from a 24-hour circadian period was found to be negatively correlated with lifespan in both rodent and primate species (Wyse et al., 2010; Libert et al., 2012). Conversely, implantation of young SCN tissue improved the molecular (Cai et al., 1997) and behavioral rhythms (Li and Satinoff, 1998) of rats and the longevity of aged hamsters after surgery compared with cortex- and mock-implanted controls (Hurd and Ralph, 1998). Additionally, inducing weekly phase shifts, especially phase advances, can reduce survival of aged, but not young, mice (Davidson et al., 2006) while phase shifting can also increase the vulnerability of mice to an lipopolysaccharide (LPS) challenge (Curtis et al., 2015; Marpegan et al., 2009a). Genetically, ablating the clock via a global knockout of *Bmal1* shortens lifespan and induces a number of other “aging-like” pathologies, such as cataracts and sarcopenia in mice (Kondratov et al., 2006). Moreover, deficiencies in either *Per2* (Fu et al., *2002*) or *Clock/Bmal1* (Marcheva et al., *2010*) mediated transcription has been shown to exacerbate cancer or drive age-dependent insulin dysfunction and diabetes, respectively. The pathologies in the *Bmal1* KO model have since been partially attributed to loss of *Bmal1* during development/early life (Yang, 2016) and exhibit tissue specificity (McDearmon et al., 2006). However, these and further studies utilizing macrophage/monocyte (Curtis et al., 2015; Adrover et al., 2019; Early et al., 2018; Gibbs et al., 2012; Nguyen et al., 2013), muscle (Dyar et al., 2014), liver (Jacobi et al., 2015), brain-specific (sparing the SCN) (Musiek et al., 2013), and other tissue-specific circadian mutants have recapitulated components of aging-like phenotypes and vulnerabilities, including insulin resistance (recently reviewed (Stenvers et al., 2019)). Interestingly, a contingent of these metabolic abnormalities, including lipid accumulation and glucose intolerance, can be mitigated by time restricted feeding, highlighting the importance of the clock in maintaining metabolic homeostasis (Chaix et al., 2019; Villanueva et al., 2019; Jamshed et al., 2019). These studies also suggest time restricted feeding as a potentially viable behavioral intervention for age-related metabolic dysregulation.

Maintaining the integrity of circadian rhythms is crucial for optimizing a large host of physiological outputs including, but not limited to long-term potentiation (Barnes et al., 1977; Chaudhury et al., 2005) and associated cognition (Smarr et al., 2014; Eckel-Mahan et al., 2008), metabolic health (Paschos et al., 2012), reaction time (Graw et al., 2004; Scott et al., 2006), and muscle performance (Dyar et al., 2014; Peek et al., 2017; Sato et al., 2019; Ezagouri et al., 2019), age-associated deteriorations of which have been extensively documented. Accordingly, the perturbation of rhythms, for instance with nighttime light exposure (Fonken et al., 2012), circadian misalignment (shift work) (Wefers et al., 2018), or jet lag (Karatsoreos et al., 2011) can impair these functions. Circadian disruption also negatively impacts insulin sensitivity as well as increases risk factors (Lieu et al., 2012; Suwazono et al., 2008; Morris et al., 2016; Curtis et al., 2007) and worsens outcomes (Beker et al., 2018) for acute neurological and cardiovascular events, which already display daily rhythms in occurrence (Thosar et al., 2018; Muller et al., 1985; Panza et al., 1991). These data suggest that at the very least, disruption of the circadian clock is detrimental in the context of aging. The intriguing possibility that such disruptions could be driving the aging process itself, negatively impacting healthspan and lifespan should be of particular interest to future studies. Additionally, recent studies suggest that the efficacy and toxicity of drug therapies for age-related diseases such as cancer can be dramatically affected by the circadian phase in which they are administered (Slat et al., 2017; Paschos et al., 2010; Borniger et al., 2017). Circadian regulation of treatment efficacy may become even more complicated and warrants further investigation in the context of aging, given the age-related alterations in phase and dispersion of rhythms discussed here. The intimate interaction between the immune system and the circadian clock, discussed in the next section, adds yet another layer of complexity to be considered, and perhaps leveraged, in the development of therapeutics to treat age-related disease.

Mechanistically, the circadian clock is linked to the mammalian target of rapamycin (mTOR) and Sirtuin 1 (SIRT1) (Chang and Guarente, 2013; Ramanathan et al., 2018; Cao et al., 2013; Khapre et al., 2014; Imai, 2010). These factors are closely tied to the regulation of aging with mTOR negatively and SIRT1 positively impacting healthspan and lifespan (Wu et al., 2013; Lamming et al., 2012; Satoh et al., 2013; Imai and Guarente, 2014; Harrison et al., 2009). SIRT1 interacts with the BMAL1/CLOCK complex and may impact circadian transcription directly by deacetylating BMAL1 (Nakahata et al., 2008), PER2 (Asher et al., 2008), and histone H3, acting counter to the histone acetyltransferase functions of the CLOCK protein itself (Nakahata et al., 2008). Additionally, levels of NAD+, an essential metabolite and necessary substrate for SIRT1 deacetylase activity (Imai and Guarente, 2014; Vaziri et al., 2001), as well as the expression of NAMPT, the rate-limiting enzyme in the NAD+ salvage pathway (Revollo et al., 2004), have been shown to oscillate in the mouse liver (Ramsey et al., 2009; Nakahata et al., 2009) and human red blood cells (NADH) (O'Neill and Reddy, 2011). This circadian clock regulation of NAD+ through NAMPT is important for maintaining homeostatic levels of mitochondrial oxidative phosphorylation (Peek et al., 2013) and for feeding back into SIRT1 (Nakahata et al., 2008; Ramsey et al., 2009; Nakahata et al., 2009) (as well as mitochondrial SIRT3 (Peek et al., 2013)) activity. Although through a modestly different mechanism, modulation of the circadian clock by SIRT1 is also present in the SCN (Chang and

Guarente, 2013). In concordance with decreased expression of *Sirt1* in aged animals, this control of the clock by SIRT1 wanes with age (Chang and Guarente, 2013). An age-associated systemic decline in NAD+ (recently reviewed (Yoshino et al., 2018; Fang et al., 2017; Lautrup et al., 2019)), possibly due to decreased levels of clock-regulated NAMPT in several tissues (Stein and Imai, 2014; Yoshida et al., 2019; Yoshino et al., 2011) has been thoroughly documented. Taken together, these data suggest that a deficit in the interaction between SIRT1 and circadian signaling could bear some responsibility for the connection between circadian dysfunction and the aging process (Hood and Amir, 2017; Chang and Guarente, 2013). In support of this idea, aged mice experience a substantial dampening of the protein acetylation rhythms under dual regulation by NAD+/SIRT1 and the circadian clock in the liver (Sato et al., 2017). These rhythms are restored by caloric restriction (Sato et al., 2017), currently the most robust lifespan extension intervention (Mitchell et al., 2016). Caloric restriction can also induce circadian reprogramming in both young (Makwana et al., 2019) and old animals as well as greatly enhance NAD+ levels and SIRT1 activity (Sato et al., 2017).

Circadian physiology is also inextricably linked with a number of other metabolic pathways (Panda, 2016), including the insulin signaling (Stenvers et al., 2019) and mTOR pathways (Ramanathan et al., 2018; Cao et al., 2013; Khapre et al., 2014; Zhang et al., 2014b), the suppression of which have both been shown to extend lifespan and healthspan (Wu et al., 2013; Lamming et al., 2012; Harrison et al., 2009; Kenyon et al., 1993; Tatar, 2001; Selman et al., 2008). Insulin induces phosphorylation of BMAL1 via AKT, thereby inhibiting BMAL1 transcriptional activity (Dang et al., 2016). On the other hand, downstream insulin signaling target mTOR can also induce BMAL1 phosphorylation via S6K1, a modification that enables BMAL1 to play a critical role in mTOR-regulated translation (Lipton et al., 2015). Additionally, activation or inhibition of mTOR results in acceleration or dampening of the circadian clock, respectively (Ramanathan et al., 2018; Cao et al., 2013). Calorie restriction, which extends lifespan, impairs insulin signaling, and inhibits mTOR, also increases *Bmal1* expression and BMAL1 mediated transcription (Patel et al., 2016). Finally, loss of *Bmal1* has been found to increase mTOR activity (although not in all reports (Beker et al., 2019)), while inhibition of mTOR extends the lifespan of *Bmal1* KO mice by 50% (Khapre et al., 2014). Taken together, these data suggest a bidirectional relationship whereby maintaining a metabolic equilibrium that favors longevity also promotes robustness of the circadian clock, while maintaining the integrity of the clock may promote longevity by sustaining metabolic homeostasis.

8. Glial clocks and aging

In addition to in the SCN and throughout the body (Yoo et al., 2004), oscillating molecular clocks have been documented in a variety of extra-SCN brain regions (Abe et al., 2002) as well as in astrocytes (Prolo et al., 2005) and microglia (Fonken et al., 2015; Hayashi et al., 2013). In the SCN, astrocytic clocks are synchronized by VIP (Marpegan et al., 2009b) and can be altered by immune factors such as TNFα (Duhart et al., 2013). Astrocytic extracellular ATP release (Marpegan et al., 2011), which has potential implications for allodynia (Koyanagi et al., 2016), gliotransmission (Womac et al., 2009), and glutamate uptake (Beaule et al., 2009) are regulated by the clock. Additionally, astrocytes play a substantial role in maintaining behavioral circadian rhythms. For instance, under certain conditions, glial clock dysfunction can cause behavioral arrhythmicity in flies (Ng et al., 2011). Several recent studies have independently documented an even more impressive role for the clock in SCN astrocytes in determining the phase and period of mouse circadian rhythms (Barca-Mayo et al., 2017; Tso et al., 2017; Brancaccio et al., 2017). Surprisingly, it was also shown that SCN astrocytes are capable of generating population-wide circadian clock oscillations and mouse activity rhythms in the absence of intact neuronal clocks (Brancaccio et al., 2019). Despite the prominence of the astrocyte clock in the SCN, relatively little is known about its function elsewhere in the brain and outside of behavioral rhythm maintenance. However, recent evidence suggests that glial clocks may play a substantial role in regulating the neuroimmune system – discussed in more detail in the next section - with potential implications for neurodegeneration (McKee et al., 2019). Notably, glia regulate blood-brain barrier permeability, which has been shown to exhibit circadian oscillation in flies (Cuddapah et al., 2019). Additionally, multiple groups have reported marked aging-induced changes to the astrocytic (Clarke et al., 2018; Boisvert et al., 2018) and microglial (Grabert et al., 2016) transcriptomes that may substantially overshadow those in neuronal populations (Soreq et al., 2017). Together, these data suggest that glial clocks may represent a fresh perspective from which to consider the ballooning interest in the role of both astrocytes and microglia in the pathogenesis of neurodegenerative diseases.

9. The clock and the immune system

Recent studies have convincingly demonstrated circadian regulation of the immune system in the periphery (Scheiermann et al., 2018), while emerging evidence links the clock to regulation of the immune response in the CNS (Leng et al., 2019; McKee et al., 2019). Indeed, the circadian clock regulates inflammatory and oxidative stress responses. For example, both lesions of the SCN (Guerrero-Vargas et al., 2014) and light induced rhythm disruption (Adams et al., 2013) can exacerbate release of cytokines TNFα (Guerrero-Vargas et al., 2014) and IL-6 (Guerrero-Vargas et al., 2014; Adams et al., 2013) in response to LPS, while LPS can differentially activate SCN neurons based on time of day (Guerrero-Vargas et al., 2014). Chronic circadian phase shifts (chronic jet lag) (Castanon-Cervantes et al., 2010) or merely varying the time of day (Curtis et al., 2015; Marpegan et al., 2009a) can heighten both inflammation and LPS-induced endotoxemic death in mice. In addition to the aging-related pathologies previously discussed, global and brain-specific *Bmal1* KO as well as global *Clock/Npas2* double KO mice have age-dependent increases in ROS damage, chronic inflammation (Kondratov et al., 2006; Musiek et al., 2013) including increased *Tnfa*, microglia and astrocyte activation, and synapse degeneration (Musiek et al., 2013). In monkeys, *Bmal1* KO can also induce immune system activation and depression-like symptoms (Qiu et al., 2019).

Importantly, clock genes including *Clock*, *Per2* (Keller et al., *2009*), *Bmal1*, and the BMAL1 target *Nr1d1* oscillate in peripheral macrophages (Nguyen et al., 2013; Keller et al., 2009) and lymphocytes (Druzd et al., 2017). In humans, the LPS-induced blood levels of cytokines Interferon-γ (IFN-γ), Interleukin-10 (IL-10) (Petrovsky and Harrison, 1997), and TNFα vary consistently based on time of day while IL-6 levels vary inconsistently (Alamili et al., 2014; Hermann et al., 2006). In mice, lymphocyte trafficking (Druzd et al., 2017), LPS-induced monocyte recruitment, cytokine levels including TNFα, IL-6 (Keller et al., 2009), IL-12 (Gibbs et al., 2012), inducible nitric oxide synthase (iNOS - reactive NO-producing enzyme) (Nguyen et al., 2013), chemokines including CCL5 (Gibbs et al., 2012), and mortality (Spengler et al., 2012) exhibit time of day dependence with a reduction during late wake/early rest periods (Nguyen et al., 2013; Keller et al., 2009). This reduction can be abolished upon monocyte *Bmal1* (Nguyen et al., *2013*) or *Nr1d1* (Gibbs et al., *2012*) KO indicating an immune-suppressive role for these proteins. Accordingly, *Bmal1* KO in monocytes reduces survival in response to infection and exacerbates chronic inflammation and glucose intolerance in a mouse model of diet-induced obesity (Nguyen et al., 2013). Deletion of *Bmal1* also induces an *Nrf2*-dependent increase in ROS and IL-1β in macrophages (Early et al., 2018). Disruption of BMAL1-regulated neutrophil aging can impair immune defense and vascular protection in mice (Adrover et al., 2019).

In vitro, *Bmal1* KO can cause increased neuronal degeneration, death, and susceptibility to oxidative damage (Musiek et al., 2013). Additionally, it was found that the BMAL1/CLOCK complex binds

chemokine *Ccl2* and *Ccl8* promoters (Nguyen et al., 2013) while BMAL1 binds the promoters of genes protective against oxidative stress, which are also downregulated in global *Bmal1* KO mice (Musiek et al., 2013). Macrophages from global *Nr1d1* KO increase IL-6 secretion while REV-ERBα (*Nr1d1*) agonist GSK4112 (Gibbs et al., 2012; Sato et al., 2014) and *Nr1d1* overexpression in culture (Sato et al., 2014) suppresses IL-6 release. In further support of BMAL1-mediated immune suppression, global KO of two repressors of BMAL1 activity, *Per2* (Liu et al., *2006*) and microRNA miR-155, can reduce TNFα (Curtis et al., 2015), IL-1β, and IFN-γ (Liu et al., 2006) secretion upon LPS treatment. Taken together, these and similar studies make a strong case for the circadian clock as an important immune regulator, providing a limiting check on immune over activation in the periphery.

The neuroimmune system, primarily under the purview of glia, may also be subject to regulation by the molecular clock. In addition to the astrocytic clock discussed previously, a few recent reports have documented oscillating clock gene expression including *Bmal1*, *Per2*, and *Nr1d1* in microglia (Fonken et al., 2015; Hayashi et al., 2013; Nakazato et al., 2011). Cytokine levels including *Il-6*, *Tnfa*, and the critical inflammasome component *Nlrp3* (only measured after LPS), among others, show circadian variation in unstimulated and LPS-stimulated whole hippocampus and microglia (Fonken et al., 2015). Aging abolishes these differences, clamping the microglial inflammatory response to LPS at its highest level in younger mice (Fonken et al., 2016). Little is known about astrocyte clock function in the immune system. However, we have shown that astrocyte clock dysfunction induces astrogliosis and can impair neuronal survival (Lananna et al., 2018). Additionally, BDNF and *Nrf2*-dependent oxidative stress protection provided by astrocytes to neurons (Ishii et al., 2019) and NF-κB-mediated inflammation may both be regulated by the astrocytic clock (Sugimoto et al., 2014). *Nr1d1* KO induces microgliosis and astrogliosis *in vivo* and exacerbates the neuroinflammatory response to LPS treatment, including NF-κB signaling, *in vivo* as well as in cultured microglia (Griffin et al., 2019). However, one study demonstrated a surprising depression of *Il-6* expression in microglia and a mitigation of stroke damage *in vivo* after deleting microglial *Bmal1* (Nakazato et al., *2017*). The varied results from glial clock manipulations suggest a more nuanced clock regulation of the glial immune response and underscore the need for further investigation. Such efforts may be especially relevant in the context of neurodegeneration where glial cells play an increasingly appreciated and crucial role in disease progression.

The general finding of a more active immune system at the rest to wake transition (Gibbs et al., 2012; Nguyen et al., 2013; Fonken et al., 2015) is likely preemptive, preparing the body for increased possibilities of infection exposure during “morning” foraging and conservationist, minimizing both energy expenditure at unneeded times and collateral damage induced by a constitutively active immune system (Curtis et al., 2014). These studies in the peripheral and central immune systems as well as the pro-inflammatory, pro-ROS phenotypes of *Bmal1* mutants support the possibility that the circadian clock could regulate the CNS immune response in microglia and astrocytes. In total, these data suggest that alterations to circadian systems both in the SCN and in tissue-specific clocks could play a substantial role in immune hyperactivation with aging. Thus, these alterations may generate tissue environments susceptible to the overproduction of oxidative stress and prime the body for the development of neurodegenerative disease.

10. Circadian clocks and oxidative stress

Considerable evidence supports a bidirectional relationship between the circadian clock and oxidative stress, as changes in redox status can influence core clock function, while clock proteins themselves regulate redox homeostasis of cells (Stangherlin and Reddy, 2013). Binding of BMAL1/CLOCK to DNA is dependent on the NAD(H)/NADP(H) ratio, a barometer of cellular redox status, with increased binding occurring under reducing conditions (Rutter et al., 2001). Circadian rhythms in hydrogen peroxide levels are observed in cultured cells (Khapre et al., 2011) and mouse liver, and can directly regulate rhythms in CLOCK function via cysteine oxidation (Pei et al., 2019). Deletion of the redox-responsive protein $p66^{shc}$, which is itself rhythmic, disrupts these oxidation rhythms in CLOCK and alters mouse behavioral and transcriptional rhythms (Pei et al., 2019). Inhibition of the pentose phosphate pathway (PPP), which is critical for generation of NADPH to fuel ROS generation by the NADPH oxidase enzymes, as well as for glutathione production, can also alter clock function (Rey et al., 2016). PPP inhibition with resultant loss of NADPH leads to oxidative stress, activation of the NRF2 redox response pathway, increased BMAL1/CLOCK DNA binding, altered clock gene expression, and lengthened circadian period (Rey et al., 2016). NRF2 itself appears to regulate clock function, as $Nrf2^{-/-}$ cells have diminished clock gene expression and blunted circadian rhythms in *Per2* expression (Wible et al., 2018). In the SCN, circadian rhythms in redox tone regulate rhythmic neuronal activity via regulation of potassium currents (Wang et al., 2012). Thus, oxidative stress can regulate clock function by multiple pathways.

Conversely, the core clock controls expression of redox response genes and dictates cellular responses to oxidative stress. Drosophila exhibit circadian rhythms in ROS sensitivity which are lost in arrhythmic Per^{01} mutant flies. Per^{01} flies have shortened lifespans, increased oxidative damage, and age-related neuronal degeneration (Krishnan et al., 2009; Krishnan et al., 2012). Glutathione, a critical small molecule antioxidant present in all cells, is regulated by the clock at several levels. Glutathione levels, glutathione-producing enzymes, and glutathione transferase enzymes all show circadian oscillation in drosophila and mice (Beaver, 2012; Xu et al., 2012). NRF2, which strongly regulates glutathione synthesis, is a transcriptional target of BMAL1 (Early et al., 2018). BMAL1 controls *Nrf2* in pancreatic beta cells (Lee et al., 2013), macrophages (Early et al., 2018), and lung cells (Pekovic-Vaughan et al., 2014), with loss of BMAL1 causing blunted NRF2-mediated antioxidant responses and enhancing ROS levels. Accordingly, deletion of BMAL1 leads to increased oxidative damage in multiple organs, including the brain (Kondratov et al., 2006; Musiek et al., 2013). The clock protein REV-ERBα can be induced by oxidative stress and can in turn regulate expression of the antioxidant transcription factor FOXO1 as well as stimulate autophagy and mitochondrial biogenesis (Sengupta et al., 2016; Yang et al., 2014; Woldt et al., 2013). Overexpression of REV-ERBα provides protection against oxidative stressors and improves mitochondrial function (Sengupta et al., 2016; Woldt et al., 2013). Oxidative stress in flies can even reprogram genome-wide circadian transcription toward a redox stress response (Kuintzle et al., 2017). Taken together, these data suggest that the circadian clock responds to changes in cellular redox tone and regulates expression of redox response pathways. As oxidative stress is strongly implicated in many aspects of aging, age-related changes in clock function could promote oxidative damage.

11. Circadian dysfunction in Alzheimer Disease

As detailed above, the circadian clock has a panoply of effects on cellular aging, inflammation, and oxidative stress and is impacted by all of these processes. Thus, it is perhaps not surprising that circadian disruption is a common symptom of multiple neurodegenerative diseases (as reviewed in detail elsewhere (Leng et al., 2019; Musiek and Holtzman, 2016; Videnovic et al., 2014)). Among these, Alzheimer Disease (AD) is the most common age-related neurodegenerative condition and is associated with considerable circadian dysfunction (Musiek et al., 2015). The sequence of pathogenic events in AD is thought to begin with the accumulation of amyloid plaques, composed of aggregated amyloid-beta (Aβ) peptide, followed by the formation of hyperphosphorylated tau protein aggregates (neurofibrillary tangles) within neurons. Plaques appear 10-20 years before disease onset, while tau pathology is apparent within 5 years of the first symptom and is closely associated with inflammation and neurodegeneration (Jack Jr.

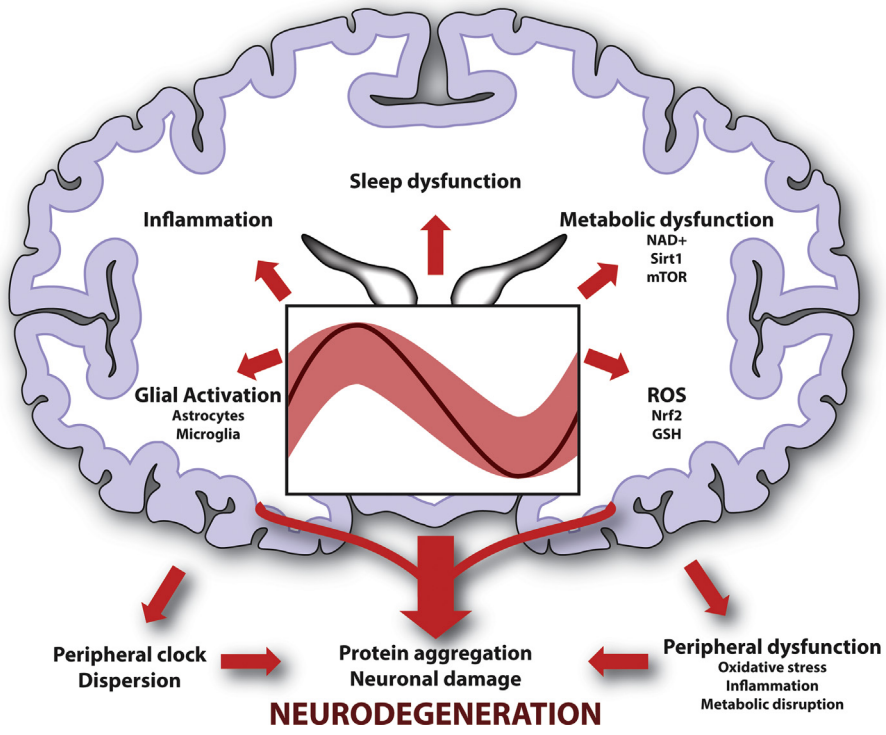

Fig. 1. Interaction of aging, circadian rhythms, and neurodegeneration. Age-related dampening and dispersion of circadian rhythms (imprecise light red oscillation depicting aged vs robust and precise dark red oscillation depicting young), can promote various pathogenic changes in the brain, including oxidative stress, inflammation, glial activation, and metabolic dysfunction. Disruption of normal sleep-wake patterns can also contribute to these pathologies. Loss of peripheral circadian synchronization can promote systemic inflammation and impact the immune system, potentially contributing to brain dysfunction. Thus, the circadian system orchestrates brain homeostasis through multiple emerging mechanisms, disruption of which may prime the brain for neurodegeneration.

et al., 2018). Several human studies using actigraphy show that circadian and sleep fragmentation occur during the presymptomatic phase of the disease and worsens with disease progression (Musiek et al., 2018; Ju et al., 2013; Lim et al., 2013; Tranah et al., 2011). This pattern is similar to that seen in normal aging, but more severe. Degeneration of the SCN, with subsequent blunting of rhythmic melatonin release, may provide a mechanistic explanation for this exacerbation (Wang et al., 2015; Swaab et al., 1985; Skene and Swaab, 2003; Uchida et al., 1996). However, alterations in *BMAL1* methylation (Cronin et al., 2017) or direct effects of Aβ on BMAL1 degradation have also been proposed (Song et al., 2015). In the mouse brain, interstitial fluid Aβ levels exhibit a clear circadian rhythm which is driven by the sleep–wake cycle (Kang et al., 2009). Deletion of *Bmal1* causes severe circadian fragmentation, significantly blunts Aβ rhythms, and increases amyloid plaque deposition in a transgenic mouse model of AD (Kress et al., 2018). The exact mechanisms underlying this effect of clock disruption on plaques is unclear. One potential mechanism is through dysregulation of sleep, as sleep deprivation can increase Aβ plaque deposition in mice (Kang et al., 2009), perhaps by increasing neuronal activity-dependent Aβ production (Bero et al., 2011) or by impairing Aβ clearance through the glymphatic system (Xie et al., 2013). Humans also have diurnal rhythms in cerebrospinal fluid (CSF) Aβ levels (Huang et al., 2012). Moreover, sleep deprivation in healthy adults acutely increases CSF Aβ (Lucey et al., 2017) and may increase amyloid deposition (Shokri-Kojori et al., 2018). However, kinetic labeling studies suggest this effect occurs via increased Aβ production, rather than impaired clearance (Lucey et al., 2017). Extracellular levels of tau also increase during wakefulness and are exacerbated by sleep deprivation in both mice and humans (Holth et al., 2019), while sleep deprivation in mice increases tau pathology (Holth et al., 2019; Zhu et al., 2018; Di Meco et al., 2014). Thus, the clock may influence amyloid deposition and tau pathology in part through effects on sleep.

Aside from sleep regulation, circadian disruption could potentially influence AD or other neurodegenerative diseases by any of the previously mentioned mechanisms, including alterations in inflammation, glial function, NAD+/SIRT1 signaling, mitochondrial function, or redox homeostasis. Circadian regulation of protein misfolding and proteostasis in the brain is also relatively unexplored, though the clock has been linked to regulation of autophagy and the proteasome (Woldt et al., 2013; Ma et al., 2011; Desvergne et al., 2014). Accordingly, the core clock could potentially be leveraged as a therapeutic mechanism to optimize these factors in the aging brain and prevent degeneration. Attempts at improving circadian function indirectly through light and/or melatonin supplementation have yielded modest or mixed results on sleep integrity and cognition (Singer et al., 2003; Gehrman et al., 2009; Xu et al., 2015), but may offer increased benefit when used in combination (Dowling et al., 2008; Riemersma-Van Der Lek, 2008). A variety of drugs which directly target the circadian system are currently being developed and tested (Solt et al., 2012; Hirota et al., 2010; Oshima et al., 2019), potentially enabling future strategies for treating age-related pathologies, including neurodegeneration (Musiek et al., 2015).

12. Conclusions

Impaired circadian function and immune dysfunction, including altered redox homeostasis, coexist consistently across aging and pathological conditions, including neurodegenerative disease (Hood and Amir, 2017; Leng et al., 2019; Scheiermann et al., 2018). Despite documented regulatory overlap between these areas, the idea that the age-worn circadian system could represent a common link between these phenomena has not been thoroughly explored. Circadian rhythm integrity, including sleep and metabolic cycle competency, is crucial for maintaining brain homeostasis, but breaks down in aging and during neurodegeneration (Fig. 1). At the same time, the circadian clock is vital in optimizing immune function, which is also compromised in aging and neurodegeneration. Elucidation of unifying threads that directly link these observations has the potential to address unanswered questions in several fields simultaneously. These efforts may reveal both innovative therapeutic strategies for tempering the ravages of time and age-related disease while also establishing intriguing avenues for future study.

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