Spring 4-27-2022

The Relationship Between Circadian Rhythms and Neurodegenerative Disease

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Honors Project

Submitted to the Honors College

at Bowling Green State University in partial fulfillment of the

requirements for graduation with

University Honors April 27, 2022

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Key Words: Alzheimer's Disease, Circadian Rhythm, Neurodegenerative Disease, Parkinson's Disease, Suprachiasmatic Nucleus

Abstract

Neurodegenerative disease is a pervasive and insidious disease affecting a large proportion of the elderly population. Leading to the degeneration of neural tissue throughout the nervous system, it is a slow and progressive disorder. Because of its nature, it is possible that it has a connection to circadian rhythms. Circadian rhythms are the endogenous approximately 24-hour rhythms of the body commonly associated with the sleep-wake cycle, but they account for much more. This review aims to ascertain the relationship between the two by covering several facets of research pursued in the past five years. Beginning with establishing a basic understanding of neurodegenerative disease and circadian rhythms before moving on to the research. Genetic disruption accounts for the subtle yet most influential factor, affecting many systems later on. Next follows the best researched avenue of sleep followed by the immune response with neuroinflammation and apoptosis in neuronal tissue. Finally, is a brief overlook of avenues pursued outside of the brain investigating strong links to the kidneys and the bacteria of the intestines. With everything combined, it is clear that the relationship here is this positive-feedback loop of ever-worsening conditions in individuals with neurodegenerative disease. At the end, brief comments are noted on potential treatments mentioned throughout the review along with the continued progression and need for new potential avenues of research.

1 Introduction

Neurodegenerative disease (ND) is a wide-encompassing term for many differing disorders of the brain. Ranging from neuromotor dysfunction (ataxias) to neurocognitive dysfunction (dementias). Many known diseases fall into this broad category, including Alzheimer's Disease (AD), and Parkinson's Disease (PD), among others. As known broadly, these diseases typically develop from the aging brain and many known and unknown risk factors. Normally, it is seen as wide-ranging cell death in neural tissue in various portions of the central nervous system (CNS) and the peripheral nervous system (PNS). These diseases are slow, progressive, and insidious. Individuals afflicted with either of these will be severely neutered mentally and physically within years of the first major symptoms. Despite what is known about the symptomatology of the diseases, little is known about their pathology. Many paths are currently being explored, and one such potential lies within circadian rhythms.

Circadian rhythms (CRs) are rhythmic and endogenous approximately 24-hour oscillations of the body. Hallmarked by their periodic continuation with or without external stimuli, these rhythms play many important roles throughout the course of any organism's day and life. The most evident to everyone is the sleep-wake cycle, of which is controlled by a circadian rhythm. While the sleep-wake is arguably one of the most important circadian cycles moderated, there are other non-circadian rhythms important to life that can influence any function of the body. Two of these are most active and not always thought of by the public to be as rhythmic as the sleep-wake cycle: the pulse of the heartbeat and the rhythmic breathing of the lungs. The latter can be voluntarily regulated by the organism, showing a good example of how a

rhythm can be influenced, which is why this path of investigation has been so important in trying to help discern the pathology of NDs.

The effects of how CRs are affected by NDs has been investigated before, yet the narrative has yet to be well established beyond a few reviews. While the past reviews explore specific paths such as explicitly genetics or specifically direct effects of neurodegeneration, little has been done to coalesce the narratives into one cohesive story. It is the hope here, that a story will be told of how neurodegeneration plays into the degradation of circadian rhythms and how this collapse leads to exacerbation of ND. A feedback-loop of ever-worsening conditions that grows unto itself, a collapse of the individual's brain.

2 Neurodegenerative Disease

As stated, ND is a set of diseases marked by the destruction of neural tissue over a long period of time. Briefly, the major diseases mentioned throughout the literature, and here too, will include Alzheimer's Disease and Parkinson's Disease. These two are the most researched in the field of neurodegeneration and feature frequently in research and study.

First, the most well-known is Alzheimer's Disease, characterized by a typical late-life onset, usually developing strong symptoms in individuals during their 60s or 70s. In 4-5% of cases however, these individuals do develop early-onset AD (Mendez, 2012). Neurodegeneration present in AD shows atrophy of the temporal and parietal lobes, as well as the frontal cortex and cingulate gyrus, which is responsible for learning, memory, and emotion formation (Wenk,

2003). However, despite this, AD cannot be confirmed until after the patient's death, only inferred beforehand.

Those who were inflicted with AD present with Amyloid-β (Aβ) plaques and neurofibrillary tangles formed from excess tau protein. The former, Aβ is a normal byproduct of the amyloid precursor protein (APP) being cleaved by beta and gamma secretase. Normally, this byproduct is removed from the cerebrospinal fluid and cell bodies during sleep. However, in individuals with AD this does not appear to be the case as there are large plaques of Aβ mixed with cellular material densely packed outside of neurons (Ohnishi & Tahano, 2004). And, beyond the presence of these plaques outside of neurons, there are within neurofibrillary tangles (NFTs) made of the tau protein, which stabilizes the cytoskeleton of neurons. Tau protein in AD becomes hyperphosphorylated and collapses, forming these NFTs, destroying the neuron's transport system (Hernández & Avila, 2007). While not all-encompassing of the basics for AD, it is still a poorly understood disease. Though another poorly understood disease is Parkinson's Disease

Parkinson's Disease, much like AD, can only be confirmed after the individual has died. Because of this, it is difficult to determine the course of the disease within the brain. What is known is that the major pathological characteristics are Lewy Bodies. Composed of the protein alpha-synuclein and other minor contributors, are believed to be a clump of severely misfolded proteins referred to as an aggresome (Tanaka et al., 2004). Alpha-synuclein is responsible for much of DNA repair and its function is heavily reduced in neurons possessing Lewy Bodies and because of the lack of DNA repair, neurons would eventually undergo apoptosis. It is unfortunate that these two diseases are poorly understood and while discussion will not focus on explicitly

the diseases, it will focus on how one major function plays into their development, circadian rhythms.

3 Temporal Order of the Body

Circadian rhythms are a complicated feature of the brain and the cells of the body, an endogenous, rhythmic cycle repeating roughly every 24 hours. Any biological rhythm can be called circadian if it falls under the following three criteria: 1. The rhythm is an endogenous period lasting approximately 24 hours persisting through constant conditions such as constant darkness; 2. The rhythm is entrainable, meaning it can be reset to external stimuli; and 3. The rhythm compensates for temperature, maintaining consistent periodicity throughout a range of physiological temperatures. Practically every rhythm of an organism falls under these criteria, however there would be chaos if not for the suprachiasmatic nucleus (SCN).

Within a small part of the hypothalamus lies the SCN, which is responsible for the control of nearly half of the circadian rhythms in the body. The so-called “master clock” consists of approximately 20,000 neurons and exerts much influence over the body of organisms (Gumz, 2016; Weaver, 1998). These neurons within the SCN are special compared to other circadian clocks present within the body. Other clocks can be entrained by environmental stimuli, and the SCN is no exception, although it has a special topography. It contains its own “coupling mechanisms, which allow them to remain synchronized to one another even in constant darkness” (Welsh et al., 2010), meaning the SCN can act independently of external stimulation, not in totality however.

A common term used is the “free-running period” which is the period of a circadian oscillator in the absence of external stimuli. In a human left in constant light conditions, their free-running period is about 24 hours and 20 minutes, meaning they will slowly shift out of alignment. This is due to the SCN not being able to do its job as it controls much of the CRs present throughout the body by entraining to light. It is a well known statement as mammals are entrained through photoreception via their eyes, the removal of which destroys the circadian response to light (Gumz, 2016; Yamazaki et al., 1999). The entrainment of the SCN with the cycle of night and day is seen on the genetic level with the cyclic manipulation of multiple genes.

Regulation of the SCN’s CR falls down to the molecular level with the oscillation of transcriptional-translational feedback loops that include *BMAL1* and *CLOCK*. These two genes heterodimerize to begin modulation of various genes including ones expressing the cryptochrome (CRY) and period (PER) proteins (Chauhan et al., 2017). Nominally, they promote the transcription of *CRY1/CRY2* and *PER1-PER3* which go on to heterodimerize themselves and inhibit expression of *BMAL1* and *CLOCK*. With a roughly 24-hour oscillation, these four go on to influence transcription of other clock-controlled genes. It has been estimated that, “... 40-50% of all protein encoding genes in mice and humans are regulated by the circadian clock …” (Buijink & Michael, 2021). Seen in the hunger response of the liver to the sleep-wake cycle of the brain, the SCN establishes a temporal order over the mind and body. Though, this temporal order can be broken with the development of ND, which is first seen below with breaking the genetic disposition of the SCN.

4 Genetic Disruption of the Molecular Clock

The molecular clock of the SCN, responsible for much of the CRs present in the body is a tenuous cycle as it is dependent on the BMAL1:CLOCK dimer forming and promoting the cryptochrome and period genes. Neurodegeneration has been observed to disrupt the cyclic methylation of these parts. In patients with AD, the rhythmic methylation of *BMAL1* is altered with respect to unafflicted individuals (Maiese, 2021). The actual change in rhythmicity is different in each individual, yet the result is the same; the dimerization of *BMAL1* and *CLOCK* is disrupted due to the unmatched prevalence of *BMAL1* to *CLOCK*. Considering that the two work on a cycle akin to a sine wave, if the waveform for *BMAL1* is shifted to later, then in the morning hours there would be an under-expression of genes reliant on the rhythmic oscillation of *BMAL1* and *CLOCK*. In the evening hours, the expression would be nominal, however, as *CLOCK* would become the limiting reagent. Of course, the situation would be reversed if the waveform was shifted to earlier. Effects of this would be wide-ranging, however an evident one that will be explored later in-depth is sleep. Individuals with AD are not the only ones to suffer from a shifted rhythmicity of *BMAL1*. PD patients also exhibit a change.

Patients with PD present with a blunted rhythmicity of *BMAL1* within their blood cells (Hood & Amir, 2017). A study by Delgado-Lara et al. in 2020 found that the expression of *BMAL1* and *PER1*, in general, was inhibited throughout the body of the 28 human subjects tested. The relative expression was also measured, of which *BMAL1* is normally expressed 30% less than *PER1* (Breen et al., 2014). In the patients measured, they found that the relative expression was 57% lower than *PER1* (Delgado-Lara et al., 2020). Unlike in AD patients where the cycles are out of phase, here *BMAL1* is explicitly dampened. This dampening is present

across the full day with various effects at day and night. Throughout the day, PD patients exhibit excessive daytime sleepiness, significantly decreased melatonin circulation in the bodily fluids, and there is a loss of the circadian dip in blood pressure at night in 71% of patients (Leng et al., 2019). Part of this may be due to effects of ND seen in the pineal gland as AD also has a role to play.

AD is also affected in the pineal gland with a chronogenetics study as referenced by Videnovic et al., who showed that "… the diurnal pattern in the expression of the clock genes *ARNTL,* … is lost in the pineal gland of patients with AD" (Videnovic et al., 2014). With the pineal gland responsible for the secretion of melatonin and many patients of ND known to have a decreased presence of melatonin, it is reasonable to assume a malfunction within this part of the brain. *CRY1* and *PER1* mRNA expression is lost within the pineal gland in patients with ND (Hood & Amir, 2017). Because of the heterodimerization of these two proteins and their direct inhibition of the BMAL1:CLOCK heterodimer, it is a logical continuation that there would be a subsequent decrease in inhibition. Because there is no subsequent damping of the BMAL1:CLOCK heterodimer, the production of melatonin is inhibited, thus degrading sleep, the next topic.

5 Sleep of a Decaying Mind

Observations of the elderly population has shown that their length and quality of sleep goes down as they get older, an adamant symptom of aging. Patients with ND, however, experience this degradation in sleep quality at a hastened pace. Individuals with ND suffer from

REM sleep behaviour disorder before classic ND symptoms (Chauhan et al., 2017). Chauhan goes on to add that 90% of individuals diagnosed with REM sleep behaviour disorder will develop a ND associated to α-synuclein aggregation, a major component of Lewy Bodies. While REM sleep behaviour disorder is common to ND patients, there are other factors with sleep at play.

Mentioned before was melatonin. It is known that the SCN entrains melatonin secretion (Wu et al., 2019), ultimately, it is the pineal gland that secretes melatonin, and with the pineal gland losing its expression of *BMAL1* (Videnovic et al., 2014) the immediate outlook is poor. Even early research has shown that there is a marked decrease in the prevalence of CSF melatonin, and as noted by Uddin et al. melatonin abates the accumulation of Aβ in AD patients (Uddin et al., 2020). Melatonin has another role beyond abating Aβ accumulation as it also attenuates the hyperphosphorylation of tau while also limiting oxidative stress in AD (Chen et al., 2020). There are also effects seen in PD, acting similarly to AD. Melatonin improves neurotoxicity "... by inhibiting autophagy and α-synuclein aggregation by enhancing the ubiquitination of α-synuclein in kainic acid-induced mouse model *[sic]*" (Chen et al., 2020). Mitochondrial damage seen in some PD patients has also been shown to be reduced in yeast models. There are other effects of melatonin in ND, however they tend to be less significant, only showing effects later in life or in rarer ND cases such as those with Batten Disease or Creutzfeldt-Jakob Disease. Because of the continual decline of sleep quality and length in ND patients it is not hard to create a causal link between the decline of the CR controlling melatonin secretion, sleep, and the progression of ND (Chen et al., 2020; Uddin et al., 2020). Melatonin is also not the only sleep-involved hormone that is affected.

With much of the research falling into melatonin's court in earlier research, there has been a recent surge in studies of orexin. Gene-knockout mice of orexin, a peptide responsible for wakefulness, "… modestly increases sleep time but strongly suppresses the formation of amyloid plaques in AD model mice" (Musiek, 2016). It is not well known the mechanism by which this occurs, however orexin is mostly independent of influence from the SCN, and has its own influence over the sleep-wake cycle. Research has shown that CSF orexin levels are positively associated with increased Aβ levels and that infusion in mice, "significantly raised *interstitial fluid* [unabbreviated] Aβ levels …" and infusion of antagonist, "... almorexant, for 24 h suppressed ISF Aβ levels in mice" (Wu et al., 2019). Almorexant was intended to be used in humans; however, research was abandoned. There has been another drug developed as an antagonist to orexin receptors under the name Lemborexant. Approved by the FDA in 2019, it was originally used to treat insomnia, however recently, it is under investigation for its potential in treating irregular sleep-wake rhythm disorder in AD patients. It has shown generally positive results in ameliorating sleep disruption and is currently in phase II to evaluate long-term exposure and potential circadian improvements (Scott, 2020). Moving from specific sleep-wake cycle hormones, comes a short focus on the unfolded protein response.

The unfolded protein response is initiated in the endoplasmic reticulum and is meant to maintain proteostasis by either removing misfolded proteins or salvaging those that are still usable. This response is activated often in individuals of ND, as expected. However, the decreased quality of sleep has shown to alter this response. Researchers have found that a decrease in sleep leads to an over-activation of the unfolded protein response and that this, "... over activation of the UPR/maladaptive ER stress response could contribute to neurodegenerative disease" (Hafycz & Naidoo, 2019). With the sleep cycle being controlled by

the SCN, the over-activation of the UPR could lead to changes throughout other CRs and may be another contributor to worsening sleep in ND patients. With α-synuclein being a common misfolded protein, some research has gone into studying its prevalence in sleep. Transgenic mouse models for α-synuclein showed changes in the firing rate of the SCN early in the development of PD along with sleep-wake disturbances separate from SCN misfiring (Videnovic & Golombek, 2017). All combined so far, sleep presents a poor outlook for ND patients. However, this field has spawned the most research into potential treatments for ND patients.

Studies have found that poor sleep and sedentary behaviour are linked to negative health outcomes, one of which is an increased risk for developing "... clinical all-cause dementia and Alzheimer's disease …" (Lysen et al., 2020). Thus, there has been a large influx of research on studying how modulating sleep behaviors among others, can contribute to improving CRs and the sleep-wake cycle itself while reducing the pathogenesis of ND. Much of the research has shown improved results, but as noted by Ferini-Strambi et al. well designed control experiments are a necessity with how unreliable they can be (Ferini-Strambi et al., 2020). Thus, the following had more strict requirements to enter this review. One of these experiments included studying the effects of tailored light intervention. This is a method by which individuals are entrained forcefully by tailoring the day/night cycle to maximize the effects on the circadian system. One study found that by performing this method, there was a significant improvement in self-reported sleep quality and objective sleep efficiency (Figueiro et al., 2019). While not immediately indicative of much, as shown before, decreased sleep quality does lead to exacerbated progression of symptomatology in individuals with ND. Thus controlling one major CR, the sleep-wake cycle, will have a positive impact on pathogenesis.

Another promising study investigated the potential of intermittent fasting and time-restricted feeding. This study was conducted by Jamshed et al. in 2019. The methodology here was to restrict the eating patterns of individuals to an early schedule, from 8 A.M. to 2 P.M. Results measured in this experiment included glucose monitoring of course, but also expression of those genes related to glucose metabolism and the circadian system. One of the results found that cortisol levels, another important hormone in wakefulness, had slightly increased levels in the morning hours and slightly decreased in the evening hours. And of the circadian genes, the treatment "significantly increased the expression of the circadian clock genes *BMAL1*, *CRY1*, *CRY2*, and *RORA* in the morning" (Jamshed et al., 2019). The evening hours also showed a decreased expression of *PER1* and another increase in *CRY1*, *CRY2*, and *RORA* along with an increase to *REV-ERBA*. As seen earlier, with the loss of expression of *BMAL1* and *CRY1* in the pineal gland of ND patients, having an overall increased expression of the two throughout the body is promising. While not immediately indicative of increased sleep length, it is promising. Though sleep is a well researched field, the following is not as well understood and likely has a stronger influence over pathogenesis.

6 Neuroinflammation and the Interstitial Space

Neuroinflammation is another complex facet of the CNS with many key influences in ND and CRs. Microglia is one of the cell types that spearheads the neuroinflammatory response by monitoring the situation and shaping neural circuitry. They can be activated by numerous methods, some of which include amyloid-β, α-synuclein, proinflammatory cytokines, among others (Homolak et al., 2018). Astrocytes also get involved in the response by downregulating

expression of aquaporin-4, decreasing the rate of water flow between cells and the interstitial fluid (Homolak et al., 2018; Valori et al., 2021). Astrocytes also regulate neuronal transmission (Wang & Li, 2021). CRs play into this by modulating the active and inactive phases of the neuroinflammatory response.

In the active phase, "... leukocyte recruitment is increased, along with circulating levels of epinephrine, norepinephrine and TNF-α …" and in the resting phase, "... characterized by lower expression of endothelial adhesion molecules and an enhanced pooling of immune cells from the bone marrow to the blood" (Homolak et al., 2018). This is the general circadian response to inflammation, but when applied specifically to neuroinflammation; a review by Musiek and Holtzman from 2016 references the influence of CRs on the neuroimmune system and how action employed by it can be changed by NDs. They describe how, "Neuroinflammation, often propagated by activation of astrocytes and microglia, is a major contributor to neuroinflammation," followed by "Astrocytes exhibit robust circadian clock function … Microglia also have functional circadian clocks …" describing succinctly the effects of the immune response and a circadian influence.

Astrocytes and microglia, "Upon injury and disease of the CNS, … become 'reactive' … is characterized by the generation of an inflammatory environment into the nervous tissue" (Valori et al., 2021). This activation does not need to be exogenous in origin either, as endogenous disease and injury also leads to the activation of astrocytes, microglia and the CR associated with them. A study performed by Pillai et al. in 2021 showed the circadian response to neuroinflammation in AD patients as seen before in other experiments. However, they experimented to see how CRs are disrupted due to the immune response. Pillai et al. found that

there are, “circadian rhythm irregularities accompanied by 1) altered humoral immune responses in both the CSF and the plasma, i.e., circadian disruption was associated with altered immune profiles and 2) increased CSF neurodegeneration biomarkers (p-tau and t-tau)” (2021). Emanating the proposition that there is a feedback loop present between the immune system and CR in relation to ND’s disruption of the nervous system. Expanding upon the second point, tau seems to have a rhythmic presence in interstitial brain fluid.

A study by Holth et al. examined in mice the degree to how much tau protein is prevalent in the brain’s interstitial fluid. They state the following, “... ISF tau is regulated by the sleep-wake cycle and that both ISF tau in mice and CSF tau in humans are strongly increased in sleep deprivation… Thus, changes in the sleep-wake cycle can result in rapid changes in ISF and CSF tau” (2019). With tau being one of the major components to AD gaining more prominence in sleep-deprived individuals and seeing from before how sleep deprivation is endemic to ND, it presents another spiraling feedback loop. Normally, the immune system would get involved, but again, as seen earlier in this section, its effectiveness is hampered due to the effects of ND. Ultimately, it may come down to autophagy and apoptosis as another means to hamper progression.

7 Autophagy and Apoptosis

Autophagy, the natural degradation within cells, recycling the components and breaking down non-functioning or otherwise useless organelles. Extensive research has gone into observing the relationship between autophagy and ND because this is one of the major failure

points seen in the nervous system. Autophagy is meant to destroy many of the misfolded proteins and byproducts that are seen in ND like Aβ and tau. Circadian dysfunction during the process of aging and ND has been shown to induce autophagy (Luo et al., 2020; Maiese, 2017). Certain neuropeptides in *Drosophila* models have also been shown to induce apoptosis, the rapid, programmed death of a cell. These peptides include pigment dispersing factors and insulin-like peptides. The relationship to ND, CRs, and apoptosis is summarized succinctly as, "These signaling molecules convey important network connectivity and signaling information for normal circadian function …" as they are necessary in modulating the morning and evening binding sites for circadian function, and "... convey signals that lead to apoptosis, enhanced neurodegeneration and cognitive decline in flies carrying circadian mutations or in a senescent state" (He et al., 2017). This shows a strong connection in *Drosophila* models between CRs and ND, although the connection in humans is less clear.

Humans are much more complicated than simple house flies, so there is less available research as to the connection of autophagy and apoptosis with CRs and ND. MicroRNA is a small avenue that has been explored, and it has only established a tenuous relationship. A specific miRNA sequence has been noted to be involved in autophagy, "Although the actual targets of miR-30c have not been identified, a computational algorithm revealed many target genes that are involved in neuronal autophagy, mitophagy and the regulation of dopaminergic cell death" (Kinoshita et al., 2020). It is believed that this miRNA targets and downregulates *PER* expression. The same study also found that miR-19b expression, involved in protecting against neuronal apoptosis, is lowered in PD patients. The miR-19b is believed to be a regulator of *CLOCK* and *RORA*, another clock gene responsible for stabilizing the oscillation of the molecular clock. This lowered expression has been observed in patients diagnosed with REM

sleep behaviour disorder years prior to a diagnosis of PD (Kinoshita et al., 2020). Though again, this shows a correlative relationship, and it is uncertain if either of these miRNAs are fully responsible for the effects observed. It is with this too, that research begins to move outside of just the brain, as there have been many avenues outside of the CNS that have been investigated.

8 Beyond the Brain

There are other factors that have their role in the development of ND and the existence of CRs. As stated before, CRs are present throughout the body and the majority are controlled by the SCN. Some major organs have these rhythms controlled by the SCN and are thus also affected by neurodegeneration. Organelles within cells are also affected by neurodegeneration, especially within neurons outside the CNS. A heavy focus on research has existed looking into the parts of the body affected by ND and CRs that are not a direct part of the CNS. This ranges from the urinary system to the intestinal tract and down to the mitochondria of the cells. Starting off are the larger organs, the kidneys and the intestines.

Kidneys are vital to the functioning of any organism possessing them. They possess an interesting interaction with the CNS and the response to them. It is well known that kidney dysfunction can lead to toxic uremia of the blood which can have adverse effects on the nervous system. In a review, Tanaka and Okusa in 2019 cover some of the effects that chronic kidney disease and renal failure have on the nervous system. In summary, the existence of either kidney disease or renal failure increases the incidence of both stroke and dementias. Either of these can exacerbate already present conditions of ND. Also mentioned is the direct influence the pituitary

gland has over the actions of the kidneys. Considering the pituitary gland is activated by the hypothalamus and to an extent, the SCN, it is noted in the review that there is a potential link between potential degradation of the hypothalamus and continued proper functions of the kidneys (Tanaka, 2019). Moving from the kidneys, another imperative organ, the intestines and its microbiome.

Intestinal microbiota are almost akin to an organ of their own considering the great power they may hold over everything to do with digestion and excretion. Because of this, a great deal of research has been performed on them, including research into their striking diurnal rhythmicity and the changes in ND. A study by Li et al. in 2021 collected experiments and came to discuss the role of gut microbiota in CRs and how they change to AD spreading its destruction upon the nervous system. To summarize, it is not known which happens first, the change of microbiota or the development of AD, but what is known is that there is a drastic change in the circadian response of the microbiota, their overall presence and proportions of the various bacteria, and the effects that are incurred on the individual. Li found that the change in microbiota CRs leads to a definite increase in sleep loss, increased progression of AD pathology, and the diminishment of several species of gut microbiota with their own effects. Some of the studies mentioned in Li's assessment show that transplantation of certain bacteria in murine models led to the increase of cognitive function, tryptophan metabolism, and Aβ-degrading enzymes. There was also a decrease in overall Aβ levels and deposition, neuroinflammation and related cytokines, cognitive impairment, and decreased impairment of CRs (Li et al., 2021). This comprehensive study succinctly describes how important CRs are to the gut microbiome and how this microcosm drastically changes its host's response to ND. With this striking research in the small world of the

intestinal tract, more research has progressed on another small organ found inside cells, the mitochondria.

Mitochondria are often termed “the powerhouse of the cell,” and while this is not inaccurate it is not descriptive of their entire role. In ND, mitochondria have roles separate from generating vast quantities of ATP. Such roles include the storage and dissemination of calcium, apoptosis, and, in neurons, contributing to cell quality by reporting to microglia on a rhythmic basis (Cserép et al., 2020). A review by Perez Ortiz and Swerdlow explained that in mitochondria, “Decreased regional blood flow and oxygen utilization in AD brain provide more direct evidence implicating impaired mitochondrial respiration in disease” (2019). Continuing this, they add that there are specific proteins in the electron transport chain that are dysfunctional or lost, which seems to be the cause here. Considering the importance mitochondria have in the brain, decreasing the ability of mitochondria to do anything aligns with the general issue of cognitive decline in ND. Also, the decline of mitochondrial activity would contribute to the issue presented earlier of neuroinflammation. Because the mitochondria are unable to signal microglia that something is wrong, it is up to the immune system to determine if a cell needs to undergo apoptosis. Although as seen before, apoptosis is not always reliable in individuals with ND.

Conclusions

Influence over the body is something that requires precision if it is to be rhythmic and consistent. Evidently seen in the generation of circadian rhythms, it is clear that they are a sensitive, ever present system in organisms. It is clear that with its innate sensitivity, that even a

simple disease or alteration could have drastic effects on CRs, especially the SCN. Though, simple disease is not descriptive of Neurodegenerative Disease. These diseases are pervasive throughout the brains of individuals, wreaking havoc as they progress leading to many changes of not just the mind but the delicate system setup by the SCN. Disturbances in CRs can be seen years prior to any other clinical symptom of ND (Duncan et al., 2021). Though, it is only in recent years that study of this avenue has occurred, and due to the complexity of both CRs and NDs research is slow (Videnovic & Willis, 2016). Research has shown that there are many links between CRs and ND, from the well-understood sleep disturbances to lesser understood interactions with the intestines and kidneys.

Molecular disturbances are evident in the SCN with a reduction in the expression of *BMAL1*, crucial to the stability of the rhythmicity of CRs in the brain and throughout the body. Other genes have only recently been attributed to CRs in ND such as those in the rapamycin and Wnt pathways (Maiese, 2021). The loss of expression in these genes leads to many issues further along and can be partly attributed to most other interactions seen (Carter et al., 2021) such as in sleep with the obvious sleep-wake cycle disturbance. Melatonin and orexin are the two involved hormones hit most hard. Surprisingly, little research has examined glucocorticoids such as cortisol, which are not explicitly involved in sleep but do play a role due to their influence on metabolism (Carter et al., 2021, Duncan et al., 2021). Yet, there are more factors concerning sleep as AD on its own has different sleep disturbances than PD (Phan & Malkani, 2018). Regarding sleep, while it has been the most thoroughly researched avenue, the “Mechanisms underlying the connection between circadian/sleep dysregulation and neurodegeneration remain unclear …” (Mattis & Sehgal, 2016). This connection is still not clear, but the effects are all too obvious. Though, from here research progresses to less understood mechanisms.

Neuroinflammation has been noted to occur in ND patients with disturbances to the mechanisms of astrocytes and microglia. This appreciation for the relationship between ND and immunology has led to a recent avenue into circadian control of the immune system. Astrogliosis, the increased production of astrocytes, is one point of contention that has only recently been found to be increased in ND (Carter et al., 2021), and because they are the most influential factors in neuroinflammation, they have had much scrutiny in their effects. Though, they can't do everything and may leave the immune response up to autophagy and apoptosis. Of which has been noted to completely fail in most cases or exacerbate neuroinflammation (Phan & Malkani, 2018). Beyond the brain, the kidneys and intestines provide additional points of failure. The kidneys can fail due to the alterations of the SCN and thus might induce kidney disease, hurting the brain even more. Intestinal microbiota have been shown to drastically alter the course of ND pathogenesis yet are tied to the host's CRs in rodent models. All combined, it is a poor outlook.

This vicious cycle between ND and CRs is horrific to outsiders, researchers, and the afflicted. Created from this is a positive-feedback loop between the two. As ND progresses, it begins to alter the master clock and other CRs. These alterations then produce effects that can then lead to further pathogenesis of ND. While it may seem obvious, it has only been in the past year that these conclusions could begin to be more than correlational (Sharma et al, 2021). Causation is something that is being confirmed in some cases and the hope is that soon, a direct and causational connection can be established. Hence, why there needs to be further research between the two. Therapies are also something that can be looked into now as well.

Genomic engineering has been a field of therapy targeted in animal models for the past decade and has shown progress, but the applicability to humans is tenuous (Raslan & Kee, 2013). Though recently, methods to target nuclear receptors, transcription factors regulating expression of various genes, have begun in animals. This line of therapy is more viable in humans as it does not require as much genomic engineering as in other cases (Moutinho et al., 2019). Though, this line can be considered beyond invasive. Thus, less invasive therapies have been theorized and tested. Some seen before include light therapy and intermittent fasting which have been shown to be effective. Other methods include pharmacologically based methods. Lemborexant was one mentioned, however other pharmacological agents such as histamine drugs and glucocorticoids have been suggested as effective means to pursue (Colwell, 2021). Although, more research needs to be done on the efficacy of such means.

Ultimately, the vicious relationship between ND and CRs comes down to the positive-feedback loop. Understanding what other factors play into and come from this loop are necessary to treat ND. As noted by Videnovic, "... intervening with circadian function provides a novel research avenue down which new strategies for improving symptomatic treatment and slowing of the progressive degenerative process can be approached …" (2016). This statement was made six years ago, and holds truer more now than ever. This relationship is something that can lead to targeted therapies of which some have already shown to improve individual symptoms, but have yet to show any creedence towards improving pathogenesis. Therefore, research and therapies must be further developed if humanity is ever to rid itself of ND.

Abbreviations

AD - Alzheimer's Disease

CR - Circadian Rhythm

CNS - Central Nervous System

ND - Neurodegenerative Disease

PD - Parkinson's Disease

SCN - Suprachiasmatic Nucleus

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