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Association of circadian dysregulation with retinal degeneration and Alzheimer's disease: a special focus on Müller glial cells

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This review examines circadian dysregulation and the role of Müller glial cells (MGCs) in retinal degeneration associated with Alzheimer's disease (AD). Evidence supporting the interdependence of circadian rhythm (CR) disruption and AD progression is presented. Also reviewed are reports substantiating the role of MGCs in maintaining CR. Studies documenting MGC dysfunction in AD retinas suggest that gliosis, altered diurnal patterns in water homeostasis, blood-retina barrier breakdown, and impaired ocular glymphatic clearance are relevant to disease progression. Similarities between AD and various retinopathies are explored with respect to MGC physiology and CR dysfunction. We propose that MGC circadian dysregulation is diagnostically and therapeutically relevant to AD retinopathy.

KEYWORDS

Alzheimer's disease, retinal neurodegeneration, circadian rhythm, glymphatic clearance, Müller glia, optical coherence tomography (OCT)

Circadian Rhythm (CR) disruption and Alzheimer's disease (AD)

CR refers to the timing of biological processes based on a 24-h master clock. These processes are further controlled through the oscillating expression of core clock genes. Clock gene oscillations are influenced by external environmental cues. In their review, Xie et al. (2019) describes CR coordination as consisting of three pathways: the input pathway, the "master clock" pathway, and the output pathway. The input pathway senses external CR synchronizing cues. These are predominantly photic (light intensity) cues detected by the retina. Non-photic cues that regulate CR include external temperature, sustenance, and stress. Both photic and nonphotic cues are sent to the master clock—the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN communicates with peripheral tissues through endocrine and neural pathways to dictate clock gene oscillations. Two core clock transcriptional activators are *Clock* and *Bmal-1*. *Clock* and *Bmal-1* promote expression of its own repressors, such as *Per1* and *Per2*, to "reset the clock" of circadian gene expression. These gene expression oscillations modulate the sleep-wake cycle, metabolism, and temperature homeostasis, among other physiological processes.

Sleep cycle and CR disruption have been noted in both early and late stages of AD. AD patients show a significant loss of REM sleep (Prinz et al., 1982; D'Atri et al., 2021). Interestingly, Park et al. (2020) found decreased pineal gland size in patients with concomitant REM sleep behavior disorder and AD. In Apo ϵ 4 carrier patients, degraded REM sleep is associated with faster AD progression (Pyun et al., 2019; Baril et al., 2020). NREM sleep is also diminished in AD; however, the utility of K-complex density as a prognostic EEG biomarker is controversial (De Genarro et al., 2017; Reda et al., 2017; Lucey, 2020; Chylinski et al., 2022). AD patients also show alterations in diurnal temperature regulation. Some of these changes include higher proximal amplitudes of core body temperature oscillations and delayed temperature peaks (Homolak et al., 2018). Most et al. (2012) reported that daytime sleepiness in AD patients positively correlates with skin temperature of the thighs, abdomen, and infraclavicular regions. AD patients commonly exhibit reduced daytime motor activity and increased nocturnal activity (Homolak et al., 2018). This nocturnal activity is frequently associated with agitation and aggression, a behavior referred to as 'sundowning.' These temperature and sleep regulation disturbances can be linked to SCN dysfunction. AD animal models show SCN degeneration (Zhou et al., 2016; Roy et al., 2019). A human *postmortem* study of AD hypothalamus revealed neuronal loss and neurofibrillary tau tangle formation in the SCN (Stopa et al., 1999). Chronotherapeutic studies indicate that morning light therapy improves cognitive function in dementia patients by preserving CR (Mishima et al., 1994; Ancoli-Isreal et al., 2003). Clinical observations and knowledge of SCN degeneration indicate that protein accumulation in AD brains may be correlated to CR dysfunction.

One of the best-studied mechanisms indicating CR dysregulation's contribution to AD is impaired glymphatic clearance. Glymphatic clearance refers to paravascular transport of cerebrospinal fluid (CSF) which flushes out toxic solutes from neural tissues. Furtado et al. (2020) found dysregulated rhythmicity of *Bmal-1* and *Per1* in APP/PS1 mouse choroid plexus cells, which are the cells that produce CSF. Choroid plexus rhythmicity was successfully reestablished with melatonin treatment. Furtado et al. (2020) found decreased rhythmicity of murine A β -degrading proteins produced by the choroid plexus in female APP/PS1 mice. These studies suggest that choroid plexus dysfunction is related to CR disruption and perpetuates neurotoxic A β plaque formation. Glymphatic fluid transport increases dramatically during sleep. Xie et al. (2019) performed two-photon imaging studies of CSF circulation in mice and found that: a) the volume of the cerebral interstitial space increases by 60% during sleep, b) this increase is associated with CSF-interstitial fluid exchange, and c) sleep enhances glymphatic clearance of A β . Another AD biomarker affected by CR and poor glymphatic clearance is Apolipoprotein E (ApoE). Acharyar et al. (2016) found that sleep deprivation alters cerebral distribution of ApoE. Kress et al. (2018) found that global knockout of *Bmal-1* in mouse brains promotes A β plaque formation and upregulates ApoE. These findings indicate that sleep-wake cycle dysregulation hinders glymphatic clearance, thereby promoting neurotoxic protein deposition. Lax et al. (2011) found that daily exogenous melatonin administration in Sprague-Dawley rodents homozygous for the P23H-3 rhodopsin mutation delayed and temporarily reversed vision loss.

A bidirectional relationship exists between AD-associated protein aggregation and glymphatic clearance: impaired glymphatic clearance

allows toxic solutes to accumulate, and these solutes then alter cellular pathways to further impair glymphatic clearance. A β induces astrocyte gliosis, which promotes neuroinflammation (Batarseh et al., 2016). Part of the gliosis cascade is downregulated aquaporin-4 (AQP4), the water channel responsible for glymphatic fluid exchange. Decreased AQP4 expression indicates A β is not cleared from the brain, so it remains in the brain to perpetuate glial activation. Harrison et al. (2020) found that impaired tau clearance is associated with improper AQP4 polarization. Uncleared tau can activate inflammatory cascades in microglia (Joly-Amado et al., 2020; Wang et al., 2020) and epigenetically alter astrocyte-neuron-immune crosstalk (Zhou et al., 2023).

Neuroinflammation is also consistent with blood-brain barrier (BBB) disruption as a link between CR and AD. BBB disruption diminishes A β receptor-mediated transport out of the brain (Deane et al., 2008). Bellesi et al. (2017) found that chronic sleep restriction promotes astrocytic phagocytosis and microglial activation in wild-type mouse cerebral cortices, well before obvious signs of neuroinflammation appear. Kaneshwaran et al. (2019) conducted an antemortem microglial activation study of humans with and without AD. Actigraphy results indicating greater sleep fragmentation correlated with microglial aging and activation in the neocortex. These microglial changes were associated with poorer cognition test scores proximate to death in both normal and AD subjects. Gómez-González et al. (2013) found that REM sleep deprivation in rats increased BBB permeability in the whole brain. Brief periods of sleep recovery failed to recover BBB integrity in the hippocampus and cerebellum. REM sleep deprivation also increased caveolae formation and tripled the number of pinocytotic vesicles in the hippocampus. A separate REM sleep deprivation study in a rodent model by He et al. (2014) found decreased mRNA expression of several tight junction proteins. Loss of PDGFR- β is implicated in AD pathology (Janota et al., 2015; Ding et al., 2020; Smyth et al., 2022). Medina-Flores et al. (2020) found in male Wistar rats that sleep restriction downregulated PDGFR- β . CD44-mediated epithelial-immune interactions is also associated with BBB dysfunction and may have a connection to CR dysregulation. Multiple studies have explored increases in BBB permeability mediated by CD44-hyaluronan binding in various diseases (Winkler et al., 2012; Ventorp et al., 2016; Al-Ahmad et al., 2019). In AD, CD44 is thought to create a pro-inflammatory state that further promotes A β aggregation (Miners et al., 2018; Lee et al., 2023.) Sun et al. (2020) found that sleep deprivation impaired cognition, increased inflammatory cytokine production, astrocyte activation, and BBB permeability in a CD44 overexpression mouse model. These studies correlating CR alterations with BBB permeability correlate with why poor sleep increases risk of developing AD.

Müller glial cells (MGCs)

MGCs are the dominant glial cell type in vertebrate retinas and support neuron survival via extracellular environment regulation, trophic factor release, GABA and glutamate recycling, and intercellular transport facilitation (Goldman, 2014). MGC intracellular responses and pliability help maintain structural integrity in the retina (Lindqvist et al., 2010; Govetto et al., 2020). MGCs secrete angiogenesis modulators that interact with capillary

endothelial cells during blood-retina barrier formation (Abukuwa et al., 2009). MGCs have neurogenic stem cell properties akin to embryonic radial glia (Das et al., 2006) and are especially effective at regenerating rod photoreceptors (Gianelli et al., 2011). Animal studies of retinal injury responses show MGC dedifferentiation and polarized cell division to produce retinal neuron progenitors (Fischer and Reh, 2003; Lenkowski and Raymond, 2014). These progenitors migrate along MGC radial processes to replace lost neurons. MGCs mediate innate immunity through Toll-like receptors and complement protein secretion (Vecino et al., 2016). The human MGC response to retinal injury–reactive gliosis–consists of inflammation, cell proliferation, and cell hypertrophy (Goldman, 2014; Vecino et al., 2016). Although gliosis can protect retinal neurons by preventing glutamate neurotoxicity and releasing trophic factors, excessive degrees can induce retinal neurodegeneration by creating an inflammatory state.

MGCs are the only cells whose processes span the entire retinal thickness. Their cell bodies are in the inner nuclear layer. Their processes contact photoreceptors and other retinal neurons. MGCs' length aids their ability to support neurons throughout the retina and enables MGCs to guide incident light toward photoreceptors. MGCs are oriented in the direction of incoming light propagation. MGCs have higher refractive indices than surrounding cells to limit light scattering and beam widening (Franze et al., 2007; Agte et al., 2011). Extensive branching of MGC processes increases the effective refractive index. Funnel-shaped endfeet at the vitreous-retinal interface cover nearly the whole inner surface of the retina. These funnels collect incoming light entering the retina, channel toward the cell body, and deliver to a small-diameter receptive field made of photoreceptor cells (Agte et al., 2011; Szabo et al., 2022). Optical simulations by Szabo et al. (2022) illustrate how parafoveal MGCs behave like multimodal optical fibers and guide incoming light. MGCs exhibit low light collection efficiency and optical smearing when spot size exceeds endfoot diameter. However, power is still concentrated in the “core” of parafoveal MGC pillars because increased incidence angles in these areas increase the number of guided modes. Moving further away from the pupil-fovea axis, higher order modes dominate and thus become more important in determining light transmission. These findings indicate that MGCs effectively function as multimodal optical fibers that guide visible light to photoreceptors.

MGCs play a role in retinal CR synchronization. The retina sets its own tissue-specific clock gene rhythms, which are distinct from the SCN's rhythms as well as more sensitive to gene perturbation (Ruan et al., 2012). According to Xu et al. (2016), human and murine MGCs express the whole spectrum of core clock genes and exhibit *Bmal-1*-dependent diurnal oscillations independently of surrounding tissues. Ko (2020) proposed an ATP-based mechanism for how MGCs communicate with other retinal oscillators. MGCs synthesize and accumulate extracellular ATP, which can be converted to adenosine. Extracellular adenosine in the retina is elevated at nighttime; perhaps MGC synthesis of ATP coordinated by clock genes is responsible for this. Retinal adenosine regulates circadian control of rod-cone coupling and light/dark adaptation. Wei et al. (2023) found some evidence supporting this proposal in murine retinas. Wei et al. found that light upregulates the MGC deiodinase *Dio2*. This promotes thyroid hormone T3 synthesis, which then increases ATP production for cone sodium-potassium pumps during light adaptation. Interestingly, Ríos et al. (2019) identified the blue light-

sensitive pigments Opn3 and Opn5 in chicken embryo MGCs. Marchese et al. (2021) further identified that prolonged blue light exposure triggers Ca²⁺ release from endoplasmic reticula in Opn3-expressing MGCs. This observation may help explain how MGCs detect ambient light for CR control. Peak guidance of light wavelengths toward cones (center of MGC receptive field) occurs in the green-yellow range (Labin and Ribak, 2010; Labin et al., 2014). Blue-violet light leaks out of MGCs and enters nearby rods, which are more sensitive to these wavelengths. Directing certain light spectra toward cones enhances daytime vision and minimally affects nighttime vision. The oscillatory gene expression patterns, light/dark adaptation functions, and photoreceptor-like activities of MGCs make them candidate circadian synchronizers in the retina.

Key AD pathological processes manifest in the retina, which are elaborated on throughout this review. The role MGCs play in retinal neurodegeneration is not well understood. Studying MGCs and their role in CR regulation may help understanding the relationship between CR and AD progression. This review presents evidence that CR disruption occurs in AD MGCs based on a) current knowledge of AD and MGCs, and b) similarities between AD and other retinopathies. This review focuses on MGCs, but it should be noted that intrinsically photosensitive retinal ganglion cells (ipRGCs) entrain our twenty-four circadian clocks (Aranda and Schmidt, 2021). Although the morphology and function of various ipRGC subtypes in humans is under active investigation (Mure, 2021), their function in murine models (Contreras et al., 2021) has established their importance in circadian regulation and general wellbeing. Lax et al. (2019) has reviewed the connection between ipRGC alterations, neurodegenerative diseases and circadian disorders. To date, important TRP channels associated with ipRGCs (e.g., TRPC6 and TRPC7) and MGCs (e.g., TRPV4) appear to be distinct (Križaj et al., 2023). Furthermore, ipRGCs and their associated neural circuitry are believed to be important elements in the effect of light on human and murine cognition (Mahoney and Schmidt, 2024). ipRGCs are more resilient to injury than other RGCs in murine retinal damage models while number of ipRGC's declines in humans with increased age (Zhu et al., 2022). La Morgia et al. (2016) observed significant ipRGC cell death and A β accumulation in post-mortem human AD retinas, although this did not necessarily correlate with severity of sleep-wake cycle disruption. Still, this is further indication that retinal circadian dysfunction is a characteristic of AD pathology.

MGCs and ocular A β clearance

A β accumulation in AD retinas (Gupta et al., 2016; Lee et al., 2020) may prompt MGC gliosis. For example, Xu et al. (2016) found microglial-dominant gliosis and decreased MGC metabolic activity in AD *postmortem* retinas. However, most studies indicate MGC-dominant gliosis. Blanks et al. (1996) was the first to report MGC gliosis and increased number of MGC processes in AD patients. Walsh et al. (2002) found that injecting rat vitreous humors with A β induced MGC gliosis. However, the MGCs did not uptake any A β . These results were later contradicted by den Haan et al. (2018), who found A β deposits in MGCs. These contrasting findings suggest that A β acts through both direct and indirect pathways to induce MGC gliosis. Dinet et al. (2012) found that MGC gliosis diminishes their

ability to maintain water homeostasis in murine retinas. One day after subretinal injection of the highly toxic A β isoform, A β (1–42), multiple gliosis and inflammatory markers were upregulated. Three days post-injection, retinal edema and transient AQP4 upregulation were observed. Altered distribution of fluorescently labeled Kir4.1 in MGCs was also observed. Kir4.1 is an inwardly rectifying potassium channel that regulates MGC osmo-homeostasis. Kir4.1 downregulation is observed in retinal ischemia (Liu et al., 2007; Milton and Smith, 2018). In healthy control retinas, Kir4.1 was localized in the inner limiting membrane, as well as near blood vessels in the inner and outer nuclear layers. This polarization was lost in A β (1–42)-treated retinas. Similar Kir4.1 delocalization is associated with reactive gliosis in proliferative retinopathies (Bringmann et al., 2009). These findings suggest that Kir4.1 expression in MGCs may be an interesting topic of further study in relation to AD. Treating retinas with indomethacin, an anti-inflammatory drug, prior to A β (1–42) injection restored Kir4.1 distribution. However, indomethacin failed to reduce overall retinal edema. These findings suggest that retinal edema occurs independently of Kir4.1 and inflammatory processes. It should also be noted that there are conflicting studies regarding whether or not Kir4.1 dysregulation contributes to AD brain pathology (Huffels et al., 2022; Froggett et al., 2024). Still, MGC swelling and gliosis due to Kir4.1 dysregulation should be investigated in AD retinas, especially considering the independence of retinal and cerebral CR regulation. MGC structural changes are especially important to study with respect to waveguide function, which can be disrupted by either a change in shape or composition.

Kir4.1 expression is under circadian control. Studies have shown that adenosine monophosphate-activated protein kinase (Alex et al., 2020) and insulin receptor substrate-1 (Luo et al., 2019) regulate *Bmal-1* control of *KCNJ10* expression. *KCNJ10* encodes for a member of the Kir4.1 channel family. According to Hassan et al. (2017), *Bmal-1* and *KCNJ10* oscillations are in phase with each other in clock synchronized MGCs. Hassan et al. showed that in diabetic rat retinas, damped *KCNJ10* oscillations correlated with MGC swelling in diabetes. Luo et al. (2019) similarly found a loss of *Bmal-1* gene expression and Kir4.1 protein density rhythmicity that correlated with MGC swelling in diabetic mice. Luo et al. also found a loss of Kir4.1 polarization, similar to what Dinet et al. found in A β -treated murine retinas. The similarities in these findings suggest that MGCs swelling in AD retinas may be due to Kir4.1 delocalization and CR disruption. Interestingly, Alex et al. (2020) found that metformin, the gold-standard diabetes drug, corrects MGC dysfunction in diabetic mouse models by restoring Kir4.1 and *Bmal-1* rhythms. Studies that evaluate if MGCs exhibit diurnal swelling patterns in human AD retinas may be useful.

The recent discovery of an ocular glymphatic system likely connect MGCs and A β -induced retinal pathologies. Wang et al. (2020) identified a glymphatic pathway in mice for A β clearance. Fluorescently tagged A β was injected into the vitreous humor and cisterna magna, part of the glymphatic system in the brain. A β was anterogradely transported along the optic nerve, accumulates in the perivascular spaces, and then drains into dural lymphatic vessels. AQP4 facilitates clearance in MGCs and astrocytes. Impaired ocular glymphatic clearance may cause retinal edema. These processes mirror glymphatic transport in the brain.

Wang et al. (2020) found that retinal light exposure dramatically accelerated A β transport along the optic nerve. Treatment with atropine and pilocarpine to hinder the pupillary light response diminished A β transport. These results indicate that the mechanical forces created by pupillary constriction accelerates fluid flow through the ocular glymphatic system, thereby aiding A β clearance. Interestingly, AD patients exhibit a more sluggish pupillary light response (Chougule et al., 2019). One might hypothesize that this slower pupillary contraction may be related to the decrease in ocular A β glymphatic clearance. Further research might explore if increasing retinal light exposure accelerates ocular glymphatic fluid transport and A β clearance.

Interactions between MGCs and microglia are another mechanism for A β clearance. Microglia are the yolk sac-derived primary macrophages of the retina (Ginhoux et al., 2013). Hoh Kam et al. (2010) showed that A β accumulates in Bruch's membrane and the outer segments of photoreceptors in normal aging. Severe A β -induced tissue damage induces microglia proliferation and osteopontin-mediated phagocytic activity to remove A β and other mineralized debris. During reactive gliosis, MGCs and microglia amplify each other's phagocytic activities (Caicedo et al., 2005; Bringmann et al., 2006). MGCs perform osteopontin-mediated phagocytosis of large particles (Kumar et al., 2013). Interestingly, Wahl et al. (2013) found that osteopontin is upregulated in edematous MGCs in response to hypoosmolality caused by Kir4.1 downregulation. As previously mentioned, Kir4.1 downregulation has been observed in AD murine retinas. Osteopontin activates an autocrine cascade that opens potassium channels to restore osmolarity. Ample evidence indicates that A β accumulation in the retina corresponds with A β in the brain and occurs at higher levels than during normal aging (Ratnayaka et al., 2015; Lee et al., 2020). Phagocytic activity is known to contribute to retinal neurodegeneration both via direct tissue damage and release of inflammatory factors. Hence, further research might investigate a) if MGCs demonstrate osteopontin-mediated A β phagocytosis, and b) if this phagocytic activity contributes to retinal neurodegeneration in AD.

Da Mesquita et al. (2021) found in 5xFAD transgenic mice that meningeal T cells in middle-aged mice demonstrated CCR7 downregulation compared to younger mice. CCR7^{KO} mice displayed increased regulatory T cell responses, decreased CSF flow, increased A β accumulation, and poorer spatial learning and memory. This finding suggests immune mechanisms link MGCs with poor ocular A β clearance. More research is needed on this topic.

The most direct evidence for the roles of MGCs and CR dysfunction in AD retinopathy comes from Carrero et al. (2023), which found CR-dependent downregulation of aquaporins in APP/PS1 mice. AQP1, AQP4, and AQP5 were remarkably reduced in 6- and 12-month-old mice. Aquaporin downregulation positively correlated with disrupted clock gene rhythms and A β retinal accumulation. These findings strongly suggest that MGC function in ocular glymphatic clearance is impaired in AD retinopathy due to CR changes.

Optical coherence tomography (OCT) studies of MGCs

Extensive research indicates that the retina is a “window to the brain” that can serve for noninvasive study of neuropathies. The

brain and the retina share extensive neural and vascular connections. Neurodegenerative diseases, including AD, often present with retinal complications that are direct reflections of brain pathology. Both time-domain OCT (Ascaso et al., 2014) and spectral domain OCT (SD-OCT) (Chan et al., 2019; Jáñez-Escalada et al., 2019) studies reveal thinner retinal nerve fiber layers in AD and mild cognitive impairment (MCI)—the stage preceding AD symptom presentation. OCT image meta-analysis by den Haan et al. (2017) found that retinal nerve fiber layer thickness differences between AD and healthy controls are more pronounced using time domain OCT. SD-OCT is more commonly utilized due to its faster acquisition times, higher signal-to-noise ratio, and superior resolution. OCT imaging of retinal layers can give insights into AD pathology.

Previous research on the inner nuclear layer (INL), where MGC cell bodies reside, gives some clues on the relationship between neurodegenerative disease and MGCs. Many OCT studies of the INL have focused on multiple sclerosis. In multiple sclerosis patients, studies have found INL thickening (Knier et al., 2016; Balk et al., 2019) and microcystoid structures indicating edema (Gelfand et al., 2012; Lujan and Horton, 2013; Sigler, 2014). BRB dysfunction (Birch et al., 1996) and MGC gliosis (Green et al., 2010) have also been observed in multiple sclerosis retinopathies. As previously discussed, edema, BRB dysfunction, and gliosis are also features of AD retinas. Both types of changes are correlated to MGC inflammation and trauma-induced cell damage.

Another reason the INL is interesting is that most retinal circadian activity happens in this layer—not surprising given the presence of MGC cell bodies. INL thinning and nuclear loss is observed in AD patients (Koronyo et al., 2017). Baba et al. (2018) found that INL thinning occurs in *Bmal-1*^{KO} mice. Savaskan et al. (2007) found that the INL has a high concentration of MT2 melatonin receptors, and MT2 receptor expression is decreased in AD patients' retinas. The INL is also one of the retinal layers with greatest A β and phosphorylated tau deposition (Hart et al., 2016). This finding is curious considering the evidence pointing to altered CR and poor A β clearance by AD MGCs. INL thinning and edema can be further imaged and studied to understand better the relationship between AD and MGCs.

Bissig et al. (2020) found that retinal light responses can be used as a proxy for studying changes in MGCs during early AD. SD-OCT images showed that the decrease in outer nuclear layer reflectivity (ONL) upon light exposure from a white LED was more pronounced in AD retinas. AD also affected the ONL slow intrinsic optical signal. The ONL is an avascular layer containing primarily MGCs and photoreceptors. MGCs are the only cells that span the entire thickness of the retina, so light reflectivity changes in the overall retina may result from altered MGC function. To examine how MGCs affect retinal reflectivity, AD retinas were compared to neuromyelitis optica retinas. Neuromyelitis optica results from an autoimmune attack against AQP4. Neuromyelitis optica retinas showed a 1.5% reflectivity decrease—a small but significant change. This suggests that immune reactivity against AQP4 and resulting loss of water homeostasis directly alters light reflectivity. AD and neuromyelitis optica retinas showed reflectivity changes in the same layers. ONL reflectivity changes in response to optical excitation indicate altered MGC water homeostasis in AD.

SD-OCT is capable of directly detecting individual MGCs. Chung and Byeon (2017) found that MGCs surrounding the fovea appear Z-shaped. Vitreous traction distorts this Z-shape. Notably, MGC waveguide function may be of less significance in the fovea because a) the fovea almost entirely consists of cones, and b) simulations by Szabo et al. (2022) suggest that typical incidence angles and spot sizes in the retina render additional waveguide function unnecessary. Many more SD-OCT studies visualizing MGCs outside of the fovea and across all retinal layers may aid the understanding of the mechanistic links between CR, AD, and MGCs.

Similarities between retinal neurodegeneration in AD and diabetic retinopathy (DR)

Insulin resistance precedes symptom presentation in both type 2 diabetes and AD. There is a strong link between disturbed CR and insulin resistance. The SCN and peripheral tissue oscillators control glucose metabolism and secretion of metabolic hormones (Stenvers et al., 2019). Insulin-degrading enzyme breaks down A β . Hyperinsulinemia saturates insulin-degrading enzyme, thereby hindering A β clearance (Shiiki et al., 2004; Ferreira et al., 2018). Conversely, A β oligomers are thought to induce cerebral insulin resistance by causing insulin receptor internalization (Zhao et al., 2008; Bomfim et al., 2012; Molina-Fernández et al., 2022).

DR affects approximately one-third of diabetic patients worldwide (Wong and Sbanayagam, 2020). DR is one of the best studied diseases in relation to MGC pathophysiology. Because type 2 diabetes is a known risk factor for AD, exploring MGC-related retinal neurodegeneration pathways common to both may be worthwhile.

Kir4.1 dysregulation in MGCs is a striking similarity between AD and DR. As discussed previously, Dinet et al. (2012) established that altered Kir4.1 expression is not solely responsible for overall retinal edema in A β (1-42)-treated retinas. However, similarities between diabetes and AD MGCs in terms of Kir4.1 localization suggest that MGC swelling may be observed in AD retinas. Diminished Kir4.1 rhythmicity causes MGC swelling in diabetic retinas—does the same happen to AD retinas? Hassan et al. (2017) noted the greatest difference in *KCNJ10* expression between control and diabetic rat MGCs correlates with the largest degree of MGC swelling. As discussed previously, *Bmal-1* regulates *KCNJ10* diurnal rhythms. *Bmal-1* is also thought to regulate AQP4 expression. Investigating diurnal variations in MGC swelling may provide insights about the role of CR core clock genes in mediating AD retinopathy.

Similarities in mitochondrial dynamics between AD and DR

There is evidence that mitochondrial dysfunction contributes to retinal neurodegeneration in AD. Gardner et al. (2020) found that retinas of 3xTg mouse models of AD have different Scattering angle-resolved OCT (SAR-OCT) C-parameters than control retinas. OCT C-parameters represent the angular distribution of back-scattered

light. AD retina C-parameters started at lower values and decreased more slowly *versus* age-matched controls. Gardner et al. associates the difference in OCT C-parameters to A β interference in mitochondrial function and resulting neuron loss. Bevan et al. (2020) found swelling and beading of retinal ganglion cells indicative of mitochondrial collapse (Greenwood et al., 2007) in 3xTg mice. These changes corresponded to loss of dendritic spines in the hippocampus.

Gardner et al. (2019) found altered retinal OCT C-parameters in murine models due to hypoxia-induced neuron death. Mitochondrial function and hypoxia are closely linked to CR. Communication between the *Bmal-1* and *HIFa* genes modulate hypoxia signaling (Wu et al., 2017). *HIFa* upregulation during hypoxia increases mitochondrial fission, thereby promoting apoptosis (Zhang et al., 2018). Mitochondrial fission-fusion dynamics are linked to CR via circadian *DRP1* gene oscillations (Leong, 2018). Studies have indicated that hypoxia affects functioning of AD and MCI retinas. Retinal oximetry studies indicate increased arterial oxygen saturation and decreased arteriovenous difference in AD and MCI retinas (Einarsdottir et al., 2016; Olafsdottir et al., 2018), indicating poor delivery of oxygen to retinal tissues. Li et al. (2018) found that hypoxia induces A β accumulation, and consequent mitochondrial oxidative stress, in retinal ganglion cells *in vitro*. Hypoxia is implicated in tau hyperphosphorylation in APP/PS1 transgenic mice retinas (Wang et al., 2013; Zhao et al., 2013). Investigating the circadian dynamics of hypoxia-induced retinal neurodegeneration in AD may be useful.

Based on similarities with DR retinas, mitochondrial dysfunction may occur specifically within MGCs affected by AD. In animals with vascularized retinas, such as humans, mitochondria are found throughout the length of MGCs, with the highest concentration at the endfeet (Lefevre et al., 2017). In animals with non-vascularized retinas, such as cows, mitochondria localize in areas with high cytoplasmic oxygen partial pressure (Germer et al., 1998; Lefevre et al., 2017). AD and MCI retinas show decreased blood vessel density and perfusion (Cheung et al., 2014; Czako et al., 2020). Whether hypoxia and microvasculature changes alter MGC mitochondrial localization is an interesting question. Hypoxia is a known contributor to DR pathophysiology (Arden and Sivaprasad, 2011; Ramsey and Arden, 2015). In DR, mitochondrial oxidative stress induces MGC swelling (Pannicke et al., 2006; Krügel et al., 2011). Mitochondrial assays and SAR-OCT studies may determine if hypoxia contributes to the MGC swelling observed in AD retinas.

Another mitochondrial similarity between AD and DR involves thioredoxin interacting protein (TXNIP) signaling. TXNIP functions as a negative regulator of thioredoxin-1 and thioredoxin-2 to maintain a balanced redox state. Under high glucose conditions, TXNIP mediates mitophagy and oxidative stress in the retina (Devi et al., 2012; Devi et al., 2017). In AD brains, mitophagy is thought to be neuroprotective by clearing A β and tau (Fang et al., 2019; Kshirsagar et al., 2022). TXNIP is well studied for its contribution to insulin resistance in AD brains (Nasoohi, Parveen, and Ishrat, 2018). TXNIP overexpression in the retina has been implicated in increased oxidative stress and resulting neurodegeneration (Al-Gayyar et al., 2011). Lamoke et al. (2012) found increased TXNIP expression and decreased thioredoxin-1 activity in APP/PS1 transgenic mice. These changes in the thioredoxin system were associated with increased MGC GFAP expression. This finding

suggests that thioredoxin system dysfunction may explain A β -induced gliosis. In Sprague-Dawley rodent models of DR, TXNIP induces MGC autophagy and apoptosis (Ao et al., 2021). TXNIP knockdown improved the visual light response in DR mice. Whether TXNIP knockdown in AD rat models similarly enhances the visual light response is an interesting question. Enhanced TXNIP signaling on mitophagy may be one connection between insulin resistance, AD progression, and retinal gliosis.

SIRT1 downregulation is a common pathway explaining mitochondrial dysfunction in both AD brains and DR retinas. SIRT1 is a NAD-dependent deacetylase that acts on a variety of proteins to regulate gene expression, metabolism, and mitochondrial activity. In the SCN, SIRT1 binds directly to the *Bmal-1* promoter. Chang and Leonard (2013) found that SIRT1 is downregulated in aging mouse SCNs—a possible explanation for the link between AD and altered sleep-wake cycles. This explanation can be supported by Zhou et al. (2016), who found an 8 hour phase advance of SIRT1 and phase advance of *Bmal-1*, *Per-1*, and *Per-2*, in ApoE^{-/-} mouse SCNs. Zhou et al. also found decreased SCN NAD⁺/NADH ratios attributable to downregulated nicotinamide phosphoribosyltransferase because of *Bmal-1* dysfunction. SIRT1 interacts with PGC-1 α to induce neuroprotective mitogenesis in a variety of brain disorders, from Parkinson's disease to epilepsy to ischemic stroke (Chen et al., 2018; Chuang et al., 2019; Gao, Quian, and Wang, 2020; Chen et al., 2021). Jia et al. (2023) found that thioredoxin-1 promotes this process *in vitro* hippocampal neurons and *in vivo* AD rat models. Panes et al. (2020) found that SIRT1-induced mitogenesis is compromised by A β oligomers *in vitro*. SIRT1 is directly neuroprotective against tau (Min et al., 2018; Yin et al., 2022) and A β (Chen et al., 2005; Li et al., 2018). Likewise, SIRT1 mitigates MGC gliosis in DR models (Zhang et al., 2018; Kong and Zhang, 2021; Adu-Agyeiwaah, 2023). Ahmad et al. (2021) found that NADPH oxidase four induces reactive oxygen species which deplete SIRT1 *in vitro* hypoxic MGCs and *in vivo* mouse models of DR. SIRT1 control of mitochondrial dynamics and oxidative stress is a potential link between CR and AD-associated retinopathy, based on our knowledge of DR.

Melatonin neuroprotectively upregulates SIRT1 expression in AD and DR. In their review, Li et al. (2020) suggests that melatonin promotes A β degradation by ADAM10 by upregulating SIRT1 further upstream. Multiple *in vitro* and *in vivo* studies indicate an epigenetic pathway linking melatonin to SIRT1 upregulation in DR MGCs (Tu et al., 2020; Kong and Zhang, 2021; Zhang et al., 2018). In another review, Djordjevic et al. (2021) posits melatonin as an option to resolve BRB dysfunction in DR, with SIRT1 modulation as a possible therapeutic mechanism. Given the similarities between DR and AD pathologies, melatonin-SIRT1 signaling is an interesting neuroprotective topic of study in AD retinopathy. More studies investigating the neuroprotective relationship between melatonin and mitochondrial dynamics in AD retinopathy are warranted.

Similarities between retinal neurodegeneration in AD and age-related macular degeneration (AMD)

Conflicting research exists on whether a correlation exists between AMD and AD incidence rates (Williams et al., 2015;

Smilnak et al., 2019; Wen et al., 2021). However, their pathophysiology shares many similarities. A β is implicated in both, but AMD drusen formation involves non-fibrillar A β while AD recruits fibrillar A β for plaque formation. Both non-fibrillar and fibrillar A β are derived from the same nonfibrillar amyloidogenic precursor oligomers. Drusen-associated vesicles contain reactive WO antibodies, which are present in mature AD cerebral plaques (Çerman et al., 2015). MGC dysfunction is heavily involved in AMD. Pilotto et al. (2019) noted increased INL thickness owing to MGC swelling and hypertrophy as visualized by OCT studies of AMD patients. Kim et al. (2021) observed MGC activation and migration in the outer retina for 5 days following subretinal injection of human lipid hydroperoxide to induce AMD in rats. These similarities suggest that our current knowledge on AMD may help predict what happens to AD MGCs.

A BRB protein that indicates dysregulated CR in dry AMD is claudin-5. Hudson et al. (2019) identified that claudin-5 expression is regulated by *Bmal-1*. OCT imaging of claudin-5 knockdown mice showed geographical atrophy lesions resembling dry AMD. Similar outcomes were shown in AAV-mediated claudin-5 inhibition in monkey maculae. Claudin-5 is the most enriched BBB protein and is thought to be neuroprotective in AD (Greene, Hanley, and Campbell, 2019; Zhu et al., 2022). Similarities between the AD brain and dry AMD retina suggest a common CR-controlled mechanism that may present in AD retinopathy.

Aberrant VEGF expression in wet AMD indicates MGC circadian dysfunction. Intravitreal injection of A β (1–42), but not the more common and less toxic variant A β (1–40), increases VEGF in the retinal pigmented epithelium of AMD retinas (Liu et al., 2013). Antes et al. (2015) found that following laser-induced retinal injury, mice expressing human Apolipoprotein E4 (apoE4) experienced a greater increase in VEGF and resultant neovascularization than apoE3 and control mice. ApoE4 is the strongest known genetic predictor of AD. Zhou et al. (2016) found that in the SCNs of ApoE^{-/-} mice, expression of the clock genes *Bmal1*, *Per1*, and *Per2* show phase advance and greater variation compared to control mice. In hypoxic MGCs, *Per1* and *Per2* downregulation increases VEGF production. *Per1* controls *Per2* cyclical expression patterns, and *Per1* is required for maintaining CR in MGCs (Xu et al., 2016). The relationship between SCN and MGC physiology suggests that AD induces VEGF overproduction in both. Future research might explore how A β and ApoE affect MGC production of VEGF.

An interesting relationship exists between the BRB protein occludin and A β . Park et al. (2020) found retinal pathology resembling dry-type AMD in 5xFAD mouse models of AD. The breakdown of the retinal pigment epithelium was specifically associated with A β (142)-induced occludin degradation. MGCs produce matrix metalloproteinases (MMPs), namely, MMP-9, that degrade occludin. MMP-9 expression in the retina is altered in exudative AMD (Fiotti et al., 2005; Liutkeviciene et al., 2015; Lauwen et al., 2021) and DR (Kowluru, 2010) retinas. MMP-9 degradation of occludin is observed in DR. Non-exudative AMD often converts into wet-type AMD if untreated. It would be interesting to explore how A β (142) affects MMP-9 production in AD retinas, and if overproduction of MMP-9 by MGCs is a common link between AD, DR, and the transformation of dry-type into wet-type AMD.

BRB dysfunction and resulting albumin leakage are potential links between AMD and AD. Schultz et al. (2019) found increased retinal albumin in a post-mortem study of dry-type AMD retinas. Anderson et al. (2008) found that A β (1–42)-injected retinas experienced increased leakage of albumin from retinal blood vessels. It would be interesting to see if a connection exists between Kir4.1 downregulation in AD MGCs and leaked albumin. Löffler et al. (2010) reported that retinal albumin leakage induces MGC swelling in healthy rodent retina slices. Ivens et al. (2007) found that Kir4.1 was downregulated in normal rat brain slices exposed to albumin. Frigerio et al. (2012) found that intracerebroventricular injection of albumin into normal rat brains induced Kir4.1 downregulation in the hippocampus *in vivo*. How the effects of albumin on Kir4.1 would change in a diseased retina is unclear. No changes in Kir4.1 or AQP4 expression were found in a post-mortem study of AMD retinas (Madigan et al., 2014)—different from AD retinas and brains. This is quite interesting given that A β retinal accumulation occurs in both diseases. Future research might explore a) if albumin leakage from retinal microvasculature occurs in AD, and b) how albumin affects Kir4.1 expression patterns in AD.

Similarities between retinal neurodegeneration in AD and glaucoma

AD and glaucoma pathology share several similarities. Yan et al. (2017) found elevated levels of A β (1–42) and phosphorylated tau in the lateral geniculate nucleus in a Rhesus monkey model of chronic glaucoma. MGC gliosis happens in glaucoma (Graf et al., 1993; Guo et al., 2010). MGC physiology changes observed in glaucoma could give insights into what happens in AD.

Guo et al. (2010) found that chloride ion channel CLIC1 is upregulated over four-fold in a rat glaucoma model. Interestingly, Maraschi et al. (2023) found that CLIC1 activates MGCs in response to A β accumulation *in vitro*. More research is needed to understand the function of CLIC1 in healthy, glaucoma, and AD retinas.

Extracellular ATP release is a common response to mechanical stress throughout the human body, such as the pressure on MGCs resulting from increased intraocular pressure in glaucoma. Multiple studies of human glaucoma patients have indicated increased ATP release into the aqueous humor (Zhang et al., 2007; Li et al., 2018). Lu et al. (2015) found increased extracellular ATP concentration in the vitreous humors of rodent and primate models of glaucoma, as well as altered purinergic signaling. Excess ATP stimulates P2X₇ purinergic receptors (P2X₇R) on retinal ganglion cells, causing cell death. Xue et al. (2016) found that both extracellular ATP and MGC activation upregulates P2X₇R in a rodent glaucoma model. This suggests that activated MGCs may cause ganglion cell death by releasing ATP. In healthy mammalian retinas, there is bidirectional purinergic communication between MGCs and ganglion cells (Newman, 2006). ATP released by MGCs hyperpolarizes ganglion cells. ATP released by ganglion cells amplifies calcium potentials in MGCs upon flickering light exposure. In an APP/PS1 mouse model of Alzheimer's disease, retinal extracellular ATP increased in the first 14 months, then decreased to normal in the following 18 months (Perez de Lara and Pintor, 2015). Exploring

TABLE 1. Comparison of hypothesized pathological features of AD retinopathy vs other conditions as discussed in this review.

	Alzheimer's disease (AD) retinas—hypothesized	AD brains	Multiple sclerosis retinopathy	Neuromyelitis optica	Diabetic retinopathy	Age-related macular degeneration	Glaucoma	Light damage model
Direct correlation with AD brain pathology	✓	n/a			✓	✗	✗	n/a
AQP4 dysfunction	✓	✓		✓	✓	✗		✗
Kir4.1 downregulation	✓	?			✓	✗		✓
Reactive gliosis	✓	✓	✓	✓	✓	✓	✓	✓
Barrier (BRB/BBB) dysfunction	✓	✓	✓		✓	✓	✓	✓
Abeta deposits	✓	✓				✓		
Change in INL Thickness	✓ (thinning—cell death)	n/a	✓ (thickening—edema)			✓ (thickening—edema)		

how changing extracellular ATP levels in AD retinas affects MGC activity, and thereby affects the rate of retinal ganglion cell death may be beneficial. Light exposure is involved in MGC-ganglion ATP signaling, so investigating this pathway may also provide insight into how CR affects retinal ganglion death.

Interestingly, BRB disruption in glaucoma could serve a neuroprotective function. Keaney et al. (2015) found that siRNA inhibition of occludin and claudin-5, another essential blood-retina barrier (BRB) protein, in DBA/2J glaucomatous mice decreased the retina/plasma ratio of Aβ(1–40). Aβ(1–40) loss indicates diminished BRB function that may potentially enhance Aβ clearance. Enhanced Aβ(1–42) diffusion across the BRB was also observed. Exploration of whether limited BRB opening in AD retinas may be neuroprotective may be useful. A research area that has gained interest is the application of transcranial therapeutic ultrasound in AD patients for opening the BBB to accelerate Aβ clearance (Lustbader et al., 2004; Rezaei et al., 2020). Understanding more about BRB opening in glaucoma can help better understand how MGCs behave in AD.

Glaucoma has been specifically linked to non-proliferative gliosis. Inman and Horner (2007) found that reactive gliosis in DBA/2J mice was not accompanied by MGC proliferation. Bolz et al. (2018) found that DBA/2J mouse models of glaucoma did not experience a change in MGC potassium currents, which indicates that rapid proliferation does not occur. Since previous studies have found potassium current alterations in AD MGCs, suggests that gliosis in AD retinas is not limited to the non-proliferative kind. More research that quantifies the rate of MGC proliferation in AD retinas versus other retinal conditions may be beneficial.

Light-damaged animal retinas as putative models of MGC gliosis in AD

Sambamurti et al. (2007) found that prolonged exposure to both low and high-intensity light caused APP C-terminal fragments to accumulate in the vitreous humors of BALBC mice. This is the only report describing a light-induced retinal amyloidosis model. However, further development of this model may contribute to our understanding of the effects of artificial light on the retina. As discussed throughout the paper, AD is associated with CR dysfunction. Blue light is especially important for CR synchronization. Blue light daytime therapy for AD has gained increasing interest as a research topic. Blue light's negative effects on CR, however, especially regarding nighttime exposure and how that may contribute to AD is poorly understood. Such a model could be developed and studied with respect to MGC physiology.

MGC gliosis contributes to light-induced retinal degeneration characterized by CR disruption. Chan et al. (2023) observed BRB breakdown in mice after prolonged low-level blue light exposure that correlated with altered electroretinogram signals. *In vitro* culture of human retinal microvascular endothelial cells suggest these results are due to claudin-5 degradation by metalloproteinase ADAM17. They attribute ADAM17 hyperactivity to failure of ADAM17 sequestration by GNAZ, a blue-light and CR-sensitive retinal G protein. Iandiev et al. (2008) characterized rat MGC alterations due to 30 minutes of intense blue light exposure. They found increased GFAP, MGC swelling, loss of Kir4.1 polarization, and loss of AQP1. Interestingly, AQP4 was

upregulated in the outer regulatory layers, further contributing to MGC swelling. Bruera et al. (2022) found that Wistar rodent MGCs undergo marked gliosis after 6 days of low-level light exposure. This was a late response compared to the deaths of photoreceptors within the first 4 days, indicating that MGC gliosis is a secondary response. Kang et al. (2021) found bright light induced MGC gliosis in mouse retinas after only 8 hours of exposure. Subsequently, another group of mice were exposed to bright light for 7 days. These 7-day bright light-damaged MGCs exhibited miRNA profiles resembling *Dicer*^{CKO} mice. *Dicer* is an enzyme required for post-translational processing of most miRNAs. Interestingly, *Dicer*^{CKO} mice exhibit retinal layer disorganization resembling retinitis pigmentosa. Seven-day bright light-damaged and *Dicer*^{CKO} mice both feature MGC cell body migration to the outer nuclear layer. In both groups of mice, the center of the retina is thinned due to photoreceptor death. Only *Dicer*^{CKO} mice retinas also have dilated and stretched areas. Despite this difference in retinal layer structure, both sets of MGCs upregulate the *Atf3* and *Egr2* genes that normally protect from retinal stretching (Wang et al., 2013; Kole et al., 2020). Interestingly, *Atf3* and *Egr2* are upregulated even though thinning, not stretching, results from bright light damage.

Atf3 is an interesting gene to study with respect to MGCs and AD. The *Atf* gene family is thought to have a causative role in AD (Yang et al., 2023). *Atf3* is an inducible transcription factor that regulates cellular stress responses and reduces neuroinflammation. *Atf3* is not highly expressed in neurons, except during axonal regeneration. Heinrich et al. (2018) found that *Atf3* downregulates acetylcholinesterase to prevent apoptosis in the retinal inner nuclear layer (INL), the layer containing MGC cell bodies. The INL is thinned in AD patients. A β and APP accumulate in the INL of AD animal models and human patients (den Haan et al., 2018; Maran et al., 2023). Acetylcholinesterase forms complexes with A β that worsen amyloid-induced neurotoxicity (Alvarez et al., 1997; Alvarez et al., 1998; Melo et al., 2003). The neuroprotective role of MGC-expressed *Atf3* against retinal A β deposition may be a research topic that provides useful insights.

Discussion

As summarized in Table 1, MGC dysfunction is a potential link between AD, CR, and retinal neurodegeneration. CR dysregulation is directly involved in multiple pathways related to gliosis and AD. Impaired ocular A β clearance—both glymphatic and macrophagic—induces gliosis and Kir4.1 downregulation, causing hypo-osmolarity and swelling. SD-OCT imaging studies reveal INL thinning in AD retinas which can be attributed to MGC cell death. The ONLs of AD retinas exhibit altered light reflectivity responses resembling that of neuromyelitis optica, an autoimmune attack against the channel responsible for glymphatic clearance of AD-associated proteins, AQP4. Similarities in AD and DR retinas indicate that insulin resistance is common to both. Such similarities include loss of Kir4.1 rhythms and mitochondrial dysfunction. Pharmacological agents, such as metformin, that target Kir4.1 rhythmicity might be investigated for their therapeutic potential in AD retinopathy. OCT studies of

mitochondrial dysfunction in AD retinas may beneficially look for fission, altered distribution throughout the lengths of the MGC fibers, and hypoxia. Based on findings in AMD, research in AD retinas should investigate VEGF expression, occludin degradation, and albumin leakage due to BRB dysfunction. Similarities between AD and glaucoma indicate that CLIC1 expression and extracellular ATP signaling may represent directions for mechanistic research. Also, of interest may be to investigate a chronotherapeutic approach of intentionally opening the BRB to allow faster A β clearance. Because regular aging alters retinal physiology, and because multiple retinal diseases are comorbid with AD, care should be taken to ensure the observed MGC changes are specifically correlated to AD. Still, these findings indicate that a) optical studies of MGCs can reflect MCI/AD changes in the brain, and b) a chronotherapeutic approach may help resolve AD-associated retinopathy.

Author contributions

GD: Conceptualization, Investigation, Writing—original draft, Writing—review and editing. TM: Conceptualization, Supervision, Writing—review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

-/-	Double Knockout	TGF- α	Tumor Growth Factor- α
A β	Amyloid Beta	TNF- α	Tumor Necrosis Factor- α
AD	Alzheimer's Disease	VEGF	Vascular Endothelial Growth Factor
ApoE	Apolipoprotein E		
AQP4	Aquaporin-4		
ATP	Adenosine Triphosphate		
ATF3	Cyclic AMP-dependent transcription factor 3		
BBB	Blood-Brain Barrier		
BMAL1	Brain and Muscle ARNT-Like 1		
BRB	Blood retinal barrier		
CD44	Cluster of Differentiation 44		
cKO	conditional Knockout		
CLIC1	Chloride intracellular channel protein 1		
CR	Circadian Rhythm		
CSF	Cerebrospinal Fluid		
DIO2	Type II iodothyronine deiodinase		
DR	Diabetic Retinopathy		
DRP1	Dynamin-Related Protein 1		
EGFR	Epidermal Growth Factor Receptor		
EGR2	Early Growth Response 2		
HIF α	Hypoxia Inducible Factor α		
IL-1 β	Interleukin-1 β		
IL-6	Interleukin-6		
INL	Inner Nuclear Layer		
Kir4.1	Inward Rectifying Potassium Channel 4.1		
KCNJ10	ATP-Sensitive Inward Rectifier Potassium Channel 10		
MCI	Mild Cognitive Impairment		
MGC	Müller Glial Cell		
miRNA	microRNA		
NAD	Nicotinamide Adenine Dinucleotide		
NREM	Non-Rapid Eye Movement		
OCT	Optical Coherence Tomography		
ONL	Outer Nuclear Layer		
Opn3	Enkephalopsin		
Opn5	Neuropsin		
PER1,2	Period circadian regulator 1, 2		
REM	Rapid Eye Movement		
SAR-OCT	Scattering Angle Resolved Optical Coherence Tomography		
SCN	Suprachiasmatic Nuclei		
SD-OCT	Spectral Domain OCT		
SIRT1	Sirtuin-1		