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REVIEW

Circadian regulation of astrocyte function: implications for Alzheimer's disease

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Abstract

The circadian clock regulates rhythms in gene transcription that have a profound impact on cellular function, behavior, and disease. Circadian dysfunction is a symptom of aging and neurodegenerative diseases, and recent studies suggest a bidirectional relationship between impaired clock function and neurodegeneration. Glial cells possess functional circadian clocks which may serve to control glial responses to daily oscillations in brain activity, cellular stress, and metabolism. Astrocytes directly support brain function through synaptic interactions, neuronal metabolic support, neuroinflammatory regulation, and control of neurovascular coupling at blood and CSF barriers. Emerging evidence suggests that the astrocyte circadian clock may be involved in many of these processes, and that clock disruption could influence neurodegeneration by disrupting several aspects of astrocyte function. Here we review the literature surrounding circadian control of astrocyte function in health and disease, and discuss the potential implications of astrocyte clocks for neurodegeneration.

Keywords Astrocyte · Circadian rhythms · Neurodegeneration · Alzheimer's disease

Introduction

Michael von Lenhossék first coined the term "astrocyte" in 1895 as he described a "star-shaped" cell with a multitude of long, fine processes in the spinal cord. Santiago Ramon y Cajal subsequently characterized astrocytes and hypothesized that there are complex interactions between astrocytes and neurons [1]. Since then, the list of astrocyte functions in the brain has steadily grown, as has appreciation for their critical role in brain homeostasis and disease [2]. Astrocytes form a "tripartite" synapse with neurons and secrete factors that are essential for the development of functional and mature synapses [3–5]. Astrocytic processes at the synapse are also integral to the uptake and recycling of neurotransmitters, especially glutamate [6, 7]. Astrocytes are also crucial for brain glucose metabolism and supply neurons with energy via the lactate shuttle system [8, 9] and are capable of generating complex, microdomain-specific calcium transients, both spontaneous and evoked by neuronal signaling [10] or neurovascular coupling [11]. Astrocytes can also shape neuronal circuits by directly phagocytosing synapses [12] and regulating microglial phagocytosis [13]. Finally, astrocytes contribute to neuronal redox homeostasis by facilitating neuronal glutathione synthesis [14].

Aside from their roles in neuronal support and neurotransmission, astrocytes are also critically involved in the regulation of neuroinflammation. Astrocytes exhibit morphologic and transcriptional changes in response to stress, inflammation, and injury in a response termed astrogliosis [15]. Typically characterized by the upregulation and accumulation of the intermediate filament glial fibrillary acidic protein (GFAP), astrogliosis is now known to be a complex phenomenon with a spectrum of transcriptional and functional changes [15]. Exposure of astrocytes to different stimuli can induce distinct activation states that can be distinguished by specific gene expression patterns, and can be supportive or toxic to neurons [16, 17]. In the setting of injury, astrocytes can also form scars which influence the regeneration of damaged nerves [18].

A third branch of astrocyte function is to regulate the blood–brain barrier and glymphatic system. Astrocytic endfeet contact cerebral blood vessels and can modulate vasodilation in response to neuronal activity, thus mediating neurovascular coupling [19]. The "glymphatic system" refers to

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the lymphatic-like functions of astrocytes in mediating bulk fluid flow and allowing the exchange of solutes between the cerebrospinal fluid and brain parenchyma. This system provides a route for waste efflux into the periphery, and may be critical to regulating brain fluid volume and protein buildup in the context of injury and disease [20, 21]. Expression of the astrocyte water channel aquaporin-4 is required for efficient influx and efflux through the glymphatic system [22], confirming a role for astrocytes in brain waste clearance.

Thus, it is clear that astrocytes perform a number of key functions in the brain and are critical to brain health. Therefore, it is important to understand factors which influence astrocyte activation and function, as these may directly impact brain homeostatic mechanisms. As we will discuss, the circadian clock has recently emerged as a major regulator of astrocyte function.

The circadian system serves to synchronize internal physiology with the external environment and to allow tissues to anticipate time-of-day-related events, particularly the 24-h light:dark cycle of earth. The master clock of the body resides in the suprachiasmatic nucleus (SCN) of the hypothalamus and receives direct input from the retina, thereby sensing changes in light. This light input synchronizes a network of cellular clocks in the SCN, which in turn synchronizes cellular clocks throughout the body. At the molecular level, the core circadian clock found in each cell consists of a transcriptional-translational feedback loop controlled by the BHLH-PAS transcription factor BMAL1 (aka ARNTL), which heterodimerizes with CLOCK or NPAS2 proteins to bind E-Box motifs throughout the genome and drive transcription [23–25]. BMAL1/CLOCK drives the expression of several of its own negative feedback regulators, including PERIOD 1–3, CRYPTOCHROME 1 and 2, and REV-ERBα and β, which ultimately suppress BMAL1/CLOCK-mediated transcription. This cycle is tuned to a near 24-h rhythm by several layers of post-translation regulation [25]. Core clock machinery is present in nearly all cells in the body and is self-sustaining, as cells can maintain near 24-h oscillations without any external input. The circadian clock influences the expression of many genes: 3–14% of all transcripts exhibit circadian oscillation in a given tissue, and nearly 50% of all protein-coding genes are rhythmic in at least one tissue in mice. Indeed, more than 80% of protein-coding genes show rhythmicity in at least one tissue in primates [26–28]. The circadian clock modulates diverse processes including cellular metabolism, inflammation, cell cycle, and redox homeostasis, and circadian dysfunction has been implicated in dozens of disease states ranging from cancer to neurodegeneration [23, 29, 30].

In the brain, neurons and glia both inside and outside the SCN possess functioning circadian clocks, though the functions of glial clocks are less well understood [31]. Astrocytes in particular express clock genes and exhibit robust circadian clock function in cell culture and in the SCN [31–33]. We will discuss the functions of the astrocyte circadian clock as they relate to brain health, and will explore potential links between astrocyte clock function and neurodegenerative diseases.

Astrocyte circadian clocks

Time-of-day variations in GFAP distribution were first reported in the SCN of hamsters and rats [34, 35]. Subsequently, cultured mouse cortical astrocytes were noted to exhibit robust circadian oscillations in *Per2* gene expression in culture, which could be entrained by co-culture with an SCN explant [31]. Circadian gene expression rhythms in cultured astrocytes could be abrogated by deletion of *Bmal1*, *Clock*, or *Per1* and *Per2*, demonstrating reliance on the core astrocyte clock [36].

Since then, researchers have defined the role of the clock cycle in controlling glial responses to daily oscillations in neuronal activity and environmental cues. Astrocyte functions contribute to the synchrony of clock neurons and may ultimately control rhythms in a wide variety of brain functions including thermoregulation, hormonal secretion, and sleep. Work in *D. melanogaster* has helped define the need for astrocyte regulation of clock neurons and circadian behavior [37–39]. In addition, astrocyte-specific deletion of *Bmal1*, which disrupts circadian gene expression rhythms in SCN astrocytes, clearly impacts behavioral rhythms in mice [32, 33, 40]. Moreover, altering the period of the astrocyte clock via manipulation of the casein kinase 1 epsilon gene (*Csnk1e*) specifically in astrocytes alters overall SCN rhythmicity and wheel running activity in mice, further illustrating the critical role for the astrocyte clock in the control of SCN function and circadian behavior [32, 41].

The mechanism by which SCN astrocytes regulate circadian rhythms is still a matter of investigation. In general, astrocytes participate in neuromodulation by regulating extracellular glutamate, ATP, and potentially other gliotransmitters. In culture, astrocytes depend on their expression of *Clock* and *Per2* to regulate the proper expression of transporters for glutamate uptake [42]. However, while glutamate uptake does not appear to show significant time of day variation in astrocytes, glutamine synthetase, a non-neuronal enzyme necessary to replenish neurons with glutamate precursor, shows significantly reduced activity in the mouse SCN during circadian night. This suggests that astrocytes may control glutamate metabolism at different times of day [43], thus potentially regulating the availability of glutamate to neurons. Astrocyte glutamatergic regulation of SCN rhythms seems to be mediated through astrocytic glutamate release during circadian night, which signals to neurons via NMDA NR2C subunits [41]. As SCN

neurons are GABAergic, astrocyte glutamatergic stimulation of SCN neurons during circadian night may result in an overall inhibition of SCN activity, which may potentiate synchrony. Indeed, disruption of GABA signaling in the context of astrocyte-specific *Bmal1* knockout has been reported to lead to poor neuronal entrainment and behavioral arrhythmicity [40]. A recent study suggests that SCN astrocyte rhythms can drive circadian behavioral rhythms in mice in the absence of a functional neuronal clock [33]. The authors found that locomotor activity rhythms are restored in arrhythmic *Cry1/2* null mice with astrocyte-specific *Cry1* supplementation alone. In the SCN, *Per2* oscillations depend on synchronous rhythms of astrocyte glutamate release. This synchrony is accomplished across the astrocyte network by the function of connexin 43 hemichannels, which mediate paracrine release of ATP and glutamate. Thus, the astrocyte clock significantly contributes to overall SCN activity and daily behavior by regulating glutamate availability.

Importantly, dysregulation of glutamate uptake by astrocytes can lead to excitotoxic neuronal death through hyperactivation of NMDA channels. Glutamate toxicity plays a critical role in ischemic brain injury, but has also been implicated in ALS, AD, and other diseases. As astrocyte clock proteins regulate glutamate metabolism, clock disruption could potentially contribute to excitotoxicity. Indeed, neuronal susceptibility to excitotoxic death as well as the severity of ischemic stroke appear to follow circadian rhythms [44–46]. Thus, dysregulated astrocytic glutamate handling could exacerbate stroke-related and other types of injury at different times of day, though the role of astrocyte clocks in this phenomenon has not been addressed.

Astrocytes in the SCN may also utilize ATP as a gliotransmitter to help regulate circadian rhythms [36]. Cultured SCN cells, astrocytes, and the intact rat SCN all display circadian rhythms in ATP accumulation [47]. Clock gene mutations in cultured astrocytes result in blunted ATP rhythms, which appear to be dependent on intact IP3-dependent intracellular calcium signaling [36]. The variation in extracellular ATP in SCN astrocytes is antiphase with intracellular cytosolic calcium, but in phase with mitochondrial calcium [48]. However, another work has suggested calcium-independent mechanisms of circadian astrocyte ATP release through purinergic receptors [49]. Thus, the processes by which astrocytes rhythmically release ATP remain to be fully defined, but evidence is already emerging that astrocytic ATP rhythms have functional consequences. For example, astrocyte sensitivity to daily glucocorticoid oscillations allows them to contribute to pain signaling through rhythmic release of ATP onto microglial purinergic receptors [50]. Thus, daily oscillations in pain may be controlled through a rhythmic crosstalk between adrenal glucocorticoids, astrocyte ATP release, and purinergic stimulation of microglia.

Further roles for astrocyte rhythms in brain health may involve neuromodulation through mechanisms other than gliotransmission. It has been reported that glia (primarily astrocytes) show daily oscillations in structural contacts with dendrites in the SCN, in which glia tend to enwrap VIPergic dendrites during circadian day more so than night. This observation is dependent on neuronal subtype and BDNF/TrkB signaling, implying some specificity for astrocyte structural changes rather than a general feature of daily process extension and retraction [51, 52]. Thus, physical coverage of SCN synapses by astrocytic processes is plastic and may be under clock control. Considering their involvement in synaptic maintenance and pruning [12], daily interactions of astrocytes with synapses may be crucial to development and disease.

In addition, global, brain-specific, and even astrocyte-specific *Bmal1* knockout induces brain-wide astrogliosis. This glial activation seems to be under the control of the positive limb of the clock as it can be phenocopied by dual deletion of the BMAL1 binding partners *Clock* and *Npas2*, while *Per1/2* mutant mice do not exhibit gliosis [53]. Interestingly, clock control of astrocyte activation appears to be cell autonomous and regulates the ability of astrocytes to support neuronal survival in vitro [54]. BMAL1 in astrocytes appears to mediate astrocyte activation through an alteration in protein glutathionylation, though the specific pathways which are controlled by this mechanism are still unknown. The control of astrocyte activation by clock genes has not yet been evaluated in the setting of aging and neurodegenerative diseases, though it is tempting to speculate that loss of astrocytic circadian function in these settings could promote dysfunctional astrocyte activation, which could have important implications for brain health. Identification of downstream pathways mediated by the astrocyte clock, such as the aforementioned regulation of protein glutathionylation, could provide new therapeutic targets for the treatment of age-related neurodegenerative disorders.

Potential role of astrocyte circadian rhythms in neurodegenerative disease

As mentioned above, research into astrocyte circadian rhythms has almost exclusively explored their interactions with neurons in the SCN. While these studies have built a foundation for circadian regulation of brain health, they have not yet examined pathology-directed functions of glia in disease. An emerging theme in glial research has focused on the mechanisms by which these cells sense and respond to the damaged brain environment in early and chronic disease. Investigating how the clock influences astrocyte interactions with other cells and the brain parenchyma can provide clues into how the daily

time scale of cellular processes links lifestyle and environment to chronic neurodegeneration.

Inflammation and oxidative stress

It is clear that immune responses in astrocytes are under clock regulation, and in turn can regulate clock gene expression. Cytokine expression oscillates in astrocytes [55], and targeting the clock can increase astrocyte pro-inflammatory cytokine responses: *Per1* knockdown induces *Il6* and *Ccl2* in spinal astrocytes, [56], while *Bmal1* knockdown induces *Il6* and *Il33* in cortical astrocytes [54]. Conversely, cytokines may also modulate the astrocyte clock, as TNFα shifts the phase of *Per2* expression rhythms in SCN astrocytes in vitro as well as mouse behavioral rhythms in vivo [57].

Considerable evidence also implicates the circadian clock in the regulation of oxidative stress, a process critical to neurodegeneration [53, 58]. Astrocytes in general are key to mitigating neuronal oxidative stress, as they regulate neuronal glutathione levels and express redox-protective enzymes, in part via astrocytic activation of the cytoprotective Nrf2 pathway [59]. Deletion of *Bmal1* disrupts expression of antioxidant enzyme expression and increases brain oxidative damage [53]. *Bmal1* deletion also suppresses levels of protective glutathione-s-transferase enzymes in astrocytes [54]. It has been proposed that circadian oscillations in astrocytic expression of the neurotrophin receptor $p75^{NTR}$ may regulate Nrf2 signaling and antioxidant enzyme expression [60]. Clocks can also regulate mitochondria [61], a major source of oxidative stress, though this has not been demonstrated in astrocytes.

In addition, functions relevant to astrocytes, such as phagocytic capacity and cytotoxicity, have been shown to oscillate in other cell types, though circadian regulation of these functions has not been specifically tested in astrocytes [62–67]. These daily oscillations in immune and redox functions may help cells anticipate daily risk at times of maximum probability for exposure to damaging stimuli. In turn, periodic downregulation of inflammatory programs may prevent the excessive accumulation of toxic inflammatory signals such as cytokines, chemokines, ROS, and damage-associated molecular patterns. Given that *Bmal1* deletion in astrocytes significantly shifts their transcriptional and functional phenotypes, clock disruption in astrocytes could exacerbate neuroinflammation in the context of disease. Thus, circadian clock control of astrocyte inflammatory function is likely crucial in maintaining brain health and responding to neurological disease.

Protein aggregation and clearance in Alzheimer's disease

A prominent feature across neurodegenerative diseases is the accumulation of toxic protein aggregates in the brain over the course of aging. For example, Alzheimer's disease (AD) involves the synaptic release of amyloid beta (Aβ) monomers that oligomerize and eventually aggregate into extracellular plaques. The generation of plaques is thought to drive other pathologies in AD, including the hyperphosphorylation and intracellular accumulation of tau protein, synaptic loss, and eventually neurodegeneration and cognitive decline. A key feature of early AD symptoms is circadian disruption in the form of sleep fragmentation and arrhythmic activity [68–71]. Sleep/wake cycles clearly have a bidirectional relationship with Alzheimer's pathogenesis, as sleep deprivation can increase both amyloid plaque and tau pathology in transgenic mice [72–76]. AD pathology may directly influence circadian rhythms through its regulation of clock gene methylation in humans [77] as well as inducing degradation of clock proteins, resulting in a shift in body temperature and activity rhythms in AD mice [73].

A growing literature supports the notion that Aβ clearance is impaired in AD and may significantly contribute to the extracellular accumulation of plaques [78, 79]. Mechanisms for clearance of Aβ involve extracellular degradation by released enzymes, transport across the blood–brain barrier through perivascular efflux, and cellular degradation by glia [78]. Astrocytes express surface receptors, including the lipid-binding proteins LDLR and LRP1, which bind Aβ and mediate its internalization and degradation [80]. Peri-plaque astrocyte activation occurs in AD patients and animal models in conjunction with the development of Aβ pathology [81–84], likely influencing astrocyte interactions with Aβ aggregates which are critical to plaque removal [80, 85–89]. While the role of astrocyte activation in AD pathogenesis is complex, manipulating pathways of astrocyte activation and detection of Aβ alters the formation of plaques in APP/PS1 models [80, 90–93]. In addition, enhancing astrocytic Aβ uptake and degradation capacity by inducing lysosome biogenesis or expression of low-density lipoprotein receptors mitigates plaque formation [88, 89]. Furthermore, reciprocal cross talk of astrocytes and microglia can influence the phagocytic capacity of both cell types [16, 94]. While it is unknown if the circadian clock regulates expression of astrocytic proteins involved in Aβ uptake and degradation (such as LDLR, LRP1, TFEB, and APOE), circadian influences on astrocytic endocytosis and lysosomal function could impact Aβ plaque formation. Furthermore, loss of Bmal1 drives astrogliosis and impairs the support function of astrocytes, which could impart damage to surrounding neurons [54]. While the effect of astrocyte clock disruption on Aβ clearance is unknown, circadian regulation of astrocytic Aβ metabolic proteins and reactive gliosis could influence the clearance functions of astrocytes and modulate Aβ and tau accumulation in the AD brain.

Another intriguing possibility is that the astrocyte clock influences AD pathogenesis through modulation of sleep.

Sleep deprivation is known to increase levels of Aβ in the interstitial fluid of mice [72] and cerebrospinal fluid of humans [95], and to accelerate amyloid plaque accumulation in mice [72]. Sleep loss can also increase brain tau levels and accelerate tau pathology in mice [76]. Astrocytes have been strongly implicated in the regulation of sleep [96], though their circadian role in sleep regulation is not well understood. One potential link between astrocyte clocks and sleep is the astrocytic gene *Fabp7*, which encodes brain-type fatty acid binding protein. *Fabp7* exhibits strong circadian oscillation in the brain and its expression is directly controlled by the core clock in astrocytes [97, 98]. *Fabp7* is also required for normal sleep in mice and humans, as mutations in *Fabp7* in both species induce sleep fragmentation [99]. Thus, one hypothesis is that disruption of astrocyte clocks in aging or early AD could presumably lead to loss of normal circadian *Fabp7* regulation, causing fragmented sleep and increasing Aβ and tau pathology. Similar connections between genes under astrocyte clock control and AD are therefore likely to emerge with increasing interest and technological advances in glial and circadian research.

Blood–brain barrier function

Disruption in the blood–brain barrier (BBB) has been implicated in the pathogenesis of many neurologic disease states, including Alzheimer's disease [100]. Loss of BBB integrity is thought to facilitate entry of inflammatory mediators, metals, and even bacteria into the brain, leading to damage [100, 101]. Rhythms in blood–brain barrier function and the cell-type specific clocks involved have been demonstrated in *D. melanogaster*, as BBB permeability oscillates and promotes more efflux during the day [102]. This rhythmic permeability is determined by circadian communication between perineural and subperineural glia of the fly BBB, and is significant enough to promote enhanced retention and efficacy of seizure drugs at night compared to daytime treatment. It is unclear how well this translates to mammalian clocks as the fly BBB is different in cell type and structure, but clock regulation of the BBB in mammals has been proposed: brain-specific deletion of *Bmal1* causes alterations in activity and astrogliosis similar to other models of *Bmal1* knockout [53], but also causes higher brain weight, higher BBB permeability, and reduced markers of BBB integrity [103]. As BBB permeability determines CNS inflammatory status and interactions with the periphery, it will be critical to elucidate the clock-controlled functions of glia at the BBB.

Glymphatic function

An emerging player in the field of circadian astrocyte functions is the glymphatic system. Early research on the glymphatic system first reported that tracers injected into the CSF cycle through the brain parenchyma in a size-dependent manner [21]. The exchange of CSF contents with brain interstitial fluid requires the astrocytic water channel aquaporin-4 (AQP4) [22] and is proposed to utilize arterial pulsation to drive bulk flow for influx and clearance of brain solutes. Importantly, AQP4-dependent glymphatic clearance has been shown to contribute to the distribution of neurodegenerative disease-related proteins in the brain, such as amyloid beta [21, 104], tau [105], and ApoE [106]. Additionally, in AD patients global AQP4 expression is increased but its specific localization around astrocyte endfeet is decreased and inversely correlated with Braak stage [107]. Thus, while the actual mechanism of this pressure-directed fluid flow into and out of the brain remains unclear, the glymphatic system seems to have a potential role in neurodegenerative disease.

Interestingly, accumulating evidence points to a role for sleep and vigilance state in the efficiency of glymphatic flow. During natural or anesthetic-induced sleep, higher influx and efflux of CSF tracers into the brain can be achieved, possibly through an increase in the volume of interstitial space [108]. This work suggests that more efficient waste clearance may occur during sleep. Evidence for this theory has been somewhat contradictory, but appears to depend on how various experimental paradigms influence sleep state and autonomic tone. Recent work utilizing different types of anesthetics has shown that higher glymphatic influx seems to correlate with elevated delta slow-wave oscillations and lowered heart rate [109]. In addition, the choroid plexus exhibits robust rhythms in clock gene expression and may synchronize CSF production to the time of day [110]. Thus, several of the critical factors controlling glymphatic flow, including sleep, autonomic tone, and CSF production are regulated by the circadian clock [110, 111]. Moreover, AQP4 transcript appears to exhibit circadian oscillation in several tissues [112], and is increased in astrocytes following *Bmal1* deletion [54], though direct oscillation in astrocytes has not been reported to our knowledge. Circadian regulation of AQP4 expression and localization by the astrocyte clock could mediate diurnal fluxes in glymphatic flow. A loss of normal astrocytic clock function could disrupt influx/efflux rhythms, potentially leading to accumulation of toxic proteins aggregates as seen in neurodegenerative diseases. Therefore, while the role of the circadian clock in glymphatic regulation is not yet defined, it is tempting to speculate that circadian systems in the SCN or in astrocytes may influence glymphatic clearance.

Other circadian links to Aβ regulation

Astrocytes may also influence neurodegenerative disease through effects on brain metabolism. There is a clear link between neuronal activity and the development of AD [113–116]. Release of Aβ from neurons occurs in an

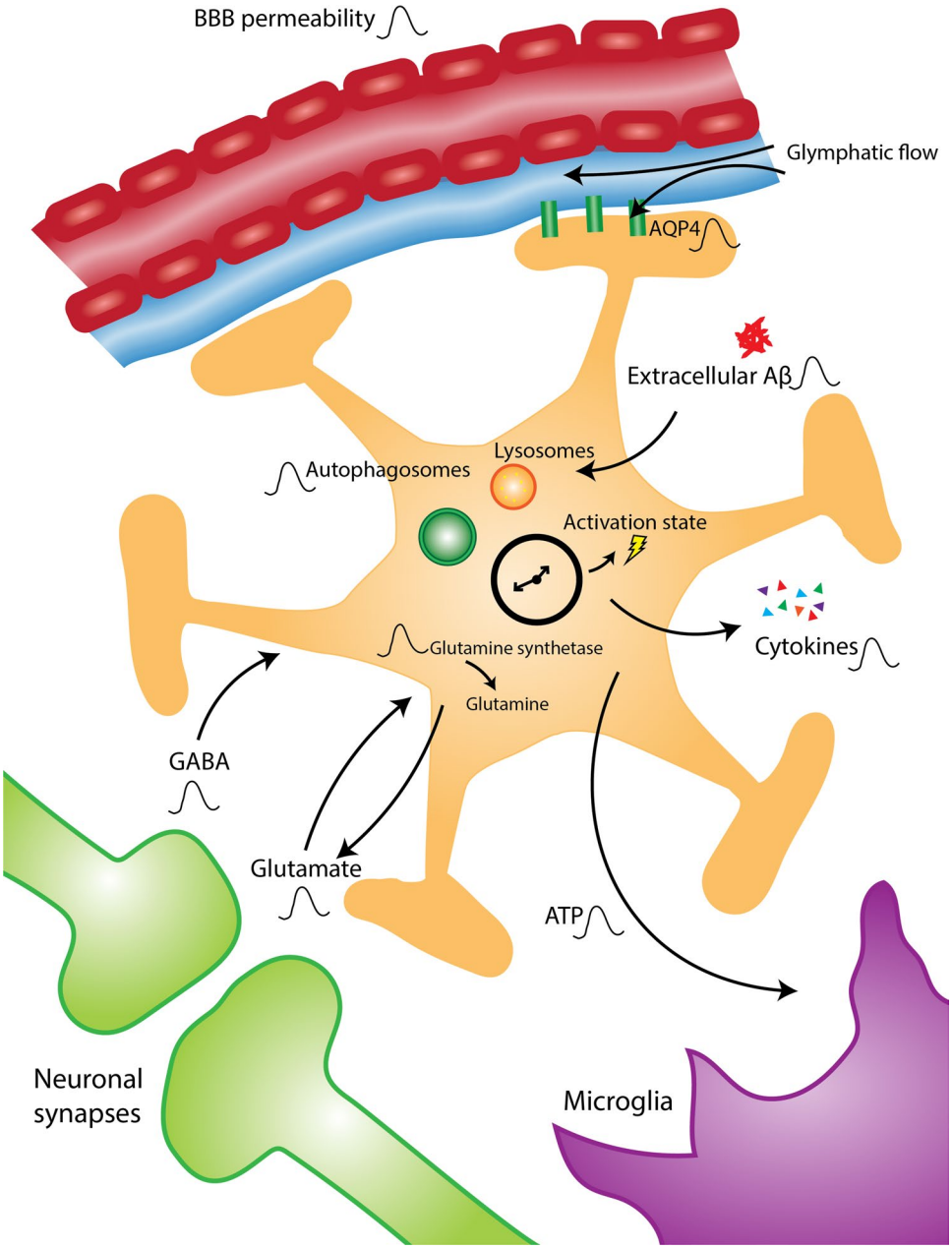

Fig. 1 Proposed influences of the astrocyte circadian clock in brain health and disease. The astrocyte circadian clock is known to control a number of important functions that oscillate with time of day, as indicated here by the oscillation symbol. Astrocytes extend their endfeet to the blood–brain barrier and regulate its permeability as well as glymphatic flow. Rhythmic AQP4 expression could influence these processes. Astrocytes modulate oscillations in extracellular levels of GABA and glutamate through modulation of transmitter uptake and metabolism, thus participating in neuronal synchrony and cellular crosstalk. Astrocyte ATP rhythms may also serve to interact with other cells in the brain such as microglia. The astrocyte clock is crucial to determining astrocyte activation state as well as rhythms in cytokine release. Finally, oscillations in the level of extracellular protein aggregates may be determined by rhythmic astrocyte uptake and degradation through clock-controlled pathways, such as autophagy

activity-dependent manner, and brain regions with high neuronal activity (such as the default-mode network of the brain) have higher amyloid plaque deposition in AD [114, 115]. Increased neuronal activity due to sleep disruption is also associated with amyloid plaque deposition [72]. As discussed above, astrocytes regulate neuronal activity and metabolism via multiple mechanisms, including the lactate shuttle. Thus, circadian astrocyte functions may regulate neuronal activity and metabolism and thus influence Aβ levels and deposition, though this has not been demonstrated.

In addition, intracellular components of astrocyte degradation machinery may also be under circadian regulation. Microglial cathepsin S expression oscillates on a circadian timescale, suggesting that the availability of lysosomal cysteine proteases is under clock control [117]. Lysosomal biogenesis by astrocytes has been shown to improve uptake and degradation of Aβ and limit plaque formation [88]. Daily rhythms in autophagy have also been observed in the mouse liver, which are disrupted in the context of inflammation altering clock gene expression [118]. Time of day analysis has revealed that autophagy substrates peaking during the day localize to the cytosol and nucleus, whereas substrates peaking during the night localize to mitochondria, the ER, and the peroxisome. Thus, the localization of autophagy machinery within a cell may itself exhibit a daily rhythm and could contribute to astrocyte degradation of Aβ or other

protein aggregates [119–121]. Future studies are needed to examine the control of protein degradation machinery by the astrocyte clock.

Conclusions

The role of astrocyte function in AD and other neurodegenerative diseases is gaining increasing attention, and the diversity of astrocytic functions in the brain provides many potential mechanisms of disease contribution. Astrocytes have robust circadian clock function, and disrupting the clock in these cells reveals striking phenotypes. We suggest a model by which the astrocyte circadian clock could influence multiple aspects of AD pathophysiology (see Fig. 1). Astrocyte clock disruption, which might occur as an effect of aging, inflammation, environment, or toxic protein aggregation, may promote plaque-related astrocyte activation and inflammatory responses, damaging neurons. Astrocyte clock dysfunction in AD may also promote Aβ and tau aggregation by disrupting the rhythmic expression of AQP4 and impairing glymphatic flow, or by decreasing the expression of proteins involved in Aβ uptake and degradation. Normal regulation of astrocytic glutamate and ATP buffering, as well as other neuronal support functions, may also be disturbed in the setting of astrocyte clock dysfunction, sensitizing neurons to other insults. Finally, loss of normal astrocyte clock influence on sleep, perhaps mediated by rhythmic *Fabp7* expression, could indirectly exacerbate inflammation, Aβ, and tau accumulation. Thus, a more detailed understanding of the many potential influences of the circadian clock on astrocyte function in both health and disease may provide new opportunities for intervention.

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Compliance with ethical standards

Conflict of interest The authors report no relevant conflicts of interest related to this work.

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