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Circadian Rhythms and Astrocytes: The Good, the Bad, and the Ugly

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Keywords

circadian clock, calcium signaling, sleep, gliotransmitter, Alzheimer's disease, glioma

Abstract

This review explores the interface between circadian timekeeping and the regulation of brain function by astrocytes. Although astrocytes regulate neuronal activity across many time domains, their cell-autonomous circadian clocks exert a particular role in controlling longer-term oscillations of brain function: the maintenance of sleep states and the circadian ordering of sleep and wakefulness. This is most evident in the central circadian pacemaker, the suprachiasmatic nucleus, where the molecular clock of astrocytes suffices to drive daily cycles of neuronal activity and behavior. In Alzheimer's disease, sleep impairments accompany cognitive decline. In mouse models of the disease, circadian disturbances accelerate astroglial activation and other brain pathologies, suggesting that daily functions in astrocytes protect neuronal homeostasis. In brain cancer, treatment in the morning has been associated with prolonged survival, and gliomas have daily rhythms in gene expression and drug sensitivity. Thus, circadian time is fast becoming critical to elucidating reciprocal astrocytic-neuronal interactions in health and disease.

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1. INTRODUCTION

1.1. The Molecular Circadian Clockwork

Circadian (from Latin *circa* and *diem*: approximately one day) rhythms are endogenously regulated daily cycles of behavior and physiology that adapt us to the solar day and night (Dunlap et al. 2004). Most obvious is the cycle of sleep and wakefulness, but this is underpinned by myriad endocrine, autonomic and metabolic rhythms that ensure that our brains and bodies are efficient 24-h machines (Reppert & Weaver 2002). The activities that the brain is prepared to execute during daytime (online sensory and motor engagement with the world in diurnal species) are necessarily very different from those for which the nighttime brain is prepared (sleep, memory consolidation, growth/repair). These daily rhythms do not require external cues to persist; generated by an internal timing mechanism, the circadian clock, they oscillate in experimental isolation, deprived of any temporal information (Czeisler & Gooley 2007). This clock entrains to daily environmental cues such that circadian time anticipates solar time. Experimental and epidemiological studies have shown that disruption of these internal daily programs, arising from shift work, genetic variation, and progressive aging and neurodegeneration, carries a heavy cost for reproductive fitness, physical well-being, cancer, and mental performance (Cederroth et al. 2019, Lee et al. 2021, Sancar & Van Gelder 2021).

The principal circadian pacemaker is the suprachiasmatic nucleus (SCN) of the hypothalamus (Hastings et al. 2018). This bilateral cluster of approximately 20,000 neurons and 2,000 glial cells flanks the third ventricle, atop the optic chiasm (**Figure 1**). Remarkably, in isolation, it generates self-sustaining 24-h cycles of metabolism, gene expression, and electrical activity and continues to oscillate with precise and high-amplitude circadian cycles indefinitely when held in organotypic slice culture. The pacemaking is so powerful that under genetic and pharmacological manipulations it can express stable periods ranging from approximately 17 to 35 h (Freeman et al. 2013, Patton et al. 2016). In vivo, this internal circadian program entrains to solar time by direct retinal

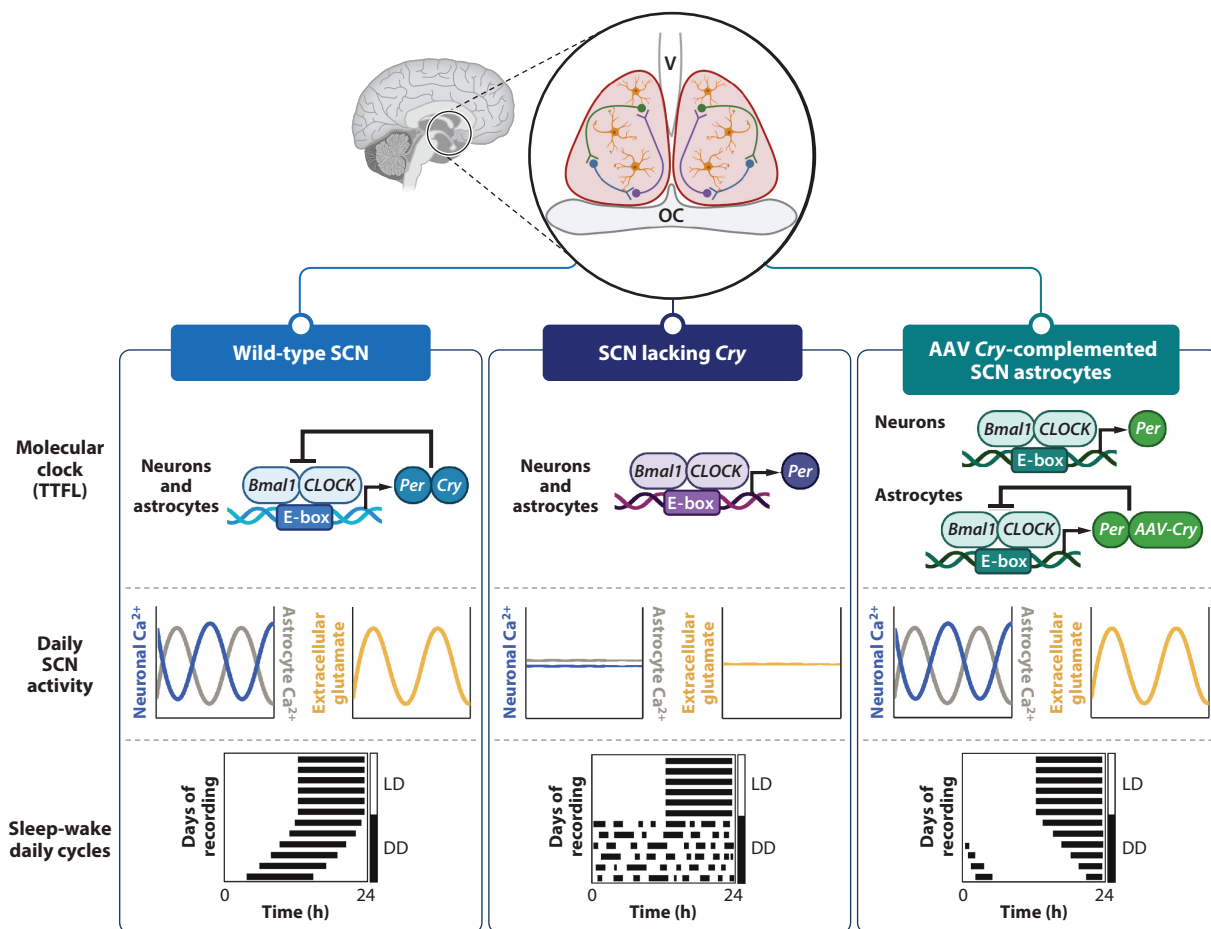


Figure 1

Astrocytes drive neuronal circadian timekeeping in the SCN and thereby control circadian behavior. (*Top*) Schematic view of localization of SCN in human hypothalamus and morphology of mouse SCN, with neuronal and astrocytic circuits. (*Bottom*) Schematic view of the molecular clock of neurons and astrocytes (*top*), circadian cycles of intracellular calcium in neurons and astrocytes and extracellular glutamate in SCN organotypic slices (*middle*), and actograms depicting rest/activity cycles of mice entrained to a LD cycle and then released into continuous darkness (DD) to monitor circadian competence. (*Left*) In wild-type mice, the clockwork is intact, calcium and glutamate rhythms are highly pronounced, and circadian control of rest/activity cycles is robust. (*Center*) In mice lacking CRY proteins, the TTFL is inactive, calcium and glutamate rhythms are lost, and rest/activity cycles lose rhythmicity. (*Right*) When CRY1 protein is restored only to SCN astrocytes in CRY-null mice, this initiates their TTFL and not only rhythms of astrocytic calcium and extracellular glutamate but also circadian rhythms of neuronal calcium. This astrocyte-dependent control of SCN neurons is sufficient to maintain circadian behavior. The more than 24-h period confirms that the behavioral rhythm is a product of the astrocyte TTFL. Abbreviations: AAV, adeno-associated virus; Bmal1, basic helix-loop-helix ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; DD, dark:dark; E-box, enhancer box; LD, light:dark; OC, optic chiasm; Per, period; SCN, suprachiasmatic nucleus; TTFL, transcription-translation feedback loop; V, third ventricle. Figure adapted from images created with BioRender.com.

afferents [the retinohypothalamic tract (RHT)] that arise from intrinsically photosensitive retinal ganglion cells that express the invertebrate-like photopigment melanopsin (Rollag et al. 2003). Through its efferent and, perhaps, paracrine connections to local hypothalamic and brainstem centers, it orchestrates body-wide neural, endocrine, and autonomic signals that coordinate in circadian time the activities of all major tissues.

The cellular basis of the mammalian circadian clockwork pivots around a transcription-translation feedback loop (TTFL) in which the positive regulators circadian locomotor cycles kaput (CLOCK) and basic helix-loop-helix ARNT-like 1 (BMAL1) heterodimerize to transactivate the expression of the *Period* (*Per1*, *Per2*) and *Cryptochrome* (*Cry1*, *Cry2*) genes via enhancer box (E-box) regulatory elements (Takahashi 2017). Over the course of the circadian day, complexes of period (PER) and cryptochrome (CRY) proteins accumulate progressively in the nucleus, recruiting accessory inhibitory transcriptional factors, with the result that *Per* and *Cry* transcription is suspended. Over the subsequent approximately 12 h of circadian night, the PER:CRY complexes are degraded until transactivation can restart on a new circadian dawn. This core loop is supported by accessory loops in which the nuclear receptors nuclear receptor subfamily 1 Nr1d1 and Nr1d2 (REV-ERB) and RAR-related orphan receptor A (RORA) are also transactivated by CLOCK:BMAL1, and they respectively negatively and positively regulate *Bmal1* expression by acting at reverb response element (RRE) regulatory sequences (Preitner et al. 2002, Sato et al. 2004, Cho et al. 2012, Abe et al. 2022). The circadian rhythms of neuronal activity and metabolism across the SCN are in turn directed by cycles of expression of clock-controlled genes (CCGs), which at their simplest are also driven by circadian transactivation of E-boxes and RREs. These CCGs include transcription factors, for example, D-box binding PAR bZIP transcription factor (DBP) (Stratmann et al. 2012) and zing finger homeobox 3 (ZFH3) (Parsons et al. 2015), which direct transcriptional cascades of downstream genes. The consequent hierarchical coordination of the circadian transcriptome of SCN cells allows the cell-autonomous TTFL to direct all aspects of SCN function (Wen et al. 2020). Of critical importance is the tight synchronization of cells across the SCN, which is maintained by neuropeptidergic signaling (Herzog et al. 2017), many elements of which are regulated by ZFH3 (Parsons et al. 2015). Daily variation of neuropeptidergic and GABAergic signals amplifies the individual cell-autonomous TTFLs and also establishes powerful coherent temporal cues that are broadcast to the body (Ono et al. 2019, Paul et al. 2020).

But circadian competence does not reside solely in the SCN. The identification of the TTFL revealed that nearly all cell types can express cell-autonomous circadian rhythms (Balsalobre et al. 1998, Yoo et al. 2004). The role of the SCN, therefore, is not to drive circadian oscillations in a passive periphery. Rather, the SCN orchestrates peripheral clocks to operate as an integrated, temporally coherent, body-wide system (Akhtar et al. 2002, Pizarro et al. 2013, Panda 2016). This principle of a coordinated network of circadian clocks applies to the TTFL of various brain regions as much as it does to the viscera (Abe et al. 2002, Zhang et al. 2014). Moreover, not only is the circadian TTFL active, inter alia, in fibroblasts, hepatocytes, lung epithelia, and neurons, but it is also active in the partners to neurons: astrocytes (Prolo et al. 2005).

1.2. Astrocytes and Neuronal Function

Astrocytes regulate a diverse range of activities in the brain. With distinctive, commonly star-shaped, morphologies, they are tiled across neural circuits with fine processes that contact thousands of synapses and are ideally placed to direct both local synaptic and circuit-level information processing (Allen & Eroglu 2017). The classical mediator for this is the tripartite synapse in which astrocytic processes envelope pre- and postsynaptic neuronal elements. By regulating the physical arrangement and chemical composition of the synaptic and perisynaptic spaces, astrocytes modulate neuronal signaling. For example, astrocyte-specific transporters for the excitatory neurotransmitter glutamate [e.g., excitatory amino acid transporter 1 (EAAT1, also called GLAST1) and EAAT2 (also called GLT)] clear glutamate from the synaptic cleft and thereby modulate the time course of excitatory signaling. Astrocytes convert glutamate to glutamine and transport glutamine to neurons for de novo synthesis of glutamate. Moreover, reciprocal chemical signaling between neurons and astrocytes is highly regulated and mediates developmental processes,

ongoing synaptic activity, and cognition (Santello et al. 2019). The expression of receptors and transporters on astrocytes confers sensitivity to neural functions, while the release by astrocytes of various gliotransmitters (e.g., serine, glutamate, and ATP) enables them to modify those functions. The mechanism of such release, especially the relative contributions of hemi-channels and other pores, and of calcium-dependent and calcium-independent vesicular release of gliotransmitters, is an area of active interest (Bazargani & Attwell 2016).

Given these intimate relationships, it is unsurprising that astrocytes exert powerful influences on behavior (Kofuji & Araque 2021, Nagai et al. 2021). For example, chemogenetic activation of astrocytes in the hippocampus enhances aversive memories, while in the hypothalamus it modulates feeding. Thus, astrocytes can influence ongoing, behaviorally relevant, local neuronal functions. But can they actually generate information in the nervous system rather than (simply) influence how neurons encode and decode existing information? In circadian rhythms and sleep, there is growing evidence that they can do just that. Time is orthogonal to the sensory world, and there are no receptors for time. Instead, circadian time is an internally generated reflection of the external world yet independent of it. In this domain, can the TTFL clocks in astrocytes generate *de novo* information?

2. CIRCADIAN COMMUNICATION AMONG NEURONS AND GLIA

2.1. Good Clocks: Astrocytes in Cortex Regulate the Sleep-Wake Cycle

Sleep is a brain-wide function involving dramatic alternations of neuronal activity between wakefulness, rapid eye movement (REM) sleep, and non-REM slow-wave sleep (SWS). It is highly circadian, coordinated by the TTFL of the SCN (Maywood et al. 2021), and is also sculpted by homeostatic need, a consequence of time spent awake (Borbely et al. 2016). Intriguingly, local metabolic mechanisms that are influenced by clock gene activity in the cerebral cortex may contribute to the homeostatic timer (Franken & Dijk 2009). Given its widespread state change across the neuraxis and prolonged time frame when compared to millisecond-scale synaptic signaling, the control of sleep provides a tempting substrate to explore astrocyte and clock interactions. Indeed, daily changes in astrocyte morphology have been associated with sleep for approximately 150 years (Tso & Herzog 2015). Spontaneous astrocytic activity changes with wakefulness and anesthesia-induced quiescence, while astrocytes, via their release of ATP, are a major source of extracellular adenosine, a potent somnogen (Hines & Haydon 2014, Frank 2019). Furthermore, astrocytes deliver lactate to the wake-promoting orexinergic neurons of the hypothalamus to maintain wakefulness (Clasadonte et al. 2017). At subcortical levels, therefore, astrocytes are potent regulators of wakefulness and sleep.

At cortical levels, astrocytic intracellular calcium ($[Ca^{2+}]_i$) signals in the mouse somatosensory cortex (Bojarskaite et al. 2020) and visual cortex (Vaidyanathan et al. 2021) exhibit distinct, state-dependent patterns across the sleep-wake cycle, being reduced during spontaneous, natural sleep, although sleep-active and wake-active astrocytes are spatially distinct. When astrocytes are genetically defective in calcium signaling, SWS is fragmented (Bojarskaite et al. 2020), and under normal conditions the transition from desynchronized to synchronized slow-wave cortical activity depends on increased astrocytic calcium and extracellular glutamate (Poskanzer & Yuste 2016). Upstream of calcium signaling, chemogenetic manipulation of G protein-coupled signaling in astrocytes not only controls $[Ca^{2+}]_i$ but also regulates sleep depth and sleep duration, emphasizing that astrocytes can control sleep state and state transitions (Vaidyanathan et al. 2021). Activation of these signaling routes by neuronally derived ligands, which facilitate astrocytic sensing of sleep state, may close an autoregulatory loop.

Daily rhythms of gene expression are intrinsic to cortical astrocytes, and their inositol trisphosphate 3 (IP_3 , or $Insp3$) signaling regulates daily release of ATP *in vitro* (Marpegan et al. 2011).

Circadian rhythms in cortical astrocytes can be entrained by daily temperature cycles or the neuropeptide vasoactive intestinal peptide (VIP) (Prolo et al. 2005, Marpegan et al. 2009), indicating that astrocytes have the potential to integrate into and influence circadian networks and sculpt behavior. In the case of SWS, the impact of astrocytes is widespread and temporally coordinated in the brain, suggesting that astrocytes do more than simply dial up or dial down ongoing neuronal computations. Rather, they impart information that changes the quality and time base of those computations. Indeed, pan-astrocytic deletion of *Bmal1*, which compromises their TTFL, suppressed global circadian gene expression in SCN, cortex, and hippocampus (Barca-Mayo et al. 2017) and is associated with impaired sleep-dependent memory and destabilized locomotor rhythms. Furthermore, wild-type cortical astrocytes synchronize the circadian TTFL of cocultured neurons, whereas small interfering RNA-mediated knockdown of *Bmal1* in the astrocytes prevents this. Signaling via extracellular GABA, but not glutamate, mediates this circadian synchronization, and in *Bmal1*-deleted mice the cortical expression of GABA transporters (GAT1, GAT3) is downregulated and extracellular levels of GABA elevated, presumably compromising the proposed astrocyte-to-neuron synchronization. Consistent with this interpretation, chronic treatment with GABA antagonists rescued the memory and behavioral phenotypes. Because the loss of *Bmal1* is pan-astrocytic, the relative contributions of SCN and cortical cells to these phenotypes are not readily attributable, nor are the relative roles of *Bmal1*- versus circadian-dependent functions in astrocytes for cortical neurotransmission, sleep, and other behaviors. Nevertheless, these results show how circadian information generated by astrocytes is conveyed to neurons to direct whole-animal behavior.

2.2. Astrocytes in SCN Regulate Circadian Timekeeping

The autonomous timekeeping of the SCN provides an ideal opportunity to dissect the relative contributions of neurons and astrocytes to daily behaviors. Early indications that SCN astrocytes have clock-like properties came from the observation that the distribution of glial fibrillary acidic protein (GFAP)-immunoreactive processes in the rodent SCN is more extensive during circadian day (Serviere & Lavielle 1996). Given that SCN neurons are metabolically most active at that phase, these changes could be triggered by neuronal cues, or they may be directed by an autonomous clock within the astrocytes. The observation of autonomous TTFL activity in cortical astrocytes supports the latter (Prolo et al. 2005). More recently, intersectional genetic approaches have revealed TTFL activity in SCN astrocytes (Brancaccio et al. 2017, Tso et al. 2017). An intriguing observation is that peak circadian *Cry1* expression in astrocytes is phase delayed by approximately 7 h relative to its peak in SCN neurons (Brancaccio et al. 2019). A comparably dramatic difference is seen in $[Ca^{2+}]_i$, which peaks in SCN neurons in the middle of circadian day, when neuronal firing is maximal (Brancaccio et al. 2013), but in the middle of circadian night in SCN astrocytes, during neuronal quiescence (Brancaccio et al. 2017). This circadian variation is evident as strongly in astrocytic processes as it is in cell bodies and so would be expected to modulate astrocytic signaling to target cells (Bazargani & Attwell 2016). Such circadian modulation of $[Ca^{2+}]_i$ presents a new, longer-term layer of complexity that awaits examination in astrocytes of other brain regions (Khakh & Sofroniew 2015).

How important is astrocytic competence for SCN timekeeping? Treatment with fluorocitrate, an astrocyte-specific metabolic toxin (Swanson & Graham 1994), reversibly reduces the amplitude of the astrocytic $[Ca^{2+}]_i$ rhythm in mouse SCN slices and reduces the amplitude of TTFL circadian gene expression and circuit-level interneuronal synchrony (Patton et al. 2022), probably by disrupting neuronal electrical activity rhythms (Prosser et al. 1994). This loss of SCN daily rhythms highlights the importance of metabolic competence of astrocytes for SCN timekeeping,

but what of the TTFL of astrocytes: Can their cell-autonomous clock direct SCN timekeeping? CRISPR-mediated deletion of *Bmal1* in astrocytes does not ablate the SCN's TTFL nor in vivo circadian behavior [consistent with the effect of *GLAST1*-mediated deletion of *Bmal1* (Barca-Mayo et al. 2017)], but it does lengthen the circadian period of the SCN and locomotor activity by approximately 0.5 h (Tso et al. 2017). This ability of SCN astrocytes to act as pacemakers, that is, to define the ensemble period of the SCN, is even more pronounced when the gain-of-function *Tau* allele of the kinase CK1 ϵ (*CK1 ϵ ^{Tau}*) is deleted in them. The mutant enzyme enhances the degradation of PER proteins and so accelerates the TTFL to approximately 20 h in homozygous mice, but deletion of the mutant allele causes the TTFL and circadian behavior to revert to wild-type, approximately 24-h, periods (Meng et al. 2008). Using genomic intersections or AAV vectors, recombinase-mediated deletion of *CK1 ϵ ^{Tau}* from SCN astrocytes lengthens the period of circadian behavior of mutant mice: an effect comparable to that following neuronally specific ablation of *CK1 ϵ ^{Tau}* (Brancaccio et al. 2017, Tso et al. 2017). Moreover, an equivalent lengthening of SCN period occurs ex vivo in slices. Thus, a slow TTFL in SCN astrocytes imposes its cell-autonomous period on circadian behavior: Information generated cell-autonomously in astrocytes is conveyed to, and directs the activity of, associated neuronal circuits.

Determination of ensemble period by astrocytes can also be observed in the SCN slice following genetic complementation. An SCN lacking *Cry1* exhibits short-period TTFL rhythms (~22 h), while AAV-mediated local expression of *Cry1* in either neurons or astrocytes rescues this phenotype to equal degree, establishing approximately 24-h periods. Notably, astrocytes take twice as long to achieve the steady state (Patton et al. 2022). In a long-period (~25.5-h), *Cry2*-null SCN, AAV-mediated expression of *Cry2* in neurons accelerates the period to approximately 24 h, whereas *Cry2* expression in astrocytes is less potent, accelerating the ensemble period by approximately 0.5 h, and again, taking longer than neurons. This presumably reflects delays associated with astrocyte-to-neuron signaling that are bypassed by direct complementation of neurons.

Perhaps the most dramatic demonstration of the circadian role of SCN astrocytes is the initiation of de novo oscillation in arrhythmic SCN and mice lacking both *Cry1* and *Cry2*. Expression of *Cry1* in neurons is known to start TTFL molecular cycles in slices and circadian rest-activity behavior in mice (Maywood et al. 2018). Surprisingly, however, complementation of *Cry* deficiency exclusively in SCN astrocytes initiates TTFL cycles and circadian behavior, albeit taking longer to reach steady state (Brancaccio et al. 2019, Patton et al. 2022). The mediation of these effects centers on the ability of *Cry1*-expressing astrocytes to drive circadian cycles of neuronal activity, as reported by rhythmic $[Ca^{2+}]_i$ levels (Brancaccio et al. 2019). Furthermore, the $[Ca^{2+}]_i$ and PER2-reported TTFL rhythms are driven in the correct phase relationship, even though the neurons do not contain any *Cry* proteins. Thus, cues that are under the control of the cell-autonomous clock of astrocytes are able to convey unique time-of-circadian day information to neurons and to maintain appropriate circadian control over SCN neuronal function, including signaling to its behaviorally relevant targets.

2.3. Signaling Circadian Time from SCN Astrocytes to Neurons

Synaptic glutamatergic signaling in the SCN mediates photic entrainment by RHT terminals (Morin & Allen 2006) on neurons expressing VIP, gastrin-releasing peptide (GRP), and AMPA- and *N*-methyl-D-aspartate (NMDA)-type (NR1, NR2A, NR2B) ionotropic glutamate receptors. Light-induced release of glutamate by RHT terminals during circadian night, when SCN neurons are quiescent, triggers electrical activity and raises $[Ca^{2+}]_i$ (Jones et al. 2018), which in turn triggers *Per* gene expression and thereby resets the phase of their TTFL (Shigeyoshi et al. 1997). Consequent VIP- and GRP-mediated signals reset the TTFLs of the surrounding SCN. These

glutamate- and peptide-induced changes are accompanied by extensive changes in gene expression across all parts of the SCN, in both neurons and astrocytes, that accommodate cell-autonomous and circuit-level readjustments to solar time (Hamnett et al. 2019, Xu et al. 2021).

Separately from retinal entrainment, SCN slices exhibit daily rhythms in extracellular glutamate concentrations ($[\text{Glu}^-]_e$), detectable by liquid chromatography or with the fluorescent reporter iGluSnFR (Shinohara et al. 2000, Brancaccio et al. 2017, Marvin et al. 2018). Intriguingly, $[\text{Glu}^-]_e$ peaks at night and has a broad wave form, such that it is superimposable on the circadian cycle of astrocytic $[\text{Ca}^{2+}]_i$, raising the possibility that it is controlled by SCN astrocytes. Indeed, pharmacological inhibition of the astrocyte-specific enzyme glutamine synthase elevates $[\text{Glu}^-]_e$, consistent with overspill of accumulated intracellular astrocytic glutamate. Moreover, in a medium lacking exogenous sources of glutamate, the $[\text{Glu}^-]_e$ rhythm persists, and given that neurons are unable to synthesize glutamate autonomously, it most likely arises from astrocytes. Consistent with this, caspase-mediated ablation of astrocytes causes $[\text{Glu}^-]_e$ to fall, whereas $[\text{Glu}^-]_e$ rises sharply after neuronal ablation. Moreover, in *Cry*-deficient SCN, $[\text{Glu}^-]_e$ is not rhythmic, but AAV-mediated genetic complementation of *Cry1* in astrocytes suffices to initiate circadian cycles (Brancaccio et al. 2019).

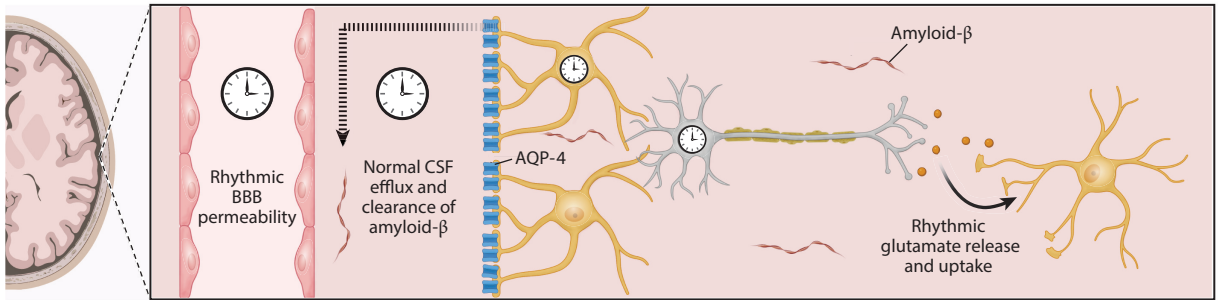
These findings support a model in which astrocytes are the source of $[\text{Glu}^-]_e$ and neurons (and possibly astrocytes) take it up. Consistent with this, a cell-permeant inhibitor of connexin 43, a component of astrocytic hemichannels, disrupts SCN $[\text{Glu}^-]_e$ rhythms (Brancaccio et al. 2019). In addition, whereas specific blockade of glial EAAT1 and 2 has a limited effect in SCN slices, their joint inhibition with the neuronal EAAT3 reversibly elevates $[\text{Glu}^-]_e$. In all cases, elevation of $[\text{Glu}^-]_e$ is associated with damping and desynchronization of TTFL rhythms. So how is $[\text{Glu}^-]_e$ sensed by SCN neurons? Blockade of NR2A and NR2B subunits, the mediators of glutamatergic retinal entrainment, does not affect the SCN's TTFL (Brancaccio et al. 2017). The dorsal SCN, however, expresses NR2C subunits, and treatment with an NR2C antagonist rapidly and reversibly damps TTFL rhythms, suggesting that dorsally expressed NMDA receptors (NMDARs) containing NR2C subunits are the target of $[\text{Glu}^-]_e$. But how might the nocturnal elevation of an excitatory transmitter be coincident with neuronal quiescence? One model is that the NR2C-containing NMDARs are presynaptic on dorsal GABAergic neurons, and $[\text{Glu}^-]_e$ acts on them to increase GABA release into the SCN by depolarizing the terminals, independent of neuronal action potential firing. Consistent with this, presynaptic $[\text{Ca}^{2+}]_i$ is elevated at night, when it falls in neuronal cell bodies, and inhibition of NR2C causes $[\text{Ca}^{2+}]_i$ in cell bodies and terminals to rise and fall, respectively. Furthermore, blockade of NR2C does not have an effect on neurons in circadian day, but during circadian night it depolarizes them, consistent with their release from the proposed tonic inhibitory tone (Brancaccio et al. 2017). If the model is correct, the astrocytic daily cycle facilitates neuronal firing in the day (low $[\text{Glu}^-]_e$) and sustained neuronal quiescence at night (high $[\text{Glu}^-]_e$), suggesting that coherent self-sustained circadian oscillations in the SCN are best understood as an emergent property from the timed interplay between neuronal and astrocytic activities rather than being purely intrinsic to neurons.

3. AGING CHANGES CIRCADIAN RHYTHMS IN NEURONS AND GLIA

3.1. Bad Clocks: Circadian Timekeeping in Aging and Neurodegeneration

Given that circadian and astrocyte interactions sustain health, their disruption has been examined in healthy aging and disease (Figure 2). Circadian functions and sleep are naturally weakened by aging (Acosta-Rodriguez et al. 2021) and disrupted in several chronic neurodegenerative conditions, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Leng et al. 2019, Hoyt & Obrietan 2022, Hunt et al. 2022, Nassan & Videnovic 2022).

Healthy brain



Alzheimer's disease

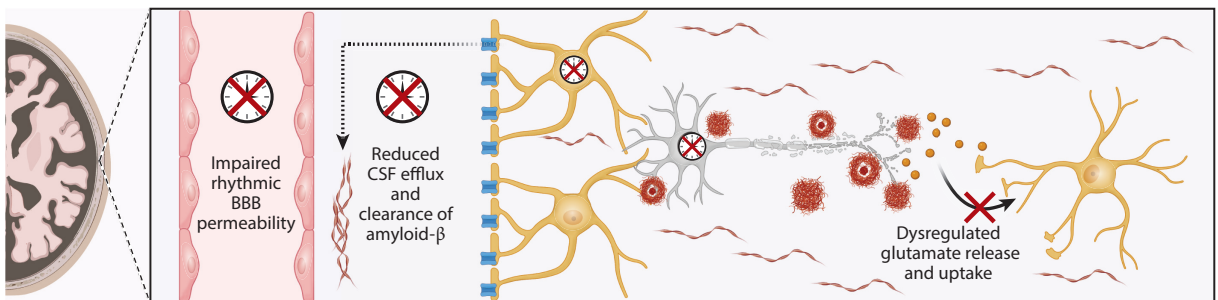


Figure 2

Disruption of circadian clocks contributes to aging and neurodegeneration. Weakening of astrocyte circadian timekeeping can impair blood-brain permeability, extracellular glutamate regulation, and clearance of metabolites such as amyloid- β . Understanding how disruption of daily rhythms in sleep and other behaviors increases the risk for neurodegenerative diseases could help identify novel therapeutic targets that could restore healthy daily rhythms in the brain. Abbreviations: AQP-4, aquaporin 4; BBB, blood-brain barrier; CSF, cerebrospinal fluid. Figure adapted from images created with BioRender.com.

The specific behavioral, circuit, and molecular signatures of circadian disruption that accompany pathology vary in a disease- and stage-specific manner. The SCN, for example, shows no protein aggregates or neuronal loss in HD, although the fractions of cells expressing arginine vasopressin (AVP) and VIP are altered. In PD, mild to moderate Lewy body pathology is commonly present within the nucleus (De Pablo-Fernández et al. 2018), whereas in AD, its involvement is conspicuous, including amyloid- β (A β) plaque deposition, hyperphosphorylated tau neurofibrillary tangles, neuronal loss, altered astrocyte-to-neuron ratios, and astrogliosis (Swaab et al. 1985, Stopa et al. 1999, Harper et al. 2008). The degree of circadian alterations largely correlates with the extent of SCN pathology in these diseases. Circadian disruption is only detectable during symptomatic stages in both HD (Shirbin et al. 2013, Kalliolia et al. 2015) and PD (Aziz et al. 2011a,b; Breen et al. 2014, Videnovic et al. 2014), whereas altered rest-activity cycles are detected early in preclinical AD, up to 15 years before disease onset (Hatfield et al. 2004, Tranah et al. 2011, Li et al. 2020), and specifically associated with increased risk of developing the disease. Moreover, in preclinical AD, amyloid deposition is already present in hippocampal and cortical brain areas in people showing altered rest-activity cycles (Musiek et al. 2018). Thus, disruption of timekeeping mechanisms in the SCN and other brain areas may contribute to early disease progression. We shall focus, therefore, on AD to explore the interplay between astrocyte circadian timekeeping and disease.

3.2. Disrupted Astrocyte Timekeeping as a Mediator of Early Vulnerability to Alzheimer's Disease

AD is likely caused by a combination of age-related changes, intertwined with genetic, environmental, and lifestyle components. The molecular and cellular path(s) leading to the extensive neuronal loss typical of AD is not fully understood, but the accumulation of misfolded neurotoxic proteinaceous aggregates, including A β plaques and tau tangles, is diagnostic. That A β plays a key early role is indicated by inherited causative mutations that increase A β in familial AD, while very recently, treatment with the anti-A β protofibril antibody lecanemab was reported to reduce amyloidosis in AD patients (Clarity AD trial, NCT03887455). In such late-onset sporadic cases, however, no mutations occur in the A β -processing genes, and so glial cellular responses to A β accumulation appear to be critical for pathology progression (De Strooper & Karran 2016). Indeed, astrocytes mediate key housekeeping functions that are disrupted by early AD pathology. These include neurotransmitter/metabolite uptake and clearance, interstitial space regulation, regulation of inflammation and redox states, and modulation of the blood-brain barrier (BBB) (Phatnani & Maniatis 2015). Disrupted timekeeping in astrocytes therefore has the potential to increase early vulnerability to AD (Brancaccio et al. 2021). Nevertheless, understanding in this area is still fragmented and largely based on evidence (summarized below) from mouse studies that model increased amyloidosis, not AD proper.

A β and tau levels in the brain undergo strong daily oscillations, which are disrupted by sleep deprivation in both mice and humans, thus suggesting that sleep-wake dysregulation may provide a mechanistic link between disrupted daily cycles and early neurodegenerative processes (Kang et al. 2009, Holth et al. 2019). Ablation of *Bmal1* or its partners *Npas2* and *Clock* causes age-dependent astrogliosis and pervasive brain inflammation in mice, accompanied by degeneration of presynaptic terminals and diminished cortical connectivity (Musiek et al. 2013). These genetic abrogations of circadian function provide proof-of-principle that disrupted clocks could promote early neurodegenerative processes by creating a widespread proinflammatory phenotype. In a more direct test for early involvement of circadian clocks in AD-like pathology, deletion of *Bmal1* in the brains of APPS1-21 transgenic mice carrying mutations causative of familial AD in the *APP* (KM670/671NL) and *Presenilin 1* genes (L166P) reduced daily oscillations of soluble A β (Kang et al. 2009) and increased plaque deposition in the hippocampus. Importantly, these effects were absent if *Bmal1* remained in the SCN or was ablated only in the hippocampus (Kress et al. 2018), consistent with the view that disrupted central timekeeping can accelerate the pathogenesis of AD. A cell-autonomous role of disrupted astrocyte timekeeping in establishing a proinflammatory AD-prone phenotype appears likely, as astrocyte-specific ablation of *Bmal1* also caused extensive astrogliosis in vivo and neuronal death in culture. Moreover, expression of proinflammatory proteins associated with accelerated AD progression is transcriptionally modulated by the molecular clockwork in astrocytes (Lananna et al. 2020). Nevertheless, whereas astrocytic ablation of *Bmal1* in amyloidosis models (*APP/PS1-21* and *APP^{NL-G-F}*) carrying the KM670/671NL, I716F, and E693G *APP* gene mutations (Saito et al. 2014) altered transcriptional patterns of genes involved in A β accumulation and degradation and triggered astrogliosis, it did not affect plaque deposition or worsen pathology (McKee et al. 2022). This finding is in contrast to brain-wide *Bmal1*-null, amyloid-prone mice (*APP/PS1-21* background) (Kress et al. 2018), suggesting that the observed increase in amyloid deposition requires key contributions from both astrocytes and neurons.

Findings from mouse models thus indicate that genetic disruption of the astrocytic clockwork alters the expression of genes involved in amyloid production and clearance and worsens the inflammatory responses and synaptic dysfunction observed in early AD pathology. This increased

neuroinflammation is consistent with the detection of alterations of rest-activity cycles in pre-clinical AD, accompanied by the accumulation of proteotoxic proteins, including amyloid and tau (Musiek et al. 2018). Several additional molecules that are produced and cleared by astrocytes, including neurotransmitters (e.g., glutamate and GABA) and proinflammatory cytokines [e.g., tumor necrosis factor alpha (TNF α), prostaglandins, IL-6] (Cuddapah et al. 2019), undergo daily oscillations in the brain and are dysregulated in AD pathology. Given that astrocytes regulate processes that maintain homeostasis of brain solutes via neuro-gliotransmitter uptake and recycling, regulation of BBB permeability, and bulk blood flow promotion via the glymphatic system (Hablitz & Nedergaard 2021), circadian disruption interfering with such processes may lead to the accumulation of toxic brain waste and accelerate pathology by several parallel pathways (Hablitz et al. 2020).

3.3. Mechanisms: Astrocytes and Neurodegeneration

As noted, astrocytes control the uptake and recycling of neurotransmitters and gliotransmitters following synaptic activity, and astrocytic EAATs are rhythmically expressed in the SCN and disrupted in clock mutants (Spanagel et al. 2005). EAAT activity is necessary to preserve circadian oscillations of extracellular glutamate in SCN slices. For example, the glutamate uptake blocker DL-threo- β -benzyloxyaspartate (DL-TBOA) raises interstitial glutamate levels, increases intracellular neuronal calcium and voltage, and desynchronizes the SCN circuit (Brancaccio et al. 2017). Dysregulation of glutamate signaling is an early event in AD pathogenesis, potentially triggering maladaptive brain circuit plasticity and excitotoxic responses (Esposito et al. 2013), and may thus constitute a mechanistic link between early circadian disruption and pathology, potentially involving the SCN. More generally, astrocytes are critical in maintaining intertwined cycles of glutamate, GABA, and glutamine release and uptake, which are sensitive to astrocyte metabolic state and are heavily impaired in AD (Andersen et al. 2022). Early clock disruption affecting astrocyte metabolism may thereby have profound implications for the regulation of these rhythms and susceptibility to neurodegeneration.

Astrocytes also regulate brain solutes by their modulation of entry into and exit from the brain at the BBB interface. The BBB is a highly specialized structure directing the distribution of solutes into the brain from the general circulation. Its (im)permeability results from the concerted activities of astrocytes alongside endothelial cells and pericytes, which are also circadian (Cuddapah et al. 2019). Disruption of the molecular clockwork impairs rhythmic permeability of the BBB in mice and humans, elicits astrogliosis, and alters overall permeability via the pericytes and endothelia (Nakazato et al. 2017, Zhang et al. 2021). The effects of astrocyte-specific manipulations in mammals, however, await clarification. Astrocytes are also important in clearing solutes from the interstitial brain space via the glymphatic system, the perivascular space running alongside blood vessels (Hablitz & Nedergaard 2021). Glymphatic activity is modulated by sleep (Iliff et al. 2012, Xie et al. 2013) and is underpinned by the expression of aquaporin 4 (AQP-4) in the astrocyte end feet. Disruption of AQP-4 reduces CSF influx and clearance of A β and tau and increases pathology (Iliff et al. 2012, 2014). Moreover, solute clearance and AQP-4 localization are circadian, persisting in free-running conditions (Hablitz et al. 2020), and the scale of the physiological variation in interstitial space volume mediated by AQP-4 is comparable to the effects observed when AQP-4 is deleted. It is likely, therefore, that circadian and sleep disruption affecting astrocytes may have a deleterious effect on AQP-4 activity and clearance of solutes via the glymphatic system and/or breakdown of BBB integrity.

In conclusion, epidemiological and clinical evidence supports the view that “bad clocks” are associated with a heightened risk of developing neurodegenerative diseases, especially AD. Clock gene ablation in mice provides proof of principle that disrupted astrocyte timekeeping may play

a critical role in mediating early vulnerability. Consistent with this, artificially imposed 20-h light-dark cycles, which desynchronize circadian clocks without genetically impairing them, also produce astrogliosis in the mouse brain (Lananna et al. 2018). But there are caveats before translating these findings to human disease. First, current data are largely based on the deletion of *Bmal1* and await corroboration by deletion of alternative TTFL components to exclude *Bmal1*-specific rather than clock-specific involvement. Second, while mouse models of circadian disruption provide critical proof of principle of a direct connection between disrupted clocks and neurodegenerative processes, genetic mutations of circadian clocks in human populations are very rare and unlikely to play a significant part in disease prevalence. Lifestyle-dependent chronodisruption (e.g., social jet lag, shift-work patterns) is, however, extensive in modern society and much more likely to trigger circadian disruption in the general population. Exploring the effects of such factors should strengthen the case for a causal connection between disrupted astrocyte timekeeping and AD progression.

4. CIRCADIAN RHYTHMS IN BRAIN CANCER

4.1. Ugly Clocks: Daily Rhythms in Gliomas

The diverse roles of daily rhythms in astrocytes may inform our understanding of brain cancer progression and treatment (**Figure 3**). In the context of gliomas, we postulate that, in contrast to the loss of daily rhythms associated with neurodegenerative disease, gliomas may accelerate their growth by integrating into functional circadian networks. Cancer involves uncontrolled growth and spread of cells that have acquired mutations as stem or precursor cells, recapitulating and

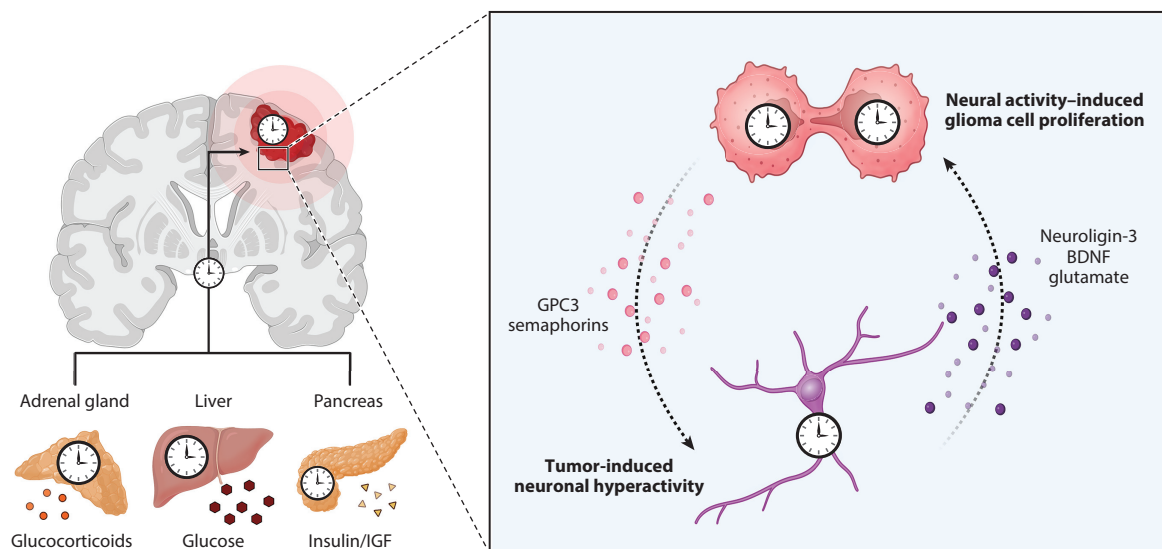


Figure 3

Daily circadian signals can act as mitogens to drive glioma progression from the periphery to the tumor microenvironment. (*Left*) Daily signals that synchronize circadian rhythms in peripheral clocks, including glucocorticoids, glucose, and insulin/insulin-like growth factor (IGF), are potential candidates in synchronizing circadian rhythms in gliomas and promoting tumorigenesis on a daily timescale. (*Right*) In the tumor microenvironment, cross talk between gliomas and neurons drives tumor progression by secretion of glioma- and neuronal-derived mitogens such as neuroligin-3, glutamate, brain-derived neurotrophic factor (BDNF), semaphorins, glypican 3 (GPC3) and others. Characterizing whether mitogen secretion and glioma growth are promoted by sleep or other daily cues will inform personalized chemotherapy that could interfere with host-tumor signaling. Figure adapted from images created with BioRender.com.

hijacking normal developmental processes and acquiring capabilities to transition to a malignant state (Hanahan 2022). Hallmarks of cancer include sustained proliferative signaling, evasion of growth suppressors and immune destruction, resisting cell death, and reprogramming cellular metabolism (Grechez-Cassiau et al. 2008, Lee & Sancar 2011, Basti et al. 2022, Diamantopoulou et al. 2022). While largely understudied in the context of malignancies, in healthy cells many of these capabilities are regulated by the circadian clock.

Gliomas are the most common primary brain malignancies, consisting of cells that resemble astrocytes, oligodendrocytes, oligodendrocyte precursor cells, or earlier neural stem cells. While they were historically referred to as astrocytomas, gliomas are thought to arise from a subpopulation of stem-like glioma cells. These cells drive tumor growth and underlie resistance to current therapies (Chen et al. 2012). Glioblastoma (GBM) is the most common and aggressive, affecting 3.2 adults per 100,000 (Dolecek et al. 2012), with median overall survival of approximately 15 months (Stupp et al. 2009). The DNA-alkylating agent temozolomide (TMZ) is the standard chemotherapy, extending median survival by approximately 2.5 months (Stupp et al. 2005). Importantly, GBM cells and cell lines exhibit intrinsic daily rhythms (Wagner et al. 2021), and tumor isolates from five GBM patients, several GBM cell lines, and a murine cell model of mesenchymal GBM (neurofibromatosis1-deficient and dominant negative *P53*, *NF1*^{-/-} DNp53) have high-amplitude daily rhythms in clock gene expression in vitro (Slat et al. 2017, Wagner et al. 2019). Moreover, in cultured U87 cells, TMZ-induced apoptosis, DNA repair, and growth inhibition are maximal around the daily peak of *Bmal1* expression (Slat et al. 2017). Perhaps TMZ works better around the peak of BMAL1 expression because of cell-autonomous, circadian downregulation of DNA repair mechanisms? Another candidate GBM therapy, 1A-116, an inhibitor of Rac family small GTPase 1 (RAC1) showed daily rhythms in efficacy in vitro and in mice (Trebutucq et al. 2021), while circadian clock modulators such as agonists of REV-ERB or CRY proteins can slow cell proliferation in GBM stem cells and differentiated GBM cells, primarily through inhibition of self-renewal and autophagy (Yu et al. 2018, Dong et al. 2019). Most recently, SHP656 and SHP1703, agonists of CRY2, were found to reduce GBM stem cell viability in vitro and have moved into Phase I clinical trials (Miller et al. 2022). The reliable daily rhythms in GBM contrast with results in other cancers where circadian rhythms tend to be disrupted. Do such agonists work equally well at all times of day by abrogating circadian rhythms in the tumor or by some other mechanism? These preliminary results highlight the potential that astrocytoma biology, including sensitivity to chemotherapy, can change with time of day. Can targeting the circadian clock in GBM produce drugs that replace or complement TMZ as the standard of care?

4.2. Host-to-Tumor Reciprocal Signaling

Recent discoveries of brain-to-tumor signaling further suggest that clinical trials should consider circadian time. Optogenetic stimulation of neurons within the mouse premotor cortex significantly increased local tumor proliferation (Venkatesh et al. 2015) and secretion of the postsynaptic protein neuroligin-3 (NLGN3), which was sufficient and necessary to promote high-grade glioma growth in mice through activation of the phosphatidylinositol 3 kinase–mechanistic target of rapamycin kinase (PI₃K–mTOR) pathway. NLGN3 is cleaved, primarily from oligodendrocyte precursor cells in the healthy brain, in a strictly activity-regulated manner by the sheddase ADAM10. This finding informed early-phase clinical trials with an ADAM10 inhibitor in children with high-grade gliomas (NCT04295759) (Venkatesh et al. 2017, Pan et al. 2021). GBM cells form long tumor microtubes that mediate invasion and growth via connexin 43 and calcium wave propagation (Osswald et al. 2015). Neuronal firing; glutamate-to-AMPA receptor signaling; increased extracellular potassium; and secretion of other mitogens, including BDNF and glutamate,

have been implicated in such invasion and proliferation (Keough & Monje 2022). Conversely, signaling by GABAergic interneurons is associated with glioma cell hyperpolarization and growth inhibition (Blanchart et al. 2017, Tantillo et al. 2020). It will be important to consider how circadian changes in the neuronal environment influence tumor growth. Furthermore, it will be intriguing to learn whether novel chemotherapeutic targets show daily cycles in their expression or activity. ADAM10 transcription, for example, varies with time of day in multiple tissues (Pizarro et al. 2013) and increases with melatonin (Shukla et al. 2015). So does circadian timing in the host and tumor influence cancer outcomes? In mice, glioma A530 cells grow nearly 25% faster when implanted into the sciatic nerve at circadian night compared to day. A530 cells also show day-night differences in their response to bortezomib in vitro and in vivo, with approximately three times greater tumor growth inhibition at night. A retrospective study of 166 GBM patients found an approximately 4-month extension of life in patients who took their TMZ in the morning compared to those who took it before bed. Moreover, survival was 6 months longer in the subpopulation of *O*-6-methylguanine methyltransferase (MGMT)-methylated GBM patients treated with TMZ in the morning compared to evening (Damato et al. 2021). Although such evidence should be balanced with the limited history of successful chronotherapy (Ruben et al. 2019, Sancar & Van Gelder 2021), discovery of new cancer treatment drugs remains an important avenue, and studies will benefit from tracking the time of day of treatment and the sleep-wake status of those being treated. This is because the body is a clock shop in which circadian cells interact, and accumulating evidence suggests a reciprocal cross talk whereby gliomas alter the neuronal microenvironment to promote glioma progression. For example, the synaptogenic protein GPC3 is secreted by glioma cells and can promote tumorigenesis, synaptic remodeling, and hyperexcitability of neighboring neurons (Yu et al. 2020). Axon guidance molecules such as class 3 semaphorins are highly expressed in glioma samples, can promote glioma cell migration (Bagci et al. 2009), and are associated with poor prognosis and survival (Rich et al. 2005). Does rhythmic brain-to-tumor communication promote tumor growth and invasion at different times of the day? Does glioma proliferation or migration involve hijacking the astrocyte-driven daily rhythms in extracellular glutamate? And does glioma metastasis increase during sleep, as was recently discovered with breast cancer (Diamantopoulou et al. 2022)? As with neurodegenerative diseases, disruption of sleep and circadian rhythms may be a marker of GBM progression, but whether restoration of daily rhythms in the patient would slow tumor progression awaits clarification.

5. CONCLUSION

Astrocytes are neither good, bad, or ugly. Their maintenance of brain homeostasis is an active one, and hyperactive astrocytes can wreak havoc by promoting inappropriate inflammatory responses. Conversely, hypoactive astrocytes can reduce clearance and recycling of neurotransmitters and toxins and even cause edema. Circadian timekeeping in astrocytes and neurons therefore plays an essential role in brain homeostasis, balancing these unwanted tendencies by adaptive fine-tuning in anticipation of the day/night cycle. The recent discovery that astrocytes can encode *de novo* circadian information raises a fundamental question: Are there specific long-term consequences for brain health and function arising from the undue degradation or amplification of circadian information? By reducing clearance and metabolism of toxic brain catabolites, hypofunctional, “bad” clocks in astrocytes (as from *Bmal1* deletion or lifestyle chronodisruption) may push toward neurodegenerative pathways. Hyperactive, “ugly” glial clocks, and consequent loss of mutual relationships with neighboring cells, may pave the way for cancer. Circadian-informed research will tell whether Janus has two faces.

SUMMARY POINTS

1. Astrocytes have robust cell-autonomous circadian clocks and exhibit high-amplitude circadian and sleep-dependent cycles of gene expression and cellular activity.
2. The cell-autonomous clock of suprachiasmatic nucleus astrocytes is sufficient to drive circadian rhythms of behavior in an otherwise clockless mouse, showing that astrocytes can create de novo temporal information and impart it to the brain.
3. Alzheimer's disease and mouse models thereof display strong reciprocal interactions between sleep/circadian disruption and disease progression, and in particular, the degradation of astrocyte-encoded circadian information is associated with increased risk of neurodegeneration.
4. Astroglomas show high-amplitude daily rhythms in gene expression and function, suggesting that controlled time of day of treatment may improve survival in glioblastoma.

FUTURE ISSUES

1. What gliotransmitter signals allow astrocytes to convey circadian time onto suprachiasmatic nucleus (SCN) neurons: Is astrocytic regulation of extracellular glutamate the pivotal cue, and where does GABA feature?
2. How do SCN neurons convey circadian time onto astrocytes, and are neuropeptides critical for this?
3. More broadly across the brain, do astrocytes play a central role in regulating neuronal excitability through circadian uptake and release of glutamate and GABA, and how is this modulated by daily environmental cues and sleep state?
4. In diseases that are marked by both sleep and cognitive impairments, we are beginning to see interactions where reduced sleep accelerates amyloid- β deposition, which in turn exacerbates sleep fragmentation. Are there times of day when astrocytes play a critical role in initiating sleep and/or are sensitive to sleep disruption? Would enforcing daily rhythms in astrocytic glutamate transport slow the progression of neurodegenerative diseases like Alzheimer's?
5. Do circadian rhythms in glioma facilitate their progression, and if so, what are the intervening mechanisms that convey daily regulation of the hallmarks of cancer?

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LITERATURE CITED

- Abe M, Herzog ED, Yamazaki S, Straume M, Tei H, et al. 2002. Circadian rhythms in isolated brain regions. *J. Neurosci.* 22:350–56
- Abe YO, Yoshitane H, Kim DW, Kawakami S, Koebis M, et al. 2022. Rhythmic transcription of *Bmal1* stabilizes the circadian timekeeping system in mammals. *Nat. Commun.* 13:4652
- Acosta-Rodriguez VA, Rijo-Ferreira F, Green CB, Takahashi JS. 2021. Importance of circadian timing for aging and longevity. *Nat. Commun.* 12:2862
- Akhtar RA, Reddy AB, Maywood ES, Clayton JD, King VM, et al. 2002. Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr. Biol.* 12:540–50
- Allen NJ, Eroglu C. 2017. Cell biology of astrocyte-synapse interactions. *Neuron* 96:697–708
- Andersen JV, Schousboe A, Verkhratsky A. 2022. Astrocyte energy and neurotransmitter metabolism in Alzheimer's disease: integration of the glutamate/GABA-glutamine cycle. *Prog. Neurobiol.* 217:102331
- Aziz NA, Pijl H, Frolich M, Roelfsema F, Roos RA. 2011a. Diurnal secretion profiles of growth hormone, thyrotrophin and prolactin in Parkinson's disease. *J. Neuroendocrinol.* 23:519–24
- Aziz NA, Pijl H, Frolich M, Roelfsema F, Roos RA. 2011b. Leptin, adiponectin, and resistin secretion and diurnal rhythmicity are unaltered in Parkinson's disease. *Mov. Disord.* 26:760–61
- Bagci T, Wu JK, Pfannl R, Ilag LL, Jay DG. 2009. Autocrine semaphorin 3A signaling promotes glioblastoma dispersal. *Oncogene* 28:3537–50
- Balsalobre A, Damiola F, Schibler U. 1998. A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* 93:929–37
- Barca-Mayo O, Pons-Espinal M, Follert P, Armirotti A, Berdondini L, De Pietri Tonelli D. 2017. Astrocyte deletion of *Bmal1* alters daily locomotor activity and cognitive functions via GABA signalling. *Nat. Commun.* 8:14336
- Basti A, Malhan D, Dumbani M, Dahlmann M, Stein U, Relogio A. 2022. Core-clock genes regulate proliferation and invasion via a reciprocal interplay with MACC1 in colorectal cancer cells. *Cancers* 14:3458
- Bazargani N, Attwell D. 2016. Astrocyte calcium signaling: the third wave. *Nat. Neurosci.* 19:182–89
- Blanchart A, Fernando R, Haring M, Assaife-Lopes N, Romanov RA, et al. 2017. Endogenous GABA_A receptor activity suppresses glioma growth. *Oncogene* 36:777–86
- Bojarskaite L, Bjornstad DM, Pettersen KH, Cunen C, Hermansen GH, et al. 2020. Astrocytic Ca²⁺ signaling is reduced during sleep and is involved in the regulation of slow wave sleep. *Nat. Commun.* 11:3240
- Borbely AA, Daan S, Wirz-Justice A, Deboer T. 2016. The two-process model of sleep regulation: a reappraisal. *J. Sleep Res.* 25:131–43
- Brancaccio M, Edwards MD, Patton AP, Smyllie NJ, Chesham JE, et al. 2019. Cell-autonomous clock of astrocytes drives circadian behavior in mammals. *Science* 363:187–92
- Brancaccio M, Maywood ES, Chesham JE, Loudon AS, Hastings MH. 2013. A Gq-Ca²⁺ axis controls circuit-level encoding of circadian time in the suprachiasmatic nucleus. *Neuron* 78:714–28
- Brancaccio M, Patton AP, Chesham JE, Maywood ES, Hastings MH. 2017. Astrocytes control circadian timekeeping in the suprachiasmatic nucleus via glutamatergic signaling. *Neuron* 93:1420–35.e5
- Brancaccio M, Wolfes AC, Ness N. 2021. Astrocyte circadian timekeeping in brain health and neurodegeneration. *Adv. Exp. Med. Biol.* 1344:87–110

- Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, et al. 2014. Sleep and circadian rhythm regulation in early Parkinson disease. *JAMA Neurol.* 71:589–95
- Cederroth CR, Albrecht U, Bass J, Brown SA, Dyhrfeld-Johnsen J, et al. 2019. Medicine in the fourth dimension. *Cell Metab.* 30:238–50
- Chen J, McKay RM, Parada LF. 2012. Malignant glioma: lessons from genomics, mouse models, and stem cells. *Cell* 149:36–47
- Cho H, Zhao X, Hatori M, Yu RT, Barish GD, et al. 2012. Regulation of circadian behaviour and metabolism by REV-ERB- α and REV-ERB- β . *Nature* 485:123–27
- Clasadonte J, Scemes E, Wang Z, Boison D, Haydon PG. 2017. Connexin 43-mediated astroglial metabolic networks contribute to the regulation of the sleep-wake cycle. *Neuron* 95:1365–80.e5
- Cuddapah VA, Zhang SL, Sehgal A. 2019. Regulation of the blood-brain barrier by circadian rhythms and sleep. *Trends Neurosci.* 42:500–10
- Czeisler CA, Gooley JJ. 2007. Sleep and circadian rhythms in humans. *Cold Spring Harb. Symp. Quant. Biol.* 72:579–97
- Damato AR, Luo J, Katumba RGN, Talcott GR, Rubin JB, et al. 2021. Temozolomide chronotherapy in patients with glioblastoma: a retrospective single-institute study. *Neurooncol. Adv.* 3:vdab041
- De Pablo-Fernández E, Courtney R, Warner TT, Holton JL. 2018. A histologic study of the circadian system in Parkinson disease, multiple system atrophy, and progressive supranuclear palsy. *JAMA Neurol.* 75:1008–12
- De Strooper B, Karran E. 2016. The cellular phase of Alzheimer's disease. *Cell* 164:603–15
- Diamantopoulou Z, Castro-Giner F, Schwab FD, Foerster C, Saini M, et al. 2022. The metastatic spread of breast cancer accelerates during sleep. *Nature* 607:156–62
- Dolecek TA, Propp JM, Stroup NE, Kruchko C. 2012. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro-Oncology* 14(Suppl. 5):v1–49
- Dong Z, Zhang G, Qu M, Gimple RC, Wu Q, et al. 2019. Targeting glioblastoma stem cells through disruption of the circadian clock. *Cancer Discov.* 9:1556–73
- Dunlap JC, Loros JJ, Decoursey PJ, eds. 2004. *Chronobiology: Biological Timekeeping*. Sunderland, MA: Sinauer
- Espósito Z, Belli L, Toniolo S, Sancesario G, Bianconi C, Martorana A. 2013. Amyloid β , glutamate, excitotoxicity in Alzheimer's disease: Are we on the right track? *CNS Neurosci. Ther.* 19:549–55
- Frank MG. 2019. The role of glia in sleep regulation and function. *Handb. Exp. Pharmacol.* 253:83–96
- Franken P, Dijk DJ. 2009. Circadian clock genes and sleep homeostasis. *Eur. J. Neurosci.* 29:1820–29
- Freeman GM Jr, Nakajima M, Ueda HR, Herzog ED. 2013. Picrotoxin dramatically speeds the mammalian circadian clock independent of Cys-loop receptors. *J. Neurophysiol.* 110:103–8
- Grechez-Cassiau A, Rayet B, Guillaumond F, Teboul M, Delaunay F. 2008. The circadian clock component BMAL1 is a critical regulator of *p21WAF1/CIP1* expression and hepatocyte proliferation. *J. Biol. Chem.* 283:4535–42
- Hablitz LM, Nedergaard M. 2021. The glymphatic system: a novel component of fundamental neurobiology. *J. Neurosci.* 41:7698–711
- Hablitz LM, Pla V, Giannetto M, Vinitsky HS, Staeger FF, et al. 2020. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat. Commun.* 11:4411
- Hamnett R, Crosby P, Chesham JE, Hastings MH. 2019. Vasoactive intestinal peptide controls the suprachiasmatic circadian clock network via ERK1/2 and DUSP4 signalling. *Nat. Commun.* 10:542
- Hanahan D. 2022. Hallmarks of cancer: new dimensions. *Cancer Discov.* 12:31–46
- Harper DG, Stopa EG, Kuo-Leblanc V, McKee AC, Asayama K, et al. 2008. Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. *Brain* 131:1609–17
- Hastings MH, Maywood ES, Brancaccio M. 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. *Nat. Rev. Neurosci.* 19:453–69
- Hatfield CF, Herbert J, van Someren EJ, Hodges JR, Hastings MH. 2004. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. *Brain* 127:1061–74
- Herzog ED, Hermansteyne T, Smyllie NJ, Hastings MH. 2017. Regulating the suprachiasmatic nucleus (SCN) circadian clockwork: interplay between cell-autonomous and circuit-level mechanisms. *Cold Spring Harb. Perspect. Biol.* 9:a027706

- Hines DJ, Haydon PG. 2014. Astrocytic adenosine: from synapses to psychiatric disorders. *Philos. Trans. R. Soc. B* 369:20130594
- Holth JK, Fritschi SK, Wang C, Pedersen NP, Cirrito JR, et al. 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 363:880–84
- Hoyt KR, Obrietan K. 2022. Circadian clocks, cognition, and Alzheimer's disease: synaptic mechanisms, signaling effectors, and chronotherapeutics. *Mol. Neurodegener.* 17:35
- Hunt J, Coulson EJ, Rajnarayanan R, Oster H, Videnovic A, Rawashdeh O. 2022. Sleep and circadian rhythms in Parkinson's disease and preclinical models. *Mol. Neurodegener.* 17:2
- Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, et al. 2014. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J. Neurosci.* 34:16180–93
- Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, et al. 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci. Transl. Med.* 4:147ra11
- Jones JR, Simon T, Lones L, Herzog ED. 2018. SCN VIP neurons are essential for normal light-mediated resetting of the circadian system. *J. Neurosci.* 38:7986–95
- Kalliolia E, Silajdzic E, Nambron R, Costelloe SJ, Martin NG, et al. 2015. A 24-hour study of the hypothalamo-pituitary axes in Huntington's disease. *PLOS ONE* 10:e0138848
- Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, et al. 2009. Amyloid- β dynamics are regulated by orexin and the sleep-wake cycle. *Science* 326:1005–7
- Keough MB, Monje M. 2022. Neural signaling in cancer. *Annu. Rev. Neurosci.* 45:199–221
- Khakh BS, Sofroniew MV. 2015. Diversity of astrocyte functions and phenotypes in neural circuits. *Nat. Neurosci.* 18:942–52
- Kofuji P, Araque A. 2021. Astrocytes and behavior. *Annu. Rev. Neurosci.* 44:49–67
- Kress GJ, Liao F, Dimitry J, Cedeno MR, FitzGerald GA, et al. 2018. Regulation of amyloid- β dynamics and pathology by the circadian clock. *J. Exp. Med.* 215:1059–68
- Lananna BV, McKee CA, King MW, Del-Aguila JL, Dimitry JM, et al. 2020. *Chb3l1/YKL-40* is controlled by the astrocyte circadian clock and regulates neuroinflammation and Alzheimer's disease pathogenesis. *Sci. Transl. Med.* 12:eaax3519
- Lananna BV, Nadarajah CJ, Izumo M, Cedeno MR, Xiong DD, et al. 2018. Cell-autonomous regulation of astrocyte activation by the circadian clock protein BMAL1. *Cell Rep.* 25:1–9.e5
- Lee JH, Sancar A. 2011. Regulation of apoptosis by the circadian clock through NF- κ B signaling. *PNAS* 108:12036–41
- Lee Y, Field JM, Sehgal A. 2021. Circadian rhythms, disease and chronotherapy. *J. Biol. Rhythms* 36:503–31
- Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. 2019. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* 18:307–18
- Li P, Gao L, Gaba A, Yu L, Cui L, et al. 2020. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. *Lancet Healthy Longev.* 1:e96–105
- Marpegan L, Krall TJ, Herzog ED. 2009. Vasoactive intestinal polypeptide entrains circadian rhythms in astrocytes. *J. Biol. Rhythms* 24:135–43
- Marpegan L, Swanson AE, Chung K, Simon T, Haydon PG, et al. 2011. Circadian regulation of ATP release in astrocytes. *J. Neurosci.* 31:8342–50
- Marvin JS, Scholl B, Wilson DE, Podgorski K, Kazemipour A, et al. 2018. Stability, affinity, and chromatic variants of the glutamate sensor iGluSnFR. *Nat. Methods* 15:936–39
- Maywood ES, Chesham JE, Winsky-Sommerer R, Hastings MH. 2021. Restoring the molecular clockwork within the suprachiasmatic hypothalamus of an otherwise clockless mouse enables circadian phasing and stabilization of sleep-wake cycles and reverses memory deficits. *J. Neurosci.* 41:8562–76
- Maywood ES, Elliott TS, Patton AP, Krogager TP, Chesham JE, et al. 2018. Translational switching of Cry1 protein expression confers reversible control of circadian behavior in arrhythmic Cry-deficient mice. *PNAS* 115:E12388–97
- McKee CA, Lee J, Cai Y, Saito T, Saido T, Musiek ES. 2022. Astrocytes deficient in circadian clock gene *Bmal1* show enhanced activation responses to amyloid-beta pathology without changing plaque burden. *Sci. Rep.* 12:1796

- Meng QJ, Logunova L, Maywood ES, Gallego M, Lebiecki J, et al. 2008. Setting clock speed in mammals: the CK1 ϵ *tau* mutation in mice accelerates circadian pacemakers by selectively destabilizing PERIOD proteins. *Neuron* 58:78–88
- Miller S, Kesharwani M, Chan P, Nagai Y, Yagi M, et al. 2022. CRY2 isoform selectivity of a circadian clock modulator with antglioblastoma efficacy. *PNAS* 119:e2203936119
- Morin LP, Allen CN. 2006. The circadian visual system, 2005. *Brain Res. Rev.* 51:1–60
- Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju YS. 2018. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol.* 75:582–90
- Musiek ES, Lim MM, Yang G, Bauer AQ, Qi L, et al. 2013. Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. *J. Clin. Invest.* 123:5389–400
- Nagai J, Yu X, Papouin T, Cheong E, Freeman MR, et al. 2021. Behaviorally consequential astrocytic regulation of neural circuits. *Neuron* 109:576–96
- Nakazato R, Kawabe K, Yamada D, Ikeno S, Mieda M, et al. 2017. Disruption of Bmal1 impairs blood-brain barrier integrity via pericyte dysfunction. *J. Neurosci.* 37:10052–62
- Nassan M, Videnovic A. 2022. Circadian rhythms in neurodegenerative disorders. *Nat. Rev. Neurol.* 18:7–24
- Ono D, Honma KI, Yanagawa Y, Yamanaka A, Honma S. 2019. GABA in the suprachiasmatic nucleus refines circadian output rhythms in mice. *Commun. Biol.* 2:232
- Osswald M, Jung E, Sahn F, Szelecki G, Venkataramani V, et al. 2015. Brain tumour cells interconnect to a functional and resistant network. *Nature* 528:93–98
- Pan Y, Hysinger JD, Barron T, Schindler NF, Cobb O, et al. 2021. *NF1* mutation drives neuronal activity-dependent initiation of optic glioma. *Nature* 594:277–82
- Panda S. 2016. Circadian physiology of metabolism. *Science* 354:1008–15
- Parsons MJ, Brancaccio M, Sethi S, Maywood ES, Satija R, et al. 2015. The regulatory factor ZFHX3 modifies circadian function in SCN via an AT motif-driven axis. *Cell* 162:607–21
- Patton AP, Chesham JE, Hastings MH. 2016. Combined pharmacological and genetic manipulations unlock unprecedented temporal elasticity and reveal phase-specific modulation of the molecular circadian clock of the mouse suprachiasmatic nucleus. *J. Neurosci.* 36:9326–41
- Patton AP, Smyllie NJ, Chesham JE, Hastings MH. 2022. Astrocytes sustain circadian oscillation and bidirectionally determine circadian period, but do not regulate circadian phase in the suprachiasmatic nucleus. *J. Neurosci.* 42(28):5522–37
- Paul S, Hanna L, Harding C, Hayter EA, Walmsley L, et al. 2020. Output from VIP cells of the mammalian central clock regulates daily physiological rhythms. *Nat. Commun.* 11:1453
- Phatnani H, Maniatis T. 2015. Astrocytes in neurodegenerative disease. *Cold Spring Harb. Perspect. Biol.* 7:a020628
- Pizarro A, Hayer K, Lahens NF, Hogenesch JB. 2013. CircaDB: a database of mammalian circadian gene expression profiles. *Nucleic Acids Res.* 41:D1009–13
- Poskanzer KE, Yuste R. 2016. Astrocytes regulate cortical state switching in vivo. *PNAS* 113:E2675–84
- Preitner N, Damiola F, Lopez-Molina L, Zakany J, Duboule D, et al. 2002. The orphan nuclear receptor REV-ERBa controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell* 110:251–60
- Prolo LM, Takahashi JS, Herzog ED. 2005. Circadian rhythm generation and entrainment in astrocytes. *J. Neurosci.* 25:404–8
- Prosser RA, Edgar DM, Heller HC, Miller JD. 1994. A possible glial role in the mammalian circadian clock. *Brain Res.* 643:296–301
- Reppert SM, Weaver DR. 2002. Coordination of circadian timing in mammals. *Nature* 418:935–41
- Rich JN, Hans C, Jones B, Iversen ES, McLendon RE, et al. 2005. Gene expression profiling and genetic markers in glioblastoma survival. *Cancer Res.* 65:4051–58
- Rollag MD, Berson DM, Provencio I. 2003. Melanopsin, ganglion-cell photoreceptors, and mammalian photoentrainment. *J. Biol. Rhythms* 18:227–34
- Ruben MD, Smith DF, FitzGerald GA, Hogenesch JB. 2019. Dosing time matters. *Science* 365:547–49
- Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, et al. 2014. Single *App* knock-in mouse models of Alzheimer's disease. *Nat. Neurosci.* 17:661–63

- Sancar A, Van Gelder RN. 2021. Clocks, cancer, and chronochemotherapy. *Science* 371:eabb0738
- Santello M, Toni N, Volterra A. 2019. Astrocyte function from information processing to cognition and cognitive impairment. *Nat. Neurosci.* 22:154–66
- Sato TK, Panda S, Miraglia LJ, Reyes TM, Rudic RD, et al. 2004. A functional genomics strategy reveals Rora as a component of the mammalian circadian clock. *Neuron* 43:527–37
- Serviere J, Lavalie M. 1996. Astrocytes in the mammalian circadian clock: putative roles. *Prog. Brain Res.* 111:57–73
- Shigeyoshi Y, Taguchi K, Yamamoto S, Takekida S, Yan L, et al. 1997. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the *mPer1* transcript. *Cell* 91:1043–53
- Shinohara K, Honma S, Katsuno Y, Honma K. 2000. Circadian release of excitatory amino acids in the suprachiasmatic nucleus culture is Ca^{2+} -independent. *Neurosci. Res.* 36:245–50
- Shirbin CA, Chua P, Churchyard A, Lowndes G, Hannan AJ, et al. 2013. Cortisol and depression in pre-diagnosed and early stage Huntington's disease. *Psychoneuroendocrinology* 38:2439–47
- Shukla M, Htoo HH, Wintachai P, Hernandez JF, Dubois C, et al. 2015. Melatonin stimulates the non-amyloidogenic processing of β APP through the positive transcriptional regulation of ADAM10 and ADAM17. *J. Pineal Res.* 58:151–65
- Slat EA, Sponagel J, Marpegan L, Simon T, Kfoury N, et al. 2017. Cell-intrinsic, Bmal1-dependent circadian regulation of temozolomide sensitivity in glioblastoma. *J. Biol. Rhythms* 32:121–29
- Spanagel R, Pendyala G, Abarca C, Zghoul T, Sanchis-Segura C, et al. 2005. The clock gene *Per2* influences the glutamatergic system and modulates alcohol consumption. *Nat. Med.* 11:35–42
- Stopa EG, Volicer L, Kuo-Leblanc V, Harper DG, Lathi D, et al. 1999. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. *J. Neuropathol. Exp. Neurol.* 58:29–39
- Stratmann M, Suter DM, Molina N, Naef F, Schibler U. 2012. Circadian *Dbp* transcription relies on highly dynamic BMAL1-CLOCK interaction with E boxes and requires the proteasome. *Mol. Cell* 48:277–87
- Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, et al. 2009. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10:459–66
- Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, et al. 2005. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352:987–96
- Swaab DF, Fliers E, Partiman TS. 1985. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res.* 342:37–44
- Swanson RA, Graham SH. 1994. Fluorocitrate and fluoroacetate effects on astrocyte metabolism in vitro. *Brain Res.* 664:94–100
- Takahashi JS. 2017. Transcriptional architecture of the mammalian circadian clock. *Nat. Rev. Genet.* 18:164–79
- Tantillo E, Vannini E, Cerri C, Spalletti C, Colistra A, et al. 2020. Differential roles of pyramidal and fast-spiking, GABAergic neurons in the control of glioma cell proliferation. *Neurobiol. Dis.* 141:104942
- Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, et al. 2011. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann. Neurol.* 70:722–32
- Trebucq LL, Cardama GA, Lorenzano Menna P, Golombek DA, Chiesa JJ, Marpegan L. 2021. Timing of novel drug 1A-116 to circadian rhythms improves therapeutic effects against glioblastoma. *Pharmaceutics* 13:1091
- Tso CF, Simon T, Greenlaw AC, Puri T, Mieda M, Herzog ED. 2017. Astrocytes regulate daily rhythms in the suprachiasmatic nucleus and behavior. *Curr. Biol.* 27:1055–61
- Tso MC, Herzog ED. 2015. Was Cajal right about sleep? *BMC Biol.* 13:67
- Vaidyanathan TV, Collard M, Yokoyama S, Reitman ME, Poskanzer KE. 2021. Cortical astrocytes independently regulate sleep depth and duration via separate GPCR pathways. *eLife* 10:e63329
- Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, et al. 2015. Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell* 161:803–16
- Venkatesh HS, Tam LT, Woo PJ, Lennon J, Nagaraja S, et al. 2017. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature* 549:533–37
- Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, et al. 2014. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. *JAMA Neurol.* 71:463–69

- Wagner PM, Prucca CG, Caputto BL, Guido ME. 2021. Adjusting the molecular clock: the importance of circadian rhythms in the development of glioblastomas and its intervention as a therapeutic strategy. *Int. J. Mol. Sci.* 22:8289
- Wagner PM, Sosa Alderete LG, Gorne LD, Gaveglia V, Salvador G, et al. 2019. Proliferative glioblastoma cancer cells exhibit persisting temporal control of metabolism and display differential temporal drug susceptibility in chemotherapy. *Mol. Neurobiol.* 56:1276–92
- Wen S, Ma D, Zhao M, Xie L, Wu Q, et al. 2020. Spatiotemporal single-cell analysis of gene expression in the mouse suprachiasmatic nucleus. *Nat. Neurosci.* 23:456–67
- Xie L, Kang H, Xu Q, Chen MJ, Liao Y, et al. 2013. Sleep drives metabolite clearance from the adult brain. *Science* 342:373–77
- Xu P, Berto S, Kulkarni A, Jeong B, Joseph C, et al. 2021. NPAS4 regulates the transcriptional response of the suprachiasmatic nucleus to light and circadian behavior. *Neuron* 109:3268–82.e6
- Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, et al. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *PNAS* 101:5339–46
- Yu K, Lin CJ, Hatcher A, Lozzi B, Kong K, et al. 2020. PIK3CA variants selectively initiate brain hyperactivity during gliomagenesis. *Nature* 578:166–71
- Yu M, Li W, Wang Q, Wang Y, Lu F. 2018. Circadian regulator NR1D2 regulates glioblastoma cell proliferation and motility. *Oncogene* 37:4838–53
- Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. 2014. A circadian gene expression atlas in mammals: implications for biology and medicine. *PNAS* 111:16219–24
- Zhang SL, Lahens NF, Yue Z, Arnold DM, Pakstis PP, et al. 2021. A circadian clock regulates efflux by the blood-brain barrier in mice and human cells. *Nat. Commun.* 12:617