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FABP7: a glial integrator of sleep, circadian rhythms, plasticity, and metabolic function

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Sleep and circadian rhythms are observed broadly throughout animal phyla and influence neural plasticity and cognitive function. However, the few phylogenetically conserved cellular and molecular pathways that are implicated in these processes are largely focused on neuronal cells. Research on these topics has traditionally segregated sleep homeostatic behavior from circadian rest-activity rhythms. Here we posit an alternative perspective, whereby mechanisms underlying the integration of sleep and circadian rhythms that affect behavioral state, plasticity, and cognition reside within glial cells. The brain-type fatty acid binding protein, FABP7, is part of a larger family of lipid chaperone proteins that regulate the subcellular trafficking of fatty acids for a wide range of cellular functions, including gene expression, growth, survival, inflammation, and metabolism. FABP7 is enriched in glial cells of the central nervous system and has been shown to be a clock-controlled gene implicated in sleep/wake regulation and cognitive processing. FABP7 is known to affect gene transcription, cellular outgrowth, and its subcellular localization in the fine perisynaptic astrocytic processes (PAPs) varies based on time-of-day. Future studies determining the effects of FABP7 on behavioral state- and circadian-dependent plasticity and cognitive processes, in addition to functional consequences on cellular and molecular mechanisms related to neural-glial interactions, lipid storage, and blood brain barrier integrity will be important for our knowledge of basic sleep function. Given the comorbidity of sleep disturbance with neurological disorders, these studies will also be important for our understanding of the etiology and pathophysiology of how these diseases affect or are affected by sleep.

KEYWORDS

BBB, synaptic plasticity, homeostasis, glycolysis, transcytosis, endocytosis, astroctye, β-oxidation

Fatty-acid binding proteins

Fatty-acid binding proteins are a family of small ~15 kDa lipid-binding proteins that belong to the calycin superfamily, which include avidins and lipocalins. FABPs share β-barrel structural motifs that bind small hydrophobic molecules (Schaap et al., 2002), despite low primary sequence similarity (Agellon, 2023). FABPs bind the hydrophobic region of fatty acids and their metabolites, particularly long-chain polyunsaturated fatty acids (PUFAs) in

higher order species, and transport them to various subcellular locations, which affect a wide range of cellular processes, including signal transduction, oxidation, membrane synthesis, transcription, fat storage, autocrine/paracrine function, inflammation, and metabolism (Furuhashi and Hotamisligil, 2008; Storch and Corsico, 2008). FABPs also bind xenobiotics, including cannabinoids, benzodiazepines, antinociceptives, non-steroidal anti-inflammatory drugs, and peroxisome proliferators, and are involved in xenobiotic absorption, distribution, and metabolism in various organs (Yabut and Isoherranen, 2023). FABPs are present across phylogeny, from invertebrates such as *Caenorhabditis elegans* and the fruit fly, *Drosophila melanogaster*, to rodents and other mammals, including humans (Zheng et al., 2013; Zhang et al., 2020). Phylogenetic studies suggest FABPs likely evolved from a common ancestor via tandem gene duplication, with the first gene duplication dated ∼930 million years ago (Schaap et al., 2002; Zheng et al., 2013; Zhang et al., 2020). Recruitment of FABPs during the evolution of animals from fungi and plants is thought to facilitate increased subcellular trafficking of ligands and mitochondrial oxidation of long-chain fatty acids (Schaap et al., 2002). FABPs were initially discovered in the cytosol of intestinal mucosa, liver, and myocardial tissues (Ockner et al., 1972). FABPs can be differentially expressed in various tissues and cell types (Furuhashi and Hotamisligil, 2008). For example, in mammals, heart-type FABP (H-FABP/FABP3), epidermal-type FABP (E-FABP/FABP5), and brain-type FABP (B-FABP/FABP7) are all present within the adult central nervous system (CNS) (Veerkamp and Zimmerman, 2001), with FABP3 primarily expressed in neurons, FABP5 in neurons and glia, and FABP7 in astrocytes and precursor cells (Owada et al., 1996b; Furuhashi and Hotamisligil, 2008; Storch and Corsico, 2008).

Fatty acid binding protein 7 in brain development and proliferation

Fatty acid binding protein 7, also known as mammary derived growth inhibitor-related gene (MRG) and brain lipid binding protein (BLBP), is an ontogenically expressed FABP with elevated expression early in development that decreases over the lifespan in mammals (Bennett et al., 1994; Gerstner et al., 2008; Clarke et al., 2018). FABP7 was first identified in radial glial cells of embryonic brain and neural progenitors of mature brain (Bennett et al., 1994; Feng et al., 1994; Kurtz et al., 1994). FABP7-expressing progenitors in early development are thought to contribute to most adult neural cell populations throughout the mammalian CNS (Anthony et al., 2004). FABP7 was identified as the first predominantly specific Notch target gene in the CNS (Anthony et al., 2005), its developmental expression is dependent on Pax6 (Arai et al., 2005) and POU/Pbx (Josephson et al., 1998) transcription factors. Following development, FABP7 expression appears to be pluripotent as it is found in multiple cells in nervous tissue, including astrocytes, radial glia, oligodendrocyte progenitor cells (OPCs), Bergman glia, Müller glia, and satellite glia of the spinal cord (Kurtz et al., 1994; Owada et al., 1996b; Yanase et al., 2002). In postnatal hippocampal neurogenesis, FABP7 is expressed in neural stem cells (NSCs) of the dentate gyrus, and proliferation of these NSCs is decreased with subsequent reduction in their survival in FABP7 knockout (KO) mice (Matsumata et al., 2012). FABP7 expression was also detected in NG2 (+) OPCs, and cultured OPCs showed a significant decrease in proliferation/differentiation in the population of FABP7- KO OPCs compared with wild-type (WT) OPCs (Sharifi et al., 2013). Following forebrain ischemia, FABP7 expression in neural stem/progenitor cells increased 7–10 days post-ischemia, consistent with peak hippocampal neurogenesis (Kato et al., 2020). FABP7 expression associated with hippocampal neurogenesis following ischemic insult was also observed in non-human primates (Ma et al., 2010; Boneva et al., 2011). In FABP7-KO mice, neurogenesis was significantly decreased compared to WT mice under both normal and ischemic conditions, suggesting that FABP7 regulates the proliferation of neuronal stem/progenitor cells. Together these findings provide compelling evidence that FABP7 is a key regulator in the growth and organization of multiple CNS cell types.

Integrated model for FABP7 in sleep, circadian rhythms, plasticity, and metabolic function

Sleep is a characteristic behavior that is exhibited broadly throughout the animal kingdom, including invertebrate and vertebrate species (Allada and Siegel, 2008; Lesku et al., 2008; Cirelli, 2009). Despite this, we know relatively little of what cellular and molecular mechanisms are fundamental to sleep drive. A long-standing hypothesis in the sleep field maintains two-processes that contribute to sleep behavior: a circadian (time-of-day) component, which is driven by phylogenetically conserved core-clock system, and a "sleep homeostasis" component, which is driven by prior time spent awake (Borbely and Achermann, 1999; Borbely et al., 2016). In one perspective, sleep homeostasis is generated via reciprocal switching between wake- and sleep-promoting neurons to inhibit each other (Strecker et al., 2000; Saper et al., 2001, 2005; Szymusiak et al., 2007; Eban-Rothschild et al., 2018), but this model is challenging for species that lack similar anatomical circuits or neurochemistries (Artiushin and Sehgal, 2017; Donlea et al., 2017; Ly et al., 2018). In another view, sleep drive is thought to occur in an independent fashion within neurons throughout brain, based on their prior history of excitation and use (Tononi and Cirelli, 2006; Krueger et al., 2008; Krueger and Tononi, 2011; Havekes and Aton, 2020; Krueger, 2020). Alterations in neuronal activity in both perspectives represent the fundamental driving force behind sleep homeostasis. Recently glial cells have received more attention for their relevance in sleep and circadian rhythm behaviors (Halassa et al., 2009; Halassa and Haydon, 2010; Barca-Mayo and López, 2021; Damulewicz et al., 2022a; Ingiosi and Frank, 2022; Hastings et al., 2023) and their contributions are evidenced across phylogenetically disparate species (Poskanzer and Yuste, 2016; Stahl et al., 2018; Artiushin and Sehgal, 2020; Ingiosi et al., 2020; Jackson et al., 2020; Blum et al., 2021; Vaidyanathan et al., 2021; Reitman et al., 2023). Exactly how circadian and homeostatic processes interact to organize sleep behavior remains unclear and are likely not operating independently (Deboer et al., 2003, 2007; Easton et al., 2004; Laposky et al., 2005; Wright et al., 2012; Deboer, 2018). Further, the likely involvement of other processes such as energy metabolism (Benington and Heller, 1995; Scharf et al., 2008;

Franken and Dijk, 2009; Dash et al., 2013; Bellesi et al., 2018; Malik et al., 2020), lipid signaling and storage (Thimgan et al., 2010, 2015; Yurgel et al., 2018; Ioannou et al., 2019a; Li Y. et al., 2023), astrocyte-neurometabolic coupling through glymphatics (Jessen et al., 2015; Haydon, 2017; Lundgaard et al., 2017), autophagy (Xie et al., 2020; Bedont et al., 2021; Damulewicz et al., 2022b; Guo et al., 2022), and the astrocyte-neuron lactate shuttle (ANLS) (Scharf et al., 2008; Petit et al., 2013) reflect a complex and multivariable network ripe for exploration.

Fatty acid binding protein 7 mRNA expression is enriched in dendritic layers of hippocampus (Zhong et al., 2006) and induced following kainate injection known to increase neural activity (Owada et al., 1996a). In addition cyclic AMP response element binding protein, stocktickerCREB, a transcription factor widely associated with synaptic plasticity, memory, sleep, and circadian rhythms (Nguyen and Woo, 2003; Gerstner and Yin, 2010; Havekes et al., 2015, 2016; Kreutzmann et al., 2015; Xia and Storm, 2017; Lisman et al., 2018), elicits a persistent form of hippocampal long-term potentiation with only a weak stimulus when made constitutively active (Barco et al., 2002). Constitutive stocktickerCREB-induced hippocampal FABP7 mRNA expression mirrors the temporal profile of stocktickerCREB-induced BDNF mRNA expression in hippocampus (Barco et al., 2005), suggesting common pathways may exist in neural plasticity-related processes coupled to astrocyte function (Stellwagen and Malenka, 2006; Ota et al., 2013; Perez-Catalan et al., 2021; Lawal et al., 2022). FABP7 is enriched in astrocytes and is involved in lipid signaling cascades that regulate changes in cell growth, morphology, and motility (Feng et al., 1994; Arai et al., 2005; Mita et al., 2007, 2010), and regulates dendritic morphology and neuronal excitatory synapse formation, and synaptic transmission (Ebrahimi et al., 2016). Neuronal activity is known to initiate lipid peroxidation, lipoprotein export, and peroxidized lipid storage of lipid droplets (LDs) in astrocytes (Ioannou et al., 2019b). LDs are lipid storage organelles consisting of a layer of polarized lipids with a neutral lipid core mostly composed of triglycerides and esterified cholesterol (Welte, 2015; Olzmann and Carvalho, 2019). Following stress, astrocytes accumulate LDs, which protects cells from lipotoxicity, reactive oxygen species (stocktickerROS)-mediated lipid peroxidation, and can be used as fuel in mitochondrial β-oxidation (Smolič et al., 2021). The ANLS has been suggested to play a role in promoting stocktickerROS waste removal tied to LD formation in glia via apolipoproteins (Liu et al., 2017). FABP7 protects astrocytes from stocktickerROS toxicity through increased LD formation (Islam et al., 2019). Following hypoxia, FABP7 induction by HIF-1α also led to LD accumulation via fatty-acid uptake to protect against stocktickerROS and support cellular survival (Bensaad et al., 2014). Interestingly, knock-down of FABP7 increased stocktickerROS and upregulated uncoupling protein 1 (stocktickerUCP1), which depolarized mitochondrial membranes, increased proton leakage, and glycolysis (Kawashima et al., 2020). Therefore, mechanisms underlying use-dependent neural-glial interactions together with lipid storage and metabolic function may provide a key mediator for coupling sleep homeostasis with circadian rhythms (**Figure 1**).

Here we propose FABP7 as a glial-derived molecule which integrates sleep and circadian rhythms, activity-dependent neural plasticity with lipid signaling and metabolism. FABP7 mRNA expression cycles in synchrony throughout the brain over a 24-h rhythm, including in sleep, wake, and circadian controlling centers (Panda et al., 2002; Ueda et al., 2002; Gerstner et al., 2006, 2008, 2011a). In mammals, the circadian core clock transcriptional translational feedback loop consists of the transcription factors, circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein (BMAL1), which heterodimerize in the nucleus to promote the expression of numerous *cis*-acting E-box promoter element containing genes, including period (PER) and cryptochrome (CRY) genes (Bass and Takahashi, 2010; Mohawk et al., 2012). FABP7 mRNA circadian oscillation is disrupted in arrhythmic BMAL1 KO mice compared to WT mice, and its baseline level of expression was elevated with no effect on either FABP3 or FABP5 transcripts (Lananna et al., 2018; Gerstner and Paschos, 2020). However, E-box elements were not detected bioinformatically in the murine FABP7 promoter, while multiple Rev-erbα (NR1D1) binding sites (called Rev-erbα response element, RORE), a nuclear receptor/transcriptional repressor and component of the metabolic arm of the clock (Bugge et al., 2012; Cho et al., 2012; Zhang et al., 2015), were identified (Vanderheyden et al., 2021). The promoter of the FABP7 gene is a direct target of Rev-erbα (Schnell et al., 2014; Vanderheyden et al., 2021), and regulates FABP7 transcription across multiple brain areas, with baseline FABP7 mRNA expression elevated ∼6–10 fold compared in Rev-erbα mutants over WT, similar to what was observed in the BMAL1 KO (Gerstner and Paschos, 2020). This suggests that the alterations in FABP7 mRNA may be indirectly regulated by BMAL1 via changes in the expression of Rev-erbα (**Figure 1**).

Murine FABP7 brain transcript levels are maximal after the normal waking phase and begin to decline at circadian times of day that correspond with the normal discharge of sleep pressure (Gerstner et al., 2006, 2008; Schnell et al., 2014; Gerstner and Paschos, 2020; Vanderheyden et al., 2021). Previous work has demonstrated that sleep disruption reduced FABP7 mRNA levels in brain tissue of multiple species, including birds and mammals (Cirelli et al., 2006; Jones et al., 2008; Guindalini et al., 2009; Hor et al., 2019). We have shown that FABP7 in turn regulates sleep in flies, mice, and humans (Gerstner et al., 2011b, 2017; Vanderheyden et al., 2022). Transgenic flies that overexpress the mouse FABP7 or *Drosophila* FABP7 homologue, dFABP, increase sleep compared to non-transgenic control flies (Gerstner et al., 2011b). *Drosophila* glia dFABP is also associated with LD formation (Kis et al., 2015), and dFABP overexpression enhanced memory in flies (Gerstner et al., 2011a,b). FABP7 KO mice show fragmented sleep compared to WT mice, similar to what is observed in human carriers of the FABP7 T61M mutation compared to non-carriers (Gerstner et al., 2017). Interestingly, flies that overexpress the human FABP7 T61M mutation compared to non-mutant human FABP7 specifically in astrocytes also show fragmented sleep (Gerstner et al., 2017). A more recent study showed that flies that overexpress dFABP in glia have normal circadian rhythmicity, while RNAi against dFABP incurred more arrhythmic flies, compared to controls (Jang et al., 2022). Together these studies suggest that glial FABP7 is a well-conserved integrated modulator of sleep and circadian behavior.

The cellular and molecular mechanisms that integrate the circadian timing of sleep/wake cycles with sleep homeostasis may be linked to the patency of neuronal-glial interactions, which may occur via Perisynaptic Astrocytic Processes (PAPs)

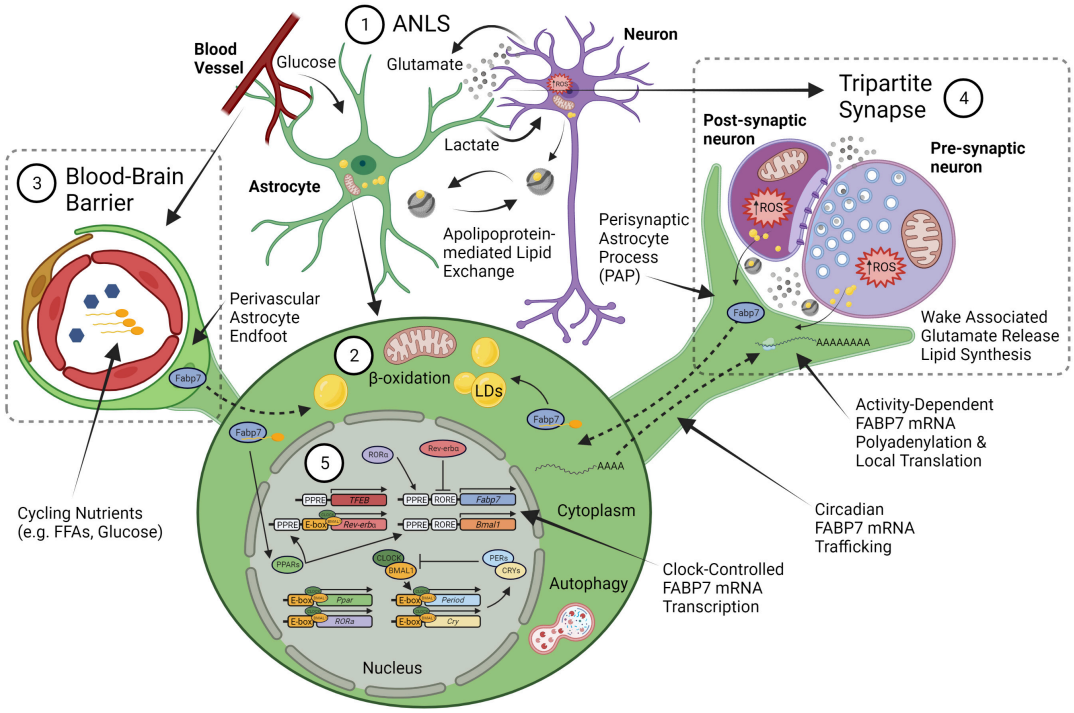

FIGURE 1
An integrated neural-glial metabolic clock-sleep model. (1) The astrocyte-neuron lactate shuttle (ANLS) hypothesis proposes that activity-dependent glutamate release at synapses triggers astrocyte glucose uptake from blood, which is then converted to lactate and sent to neurons to support the increased metabolic demand. Sleep pressure (homeostasis) would be linked to the increased energy produced by this lactate in neuronal mitochondria from wake-associated glutamate release, which generates reactive oxygen species (ROS) production and subsequent lipid formation that are transferred back to glia via apolipoproteins (i.e., ApoE). (2) These lipids will bind fatty acid transport proteins, including FABP7, to form lipid droplets (LDs) in astrocytes. The lipid stores can be used as fuel in astrocyte mitochondria via β-oxidation to produce ketone bodies. (3) Astrocyte endfeet surround the brain vasculature as one of the cellular components of the blood brain barrier (BBB). Circulating nutrients and metabolic constituents such as free fatty acids (FFA) and glucose are taken up by astrocytes and used as energy for the brain. (4) This wake-associated glutamate release would also be tied to local translation of FABP7 mRNA in the fine perisynaptic astrocytic process (PAP) of the tripartite synapse, which consists of an astrocyte ensheathment along with pre- and post-synaptic neuronal compartments, to couple on-site FABP7 protein demand with newly synthesized lipids derived from local excitatory synaptic activity in neurons. (5) The timing of FABP7 mRNA expression is regulated by the circadian clock via Rev-erbα, a transcriptional repressor that binds to RORE cis-elements in the promoters of FABP7 gene and the core-clock transcriptional activator BMAL1. Following transcription, FABP7 mRNA is trafficked to PAPs where it is locally translated upon behavioral state-dependent changes in neural activity. Therefore, clock-controlled expression of FABP7 relays the circadian timing of sleep with changes in sleep pressure through mechanisms underlying local translation at PAPs. FABP7 may in turn feedback on transcription of the core-clock via nuclear localization and activation of peroxisome proliferator-activated receptor (PPARs), for example through FFAs, such as omega-3 polyunsaturated fatty-acids known to oscillate in the peripheral vasculature, or those from PAPs. PPAR—mediated transcription of Transcription Factor EB (TFEB) may in turn initiate autophagy (Soto-Avellaneda and Morrison, 2020), or alternatively, autophagy could be stimulated via other BMAL1-dependent mechanisms in astrocytes (McKee et al., 2023). Circadian FABP7 may also regulate BBB permeability over the course of the day to influence the transmission of peripheral signals and metabolic constituents to (or from) the brain. Created with BioRender.com.

(Halassa et al., 2009; Frank, 2013). Astrocytes can extend these fine, peripheral, filamentous structures around the pre- and post-synaptic areas, collectively called the tripartite synapse (Araque et al., 1999; Perea et al., 2009; Santello et al., 2012; **Figure 1**). PAPs have been shown to influence synaptic activity by several mechanisms, including neurotransmitter uptake, metabolism, and the release of gliotransmitters (Reichenbach et al., 2010; Frank, 2013). Astrocytes can extend or retract (Bernardinelli et al., 2014a) to morphologically adjust neuron-astrocyte interactions at synapses with concomitant localization of the actin-binding protein, ezrin (Derouiche and Frotscher, 2001; Derouiche et al., 2002), which is activated by phosphorylation (Tsukita and Yonemura, 1997). We previously characterized sleep loss-induced reductions in neural-glial interactions in flies (Vanderheyden et al., 2019), however, to our knowledge PAPs have not been characterized in the adult *Drosophila melanogaster* brain. PAPs have been shown to expand with increases in synaptic activity and with heightened glutamatergic tone (Theodosis et al., 2008; Perez-Alvarez et al., 2014), and is correlated with wake behavior (Naylor et al., 2012). Ultrastructural studies report astrocytic interfaces increase near synapses and are associated with wakefulness in rodents (Bellesi et al., 2015). PAPs are known to change dynamically with circadian rhythm (Lavialle et al., 2011) and with activity-dependent synaptic plasticity (Genoud et al., 2006; Bernardinelli et al., 2014b). We also documented the circadian rhythm of mammalian FABP7 mRNA trafficking to PAPs, which coincides with cycling FABP7 PAP protein levels, and is maximal during the wake phase of the day and reduced in the sleep phase (Gerstner et al., 2012). It follows that this process in astrocytes is modulated by cytoplasmic polyadenylation element binding proteins (CPEBs) (Gerstner et al., 2012), which are known to regulate subcellular trafficking, localization, and translation of neuronal synaptic plasticity-related

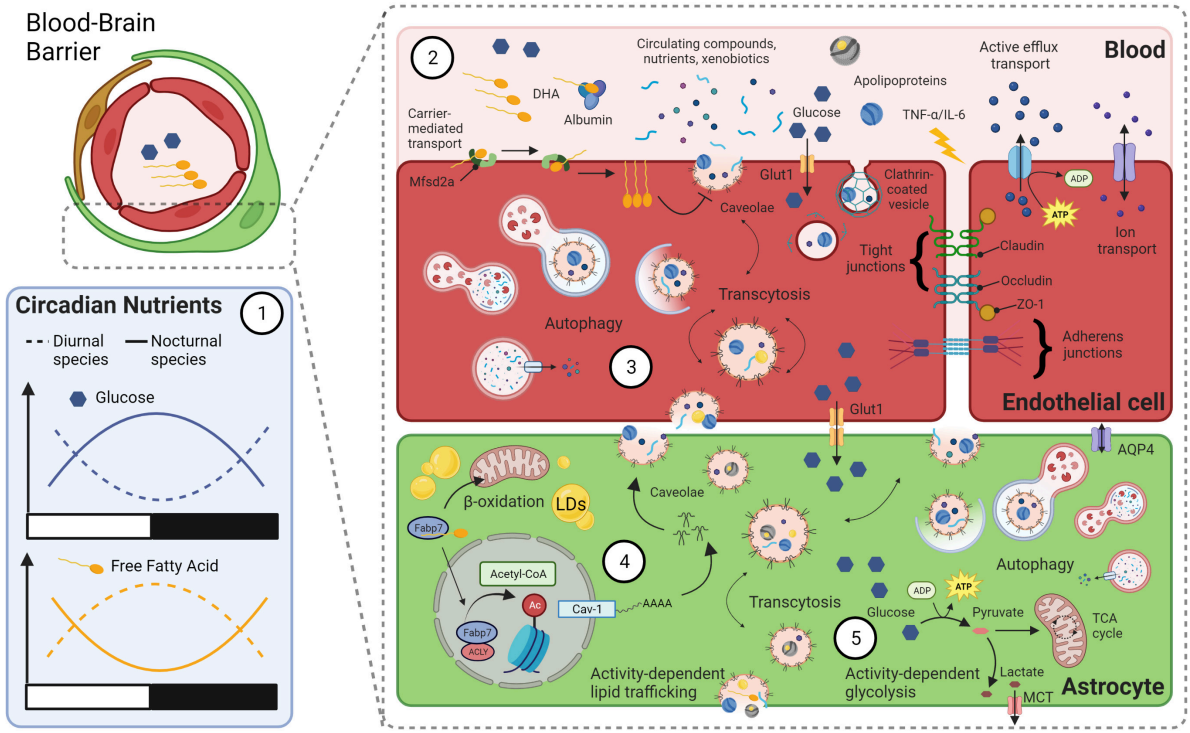

FIGURE 2
A model linking bioenergetics with integrated clock-state-dependent fluctuations in metabolism and BBB permeability. (1) Diurnal and nocturnal species have diametrically opposed rhythms in circulating levels of glucose and free fatty acids (FFAs). Within species, levels of glucose and FFAs oscillate over the day in opposite phases. (2) Various transport mechanisms across the BBB can influence permeability and are closely tied to circadian rhythms and behavioral state. For example, circadian rhythms of circulating omega-3 fatty-acid, DHA, may bind to endothelial transport protein major facilitator superfamily domain containing 2a (Mfsd2a), which flips DHA from the outer-membrane to inner-membrane surface. This is known to block caveolae formation and transcytosis at the BBB (Andreone et al., 2017). Other lipid structures, such as apolipoproteins, may bind to receptors for endocytosis. Circadian changes in circulating glucose are trafficked across the BBB by transporters (e.g., Glut1). Circulating cytokines such as TNF-α and IL-6, whose levels increase with sleep loss, can disrupt tight junction proteins and increase BBB permeability. Clock-state dependent changes in efflux and ion transport can also occur at the BBB. (3) Autophagy of endocytosed materials and cellular damage following BBB disruption due to extended wakefulness may protect endothelial cells and increase their survival. (4) Astrocyte caveolae formation is driven by FABP7-mediated acetylation of histones via an ATP-citrate lyase (ACLY) interaction that increases nuclear Acetyl-CoA levels and activates the promoter of the caveolin-1 gene. Caveolae transcytosis in astrocytes may therefore be integrated between circadian oscillation in circulating DHA levels in the vasculature and the clock-controlled expression of FABP7. Astrocyte uptake of cycling lipids and DHA may in turn influence the formation of lipid droplets (LDs) and subsequent β-oxidation in mitochondria. (5) A balance between activity-dependent energy demands and circulating nutrient availability integrates the circadian clock with behavioral state in astrocytes. For example, local use-dependent neural activity will increase the ANLS, to convert glucose into lactate that is delivered to neurons from astrocytes via MCTs. This wake-dependent neural activity is coupled to increased lipid synthesis in neurons, that is taken up by astrocytes and stored in LDs for later use as fuel (see **Figure 1**). Metabolic byproducts of this bioenergetics pathway are cleared via autophagy, exocytosis and/or by the glymphatic system, via water channels such as Aquaporin 4 (AQP4). Created with BioRender.com.

transcripts such as αCaMKII (Wu et al., 1998; Huang et al., 2002, 2003). Since FABP7 is regulated by the circadian clock, affects sleep behavior, and its PAP-enrichment oscillates over the light-dark cycle, it is a strong candidate molecule for the integration of the circadian timing of sleep with sleep-need via changes in neuronal-glial interactions. We propose that changes in neuronal-glial interactions and PAPs integrate circadian processes with sleep/wake behavior via FABP7 (**Figure 1**).

Fatty acid binding protein 7 in injury and disease

Fatty acid binding protein 7 has been shown to be involved in reactive gliosis of the CNS. Cortical FABP7-positive (+) astrocytes increased in response to a stab injury in WT mice, and the number of reactive astrocytes was decreased in FABP7-KO mice (Sharifi et al., 2011). In normal, uninjured cortex, FABP7 was localized to glial fibrillary acidic protein (GFAP) + astrocytes (21% of FABP7 + cells) and Neural/glial antigen-2 (NG2) + oligodendrocyte progenitor cells (62%). However, in injured cortex there was a significant increase in FABP7 + /GFAP + cells but no change was detected in FABP7 + /NG2 + cells (Sharifi et al., 2011). In the stab-injured cortex of FABP7-KO mice there was also a decrease in the number of the proliferation marker bromodeoxyuridine/5-bromo-2′-deoxyuridine (BrdU) + astrocytes compared with WT mice, further implicating FABP7 in repair (Sharifi et al., 2011). Using a scratch-injury model in primary cultured astrocytes, increased FABP7 was observed at the peri-injury borders compared to intact astrocytes. Moreover, FABP7-KO astrocytes showed a slower proliferation compared with WT astrocytes by BrdU + immunochemistry (Hara et al., 2020).

FABP7-assisted CNS repair extends beyond the parenchyma. In a mouse spinal cord compression model, FABP7 was primarily upregulated in proliferative astrocytes compared to non-injured control mice (Senbokuya et al., 2019). In this model, FABP7-KO mice had significantly lower surviving ventral neurons 28 days post-injury compared to WT mice, suggesting that astrocytic FABP7 has a neuroprotective role (Senbokuya et al., 2019). This is recapitulated with several reports of elevated FABP7 expression following traumatic brain injury (TBI) (Halford et al., 2017; Rui et al., 2019; Mao et al., 2020). FABP7 expression was also associated with reactive astroglial hypertrophy in spinal cord autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS) (Bannerman et al., 2007) and in astrocytes of lesions in early stage MS patients (Kipp et al., 2011). In demyelinating regions of EAE mice increased astrocytic FABP7 expression relative to non-EAE mice was observed and compared to WT mice, FABP7-KO mice manifest with early onset of EAE symptoms (Kamizato et al., 2019). The clinical score, however, was significantly reduced in the late phase of EAE, indicating a differential role for FABP7 in early versus late stages of MS. Together, these data demonstrate astrocytic FABP7 expression is integrally connected with reactive gliosis and brain injury.

Many diseases, nervous system dysfunction, and neurological disorders are associated with alterations in FABP7 expression. FABP7 has been implicated multiple cancers, Down syndrome, schizophrenia, and various neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) (Cheon et al., 2003; Sánchez-Font et al., 2003; Watanabe et al., 2007; Teunissen et al., 2011; Guttula et al., 2012; Matsumata et al., 2016; Kagawa et al., 2019; Killoy et al., 2020; Young, 2020; Asaro et al., 2021; Koga et al., 2021; Cheng et al., 2022; Needham et al., 2022; Tandon et al., 2023). In an unbiased proteomics screen, hippocampal FABP7 was elevated in a mouse model of Alexander disease (AxD), and in AxD patient brain tissue (Heaven et al., 2022). In the adult rat brain, FABP7 in gomori-positive astrocytes is enriched at cytoplasmic granules that originate from damaged mitochondria (Young et al., 1996). Moreover, aging-related mitochondrial pathology occurs in FABP7 + astrocytes, which can hinder cell function, is speculated to be linked to AD etiology (Young, 2020). FABP7 levels are elevated in serum of 29, 35, and 24% of the patients with AD, PD, and other cognitive disorders, respectively, and in 2% of the healthy donors (Teunissen et al., 2011). FABP7 levels in serum of psoriatic patients is elevated compared to controls without dermatoses and is currently being considered as a putative index of neurodegenerative processes linked to psoriasis (Nowowiejska et al., 2022a,b). A quantitative trait loci analysis for low pre-pulse inhibition (PPI), a phenotypic marker of schizophrenia, revealed a strong association with the FABP7 locus in mice, and FABP7 is significantly upregulated in human postmortem brains of schizophrenics compared to controls (Watanabe et al., 2007). FABP7-KO mice exhibit altered anxiety-like behavior (Owada et al., 2006; Vanderheyden et al., 2022) and deficits in PPI (Watanabe et al., 2007). Plasma FABP7 concentrations also correlated with Positive and Negative Syndrome Scale clinical scores, particularly in severities of depression/anxiety, cognition, and positive symptoms of schizophrenia patients (Koga et al., 2021). Together, these studies implicate FABP7 in a broad array of illnesses and disorders, underscoring the importance of its role in pathophysiological conditions associated with disease. Given that sleep and circadian disturbances are comorbid with many diseases and disorders (Wulff et al., 2010; Musiek et al., 2013; Depner et al., 2014; Musiek and Holtzman, 2016; Abbott et al., 2020; Colwell, 2021; Grandner, 2022; Harvey, 2022; Nassan and Videnovic, 2022), and coupled with a growing literature touting chronotherapy to optimize treatment for diseases (Fu and Kettner, 2013; Cederroth et al., 2019; Sulli et al., 2019; Lee et al., 2021; Van Drunen and Eckel-Mahan, 2022), the relevance of FABP7 expression in the context of sleep/wake and circadian regulation is poised for future translational studies and has clinical utility in the development of therapeutic strategies to treat a wide range of CNS-related disorders.

Conclusion and future directions

Incorporation of other inputs, such as metabolism and psycho-social behavior, into the two-process model of sleep/wake regulation has clear conceptual improvements for sleep and circadian research (Borbely et al., 2016). While most studies remain focused on neuronal function, alternative work has examined the role of glia, other cells, tissues, peripheral systems, and microbiota in sleep behavior (Anafi et al., 2013; Frank, 2013; Arnardottir et al., 2014; Ehlen et al., 2017; Matenchuk et al., 2020; Patke et al., 2020; Cable et al., 2021; Withrow et al., 2021). The proposition that FABP7 represents a molecular "node" that integrates circadian and sleep behavior with changes in neuronal-glial interactions is inherently colligated in metabolic processes.

The pleiotropic nature of FABP7 cellular signaling offers a plethora of empirical opportunities for determining functional roles of sleep and circadian rhythm biology. FABP7 has especially high binding affinity to long-chain polyunsaturated fatty-acids, especially the omega-3 docosahexaenoic acid (DHA) (Balendiran et al., 2000). DHA in blood oscillates over the day despite changes in homeostatic sleep pressure in humans (Dallmann et al., 2012). DHA is the most abundant omega-3 in the brain, makes up 10-20% of total lipids, and is implicated in many diseases, including cancer, neurodegenerative diseases, and various neurological and psychiatric disorders (Weiser et al., 2016; Sun et al., 2018; Montecillo-Aguado et al., 2020; von Schacky, 2021). Upon binding DHA a conformational shift signals nuclear localization in FABP7 to mediate peroxisome proliferator-activated receptor-gamma (PPARγ)-dependent transcription (Tripathi et al., 2017). Circadian oscillations in levels of circulating glucose and lipids are diametrically opposed, and are in opposite phases, between nocturnal and diurnal species (Kumar Jha et al., 2015; **Figure 2**). Oscillations in these metabolic nutrients are likely closely tied to transport systems at the blood brain barrier (BBB) linked to differential bioenergetics (e.g., lipid oxidation and glycolysis), recycling and waste clearance mechanisms (e.g., autophagy and glymphatics) that incorporate behavioral state with circadian rhythms. Taken together, FABP7 may integrate peripheral lipid circadian oscillations in the brain vasculature at the BBB with molecular transcriptional processes within the clock feedback loop balanced against energetic demands from wake-dependent synaptic activity and energy supply (**Figures 1**, **2**).

The BBB is a dynamic structure composed of many cell types, including endothelial cells, astrocytes, pericytes, neurons,

and microglia that form the neurovascular unit, which has been implicated in many neurological disorders, as well as sleep and circadian processes (He et al., 2014; Pan and Kastin, 2017; Artiushin et al., 2018; Hurtado-Alvarado et al., 2018; Cuddapah et al., 2019; Zhang et al., 2021; Li F. et al., 2023; Schurhoff and Toborek, 2023). FABP7 has recently been shown to regulate opioid-mediated disruption of BBB integrity, which permits infiltration of fragile-like regulatory T cells into the nucleus accumbens, a process that leads to synaptic instability and withdrawal symptoms (Zhu et al., 2023). Acute cocaine administration produces a transient increase in BBB permeability (Barr et al., 2020), and FABP7 has been implicated in cocaine-seeking behavior under stressful conditions, where WT mice showed stress-induced conditioned place preference for cocaine, FABP 5/7 double KO mice did not (Hamilton et al., 2018). A reduction in FABP7 protein and transcript levels in the nucleus accumbens was also observed in a juvenile mouse model for stress-induced cocaine seeking behavior (Lo Iacono et al., 2016). Compared to acute social stress, chronic social stress had lower levels of FABP7 mRNA in hippocampus (Stankiewicz et al., 2015). Chronic mild stress reduces brain glucose metabolism in many brain regions, including hippocampus, of WT mice but not in FABP7 KO mice (Hamilton et al., 2022). Increases in glucose transporter-1 were observed in the BBB in frontal cortex and hippocampus of rats exposed to restraint stress (Sántha et al., 2015), and chronically stressed mice show increased BBB permeability (Lee et al., 2018). Following single-prolonged stress, a rodent model for post-traumatic stress disorder, we observed disrupted unconditioned anxiety in FABP7 KO mice compared to WT mice, which was also associated with abnormal stress-dependent sleep suppression. Following TBI, FABP7 also protects BBB integrity through a caveolin-1 signaling pathway (Rui et al., 2019) and nuclear FABP7 is known to interact with ATP-citrate lyase (ACLY) to drive acetyl-coA-mediated histone regulation of caveolin-1 gene expression (Kagawa et al., 2020; **Figure 2**). Given BBB circadian disruptions occur following stress responses and in several neurological disorders, including brain metastasis, epilepsy, AD, and PD (Schurhoff and Toborek, 2023), future studies determining the relationship between FABP7 signaling, brain injury, BBB permeability, stress, and sleep/circadian rhythms will be important for the treatment of neurological disorders and diseases. The integrated glial metabolic clock-sleep model provides a conceptual framework to both appreciate and investigate these collective biologies and systems. Recently it was shown that β-oxidation in glial mitochondria provide ketone bodies to fuel neurons in the absence of glycolysis in *Drosophila*, supporting our model (McMullen et al., 2023). Further studies determining the phylogenetically conserved mechanisms within the model will be important for our understanding of the fundamental properties of sleep.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JG wrote the manuscript with input from co-authors. All authors approved the final version of the manuscript.

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Conflict of interest

JG was founder of Blood Brain Biotechnology, LLC.

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

Publisher's note

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