



From Physiology to Pathology of Cortico-Thalamo-Cortical Oscillations: Astroglia as a Target for Further Research

Davide Gobbo[†], Anja Scheller[†] and Frank Kirchhoff^{**}

Molecular Physiology, Center for Integrative Physiology and Molecular Medicine (CIPMM), University of Saarland, Homburg, Germany

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*Correspondence:

Frank Kirchhoff
frank.kirchhoff@uks.eu

†ORCID:

Davide Gobbo
orcid.org/0000-0002-4076-2697
Anja Scheller
orcid.org/0000-0001-8955-2634
Frank Kirchhoff
orcid.org/0000-0002-2324-2761

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The electrographic hallmark of childhood absence epilepsy (CAE) and other idiopathic forms of epilepsy are 2.5–4 Hz spike and wave discharges (SWDs) originating from abnormal electrical oscillations of the cortico-thalamo-cortical network. SWDs are generally associated with sudden and brief non-convulsive epileptic events mostly generating impairment of consciousness and correlating with attention and learning as well as cognitive deficits. To date, SWDs are known to arise from locally restricted imbalances of excitation and inhibition in the deep layers of the primary somatosensory cortex. SWDs propagate to the mostly GABAergic nucleus reticularis thalami (NRT) and the somatosensory thalamic nuclei that project back to the cortex, leading to the typical generalized spike and wave oscillations. Given their shared anatomical basis, SWDs have been originally considered the pathological transition of 11–16 Hz bursts of neural oscillatory activity (the so-called sleep spindles) occurring during Non-Rapid Eye Movement (NREM) sleep, but more recent research revealed fundamental functional differences between sleep spindles and SWDs, suggesting the latter could be more closely related to the slow (<1 Hz) oscillations alternating active (Up) and silent (Down) cortical activity and concomitantly occurring during NREM. Indeed, several lines of evidence support the fact that SWDs impair sleep architecture as well as sleep/wake cycles and sleep pressure, which, in turn, affect seizure circadian frequency and distribution. Given the accumulating evidence on the role of astroglia in the field of epilepsy in the modulation of excitation and inhibition in the brain as well as on the development of aberrant synchronous network activity, we aim at pointing at putative contributions of astrocytes to the physiology of slow-wave sleep and to the pathology of SWDs. Particularly, we will address the astroglial functions known to be involved in the control of network excitability and synchronicity and so far mainly addressed in the context of convulsive seizures, namely (i) interstitial fluid homeostasis, (ii) K⁺ clearance and neurotransmitter uptake from the extracellular space and the synaptic cleft, (iii) gap junction mechanical and functional coupling as well as hemichannel function, (iv) gliotransmission, (v) astroglial Ca²⁺ signaling and downstream effectors, (vi) reactive astrogliosis and cytokine release.

Keywords: astrocytes, sleep/wake cycle, NREM, network plasticity, cortico-thalamo-cortical oscillations, spike and wave discharges, sleep

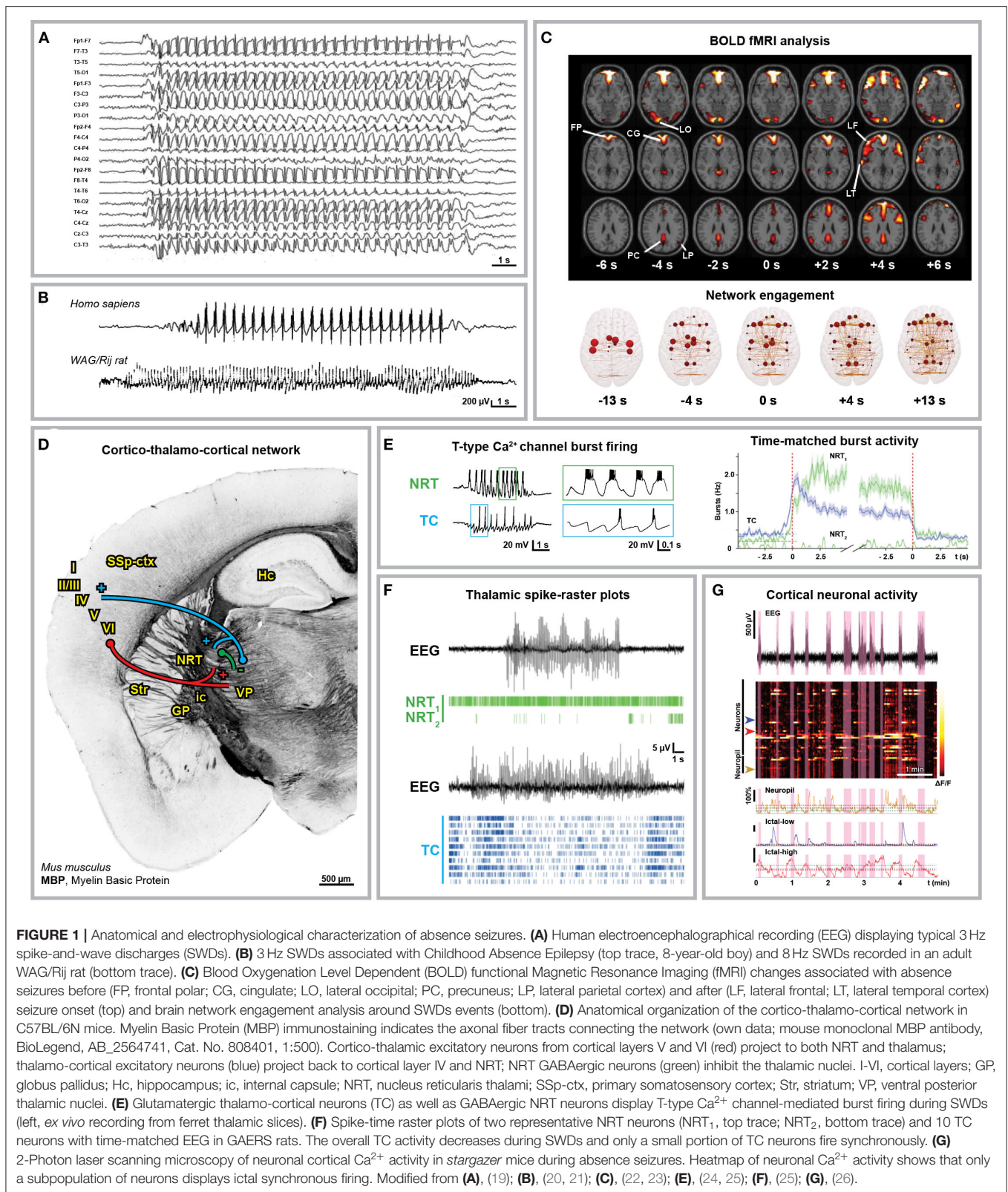
INTRODUCTION

Epilepsy is a highly heterogeneous neurological condition characterized by enduring predisposition to unpredictable pathological discharge of rhythmic activity in the brain networks, which is commonly referred as seizure activity (1). In virtue of the severity and nature of the pathological alteration (abnormal, excessive, or excessively synchronous activation) as well as the cellular and anatomical composition of the affected brain networks, seizures can cause changes in the level of consciousness, behavior, memory, and emotional status. Although the etiology of epileptiform activity is still unknown in half of the cases, understanding the pathological alteration at the basis of the epileptic phenotype may not only be of fundamental therapeutical importance but also provide further insights into the functioning of the affected neural networks in the physiology of the healthy brain. The identification of the molecular and cellular mechanisms underlying physiological oscillations is critical for a full comprehension of their relationship to the respective pathological activity. In this regard, an exceptional case of study is the cortico-thalamo-cortical network, physiologically engaged during sleep and pathologically altered in the context of non-motor (absence) seizures (2).

Absence seizures are transient non-convulsive generalized epileptic events and are also referred as *petit mal* seizures (2, 3). Phenotypically, absence seizures are coupled with sudden and brief impairment of consciousness and lack of responsiveness to external stimuli as well as variable secondary clinical symptoms (e.g., automatisms, atonic, and tonic muscular components etc.) (4, 5). Absence seizures are the sole clinical symptom of childhood absence epilepsy (CAE) but are also associated with several other idiopathic generalized epilepsies (4, 6–11). Although CAE has up to 70% remission rate (7, 12), the gold standard monotherapy, based on ethosuximide and valproic acid, is still ineffective in 30% of the cases (13). Moreover, clinical conditions displaying absence seizures are often associated with severe neuropsychiatric comorbid conditions such as impaired attention, learning, memory and cognition, which are often left unaltered or even worsened by common antiepileptic drugs (14–17).

Although absence seizures display inter- and intraindividual variability (17, 18), they exhibit generalized bilateral 2.5–4 Hz spike and wave discharges (SWDs) with no aura or post-ictal depression (Figures 1A,B) (4, 27–29). It is widely accepted that the sharp spike and the slow wave component of SWDs are functionally coupled and correspond to a state of neuronal excitation and silence in the cortico-thalamo-cortical network, respectively (30). Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) studies in humans consistently showed cortical network engagement in correspondence of and even preceding the appearance of SWDs in electrographic traces as well as an increased interictal synchrony in the sensorimotor cortex (Figure 1C) (22, 23, 31–36). Most advancements on the understanding of the cellular and synaptic mechanisms underlying SWDs derive from the extensive use of genetic animal models, particularly the genetic absence epilepsy rats from Strasbourg (GAERS)

and Wistar-Albino-Glaxo rats from Rijswijk (WAG/Rij) (20, 37–42) as well as many monogenic mouse mutants (43–45). Although sharing most electrographic and behavioral hallmarks of absence seizures, animal models are characterized by higher SWD frequencies (5–11 Hz) (Figure 1B). *Ex vivo* multi-site local field potential studies identified the peri-oral primary somatosensory cortex as initiation site of absence seizures in WAG/Rij (46) and GAERS rats (47–50). Notably, this has been proven wrong for the acute pharmacological γ -hydroxybutyric acid (GHB) model (51–54) in mice, where the prefrontal cortex was suggested as the initiation site of SWDs (55). With this in mind and considering the many areas contributing to the cortical pre-ictal BOLD changes of absence seizures, one can probably not identify a unique canonical focal onset or initiation site for absence seizures. Instead, the denomination *cortical initiation network* has been recently proposed (17), thereby settling the long-standing controversy about the SWDs initiation site (56–59). However, the existence of a cortical initiation network does not imply that manipulation of the sole thalamic components of the cortico-thalamo-cortical network is not sufficient to induce SWDs, as it is indeed the case (60–62), or that the wide thalamo-cortical innervation is not crucial for SWDs generalization, as suggested by the existence of subclinical SWDs restricted to the cortical network (48). In particular, the thalamic posterior nucleus plays a crucial role in the generalization of SWDs (61, 63–66). Till recently, *ex vivo* studies performed in different mammalian models identified the hyperexcitability and T-type Ca^{2+} channel-mediated burst activity of glutamatergic thalamo-cortical neurons and GABAergic neurons from the thalamic reticular nucleus (or *nucleus reticularis thalami*, NRT) as the rhythmogenic cortico-thalamo-cortical network mechanism of SWDs (Figures 1D,E) (24, 41, 67–71). Nevertheless, recent *in vivo* studies performed in rodents showed that only a small fraction of thalamo-cortical and cortico-thalamic neurons are synchronously active at each SWD cycle and the cellular composition of this neuronal subpopulation changes between subsequent cycles, thus excluding the existence of distinctive neuronal subpopulations (Figures 1E,G) (25, 26). This explains why, with SWD progression, the activities of the cortico-thalamic and thalamo-cortical neurons undergo a phase-shift in time (46) since different neuronal subpopulations participate in this excitatory feedback-loop with slightly different kinetics. Moreover, this progressive phase-shift between different subpopulations active at the same time accounts for the overlapping average electrical activity in the cortico-thalamic, thalamo-cortical, and NRT neurons within any SWD cycle. Moreover, although interictal T-type Ca^{2+} channel burst activity in the thalamo-cortical neurons increases right before SWD onset, overall *in vivo* ictal thalamic activity decreases and only cortical and NRT T-type channels are essentials for SWDs (25). Interestingly, all NRT neurons fire within each SWD cycle, even though a fraction of those neurons fires relatively asynchronous tonic spikes rather than T-type Ca^{2+} channel-mediated bursts in phase with the SWDs (Figures 1E,F) (25). The enhanced tonic inhibition of thalamo-cortical neurons as well as the increased thalamic GABA level are key aspects of absence seizures



(25, 72–78). Moreover, the fact that SWDs can be induced by the impairment of the cortico-thalamic glutamate release due to deletion of P/Q-type Ca^{2+} channels in the projecting

cortical neurons from layer VI could suggest that a balance shift toward GABAergic inhibition more than an absolute increase of GABA levels is the key mechanism of SWD generalization

(79). Additionally, the decreased glutamate release could lead to reduced activity of cortical interneurons, thus contributing to cortical hyperexcitability.

ASTROCYTES CONTRIBUTE TO NETWORK PRIMING AND SYNCHRONIZATION AS WELL AS SWD INDUCTION, PROPAGATION, AND TERMINATION

After more than three decades of accumulating evidence, nowadays it is widely established that astroglia constitute a ubiquitous non-neuronal communication system in the brain involved in virtually every physiological and pathological scenario of the central nervous system (80–82). Not only do they support synapses from a mechanical, metabolic as well as functional point of view, but they also participate in synaptic transmission and plasticity, neural network excitability and balance between excitation and inhibition (E/I) as active information integrators and processors (83–86). The contribution of the astroglial network to the pathophysiology of epilepsy encompasses a plethora of different molecular mechanisms which currently represent one of the most fruitful research topics in neuroscience (87–96). Pathological priming mechanisms of the astroglial network ultimately involve either E/I imbalance or enhanced network synchronization (or both simultaneously). Alternatively, astrocytes may influence spatial and temporal propagation of seizures, thus playing a key role in the phenotypical outcome of seizures and their severity and therefore representing a promising target for the development of new non-neurocentric drugs. Most of the recent evidence focuses on astroglial contribution to convulsive epileptic activity. Nevertheless, we discuss in the following the putative involvement of astrocytes in network priming as well as seizure induction and propagation which could have a role in pathological epileptic scenarios including SWDs, as well. We focus on the evidence that links to observations coming from the clinics as well as genetic and pharmacological models of SWDs, aiming to point at specific topics which may be worth further research in the field of SWDs.

The Astroglial Network Controls Extracellular Space Homeostasis Through K^+ , Water and Solute Clearance

By means of their close juxtaposition to synapses, their expression of an extraordinary assortment of membrane transporters and receptors as well as their physical and functional coupling through gap junctions (GJs), astroglial networks provide a perfect spatial buffering for neural activity (Figure 2) (97–99). Astrocytes are key regulators of the extracellular K^+ concentration. Their high K^+ permeability mediated by inwardly-rectifying K_{ir} and two-pore-domain K_{2p} channels, Na^+/K^+ pumps and $Na^+/K^+/Cl^-$ transporters associated with their extensive GJ coupling enables them to uptake and redistribute excessive

extracellular K^+ resulting from neuronal firing (100–103). Astroglial K^+ and glutamate uptake is altered in cultured cortical astrocytes after $K_{ir}4.1$ channel downregulation (104) as well as in astroglial-specific $K_{ir}4.1$ knock-out mice (105, 106). Gain-of-function (107) as well as loss-of-function mutations (108, 109) in the human *KCNJ10* gene encoding $K_{ir}4.1$ have been linked to forms of childhood epilepsies associated with ataxia and cognitive impairment, but not to CAE. Notably, artificially increasing extracellular K^+ concentration *ex vivo* is associated with propagating epileptiform discharges induced by focal optogenetic activation of parvalbumin-expressing interneurons (110). *In vivo* though, K^+ clearance impairment induced by blocking GJ was not sufficient to induce neocortical seizures (111). Interestingly, valproic acid (but not ethosuximide) induces $K_{ir}4.1$ overexpression in the cortex of healthy rats (112). Nevertheless, further research is required to address the actual contribution of $K_{ir}4.1$ overexpression in the anti-absence effects of valproic acid, as well as the putative role of astroglial $K_{ir}4.1$ itself in the development and propagation of SWDs. The combined use of cell-specific conditional knock-out of these channels and pharmacological models of SWDs could shine new light on the topic.

K^+ uptake is associated with cellular swelling due to Na^+/K^+ -pump dependent water influx (113). Although the exact molecular mechanisms are still under debate, water fluxes across the astrocytic membrane are associated with K^+ homeostasis and they influence local interstitial osmolarity as well as seizure generation and progression (114–120). Given the accumulating evidence against the predominant contribution of the astroglial water channel aquaporin-4 (AQP4) in water homeostasis (113, 121), the use of AQP4 conditional knock-out as a model of disrupted water homeostasis has been recently challenged. Nevertheless, water homeostasis impairment and the resulting volume and osmolarity dysregulation should affect neural network excitability. Indeed, a recent structural MRI study on CAE showed significant gray matter volume abnormalities in both frontotemporal cortical region and posterior thalami compared to controls (122, 123).

GJ coupling, particularly mediated by connexins Cx30 and Cx43, provides the astroglial network with a high level of intercellular structural, metabolic and functional connectivity, enabling the exchange of ions and small molecules (124–131). In the context of epilepsy, connexins mediate ATP release (into the extracellular space through hemichannels), the spreading of intercellular Ca^{2+} waves (132) and are fundamental in the spatial buffering required for K^+ and water homeostasis as well as glutamate clearance (133, 134). With respect to absence epilepsy, most advancement in unraveling the role of GJs has been obtained employing GJ blockers in well-established genetic animal models (135). The broad-spectrum GJ blocker carbenoxolone (CBX) decreased both amplitude and duration of 4-aminopyridine-induced seizure-like events (SLEs) in thalamocortical slices obtained from mice with spontaneous SWDs (136, 137) as well as the duration of SWDs seen in GAERS rats *in vivo* after systemic application (138). Interestingly,

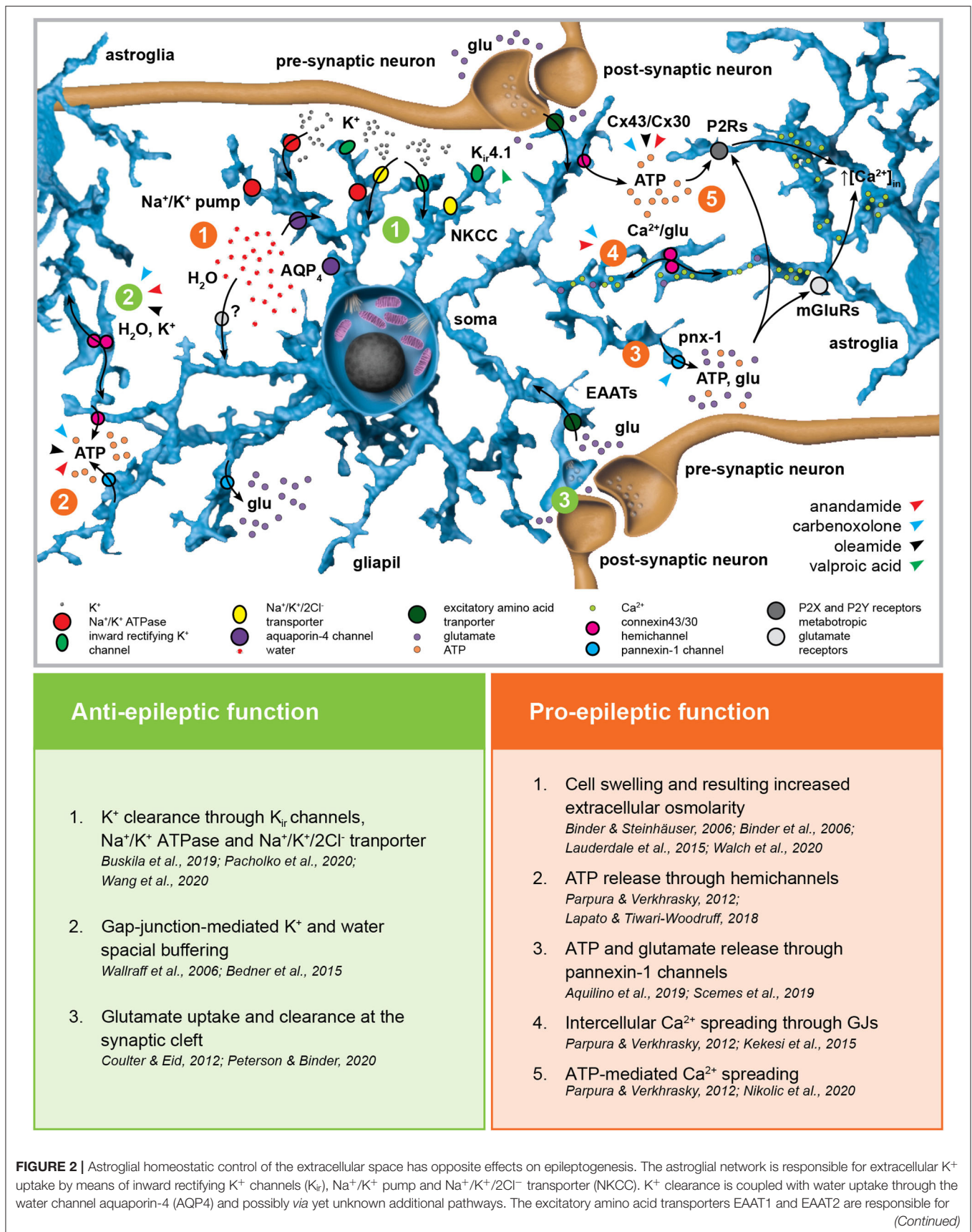


FIGURE 2 | glutamate uptake. Astroglial connexins Cx43 and Cx30 enable gap-junction (GJ) coupling responsible for spatial ionic and metabolic buffering. Connexin hemichannels as well as pannexin-1 channels (Panx1) mediate glutamate and ATP release in the extracellular space possibly activating astroglial metabotropic glutamate receptors (mGluRs) and purinergic P2X and P2Y receptors (P2Rs), respectively. This, in turn, induces intracellular Ca^{2+} increases in the neighboring astroglia. The figure summarizes the pro- and anti-epileptic roles of the mechanisms described above and points to the putative targets of valproic acid and the GJ blockers carbenoxolone, anandamide, and oleamide in this scenario.

in vivo injection of CBX in the NRT of rats with atypical absence seizures and spontaneous SWDs decreased the duration of SWDs (139), whereas no alteration of SWD phenotype was observed if CBX was injected in the posterior thalami of WAG/Rij rats and the *lethargic* mouse genetic model of absence epilepsy (140). Recently, intraperitoneal injection of CBX was associated with absence seizures worsening in WAG/Rij rats (141), hinting at non-obvious and non-trivial differences across the absence epilepsy models. The endocannabinoids anandamide (*N*-arachidonylethanolamine, ANA) and oleamide (*cis*-9,10-octadecenoamide, OLE) are specific Cx43 blockers (142, 143). Intracerebroventricular injection of ANA decreased in a dose-dependent manner the recurrence and duration of SWDs, although its mechanism of action likely involves type-1 cannabinoid (CB1) receptor activation (144) or even direct inhibition of T-type Ca^{2+} channels (145). Interestingly, although specific studies addressing the impact of OLE in absence epilepsy are still required, OLE has a sleep-inducing effect and enhances GABA_A receptor-mediated responses, thus possibly affecting the physiological, temporal-spatial pattern of cortico-thalamo-cortical oscillations (146, 147). CBX as well as ANA and OLE block both GJ activity and connexin hemichannels regulating water and solute (notably ATP) exchanges between the intra- and extracellular space, thus challenging the attribution of any observed phenotype to the sole GJ coupling (131, 148). Moreover, regional differences in connexin isoform expression may be at the basis of different contributions of GJ and hemichannel inhibition in different neural networks, and thus the net phenotypical outcome of the pharmacological manipulation (149). CBX is also known to block pannexin-1, which bears significant topological and pharmacological similarities with the connexins and forms single-membrane channels which have been linked to network hyperexcitability and hypersynchronization by mediating both ATP and glutamate release (150, 151). The use of antibodies or small peptides targeting specific amino acid sequences of different connexins (152–155) could shed new light into the differential contribution of GJ coupling and hemichannel function as well as into the role of different connexin isoforms and pannexin-1 channels in the generation and propagation of SWDs. Finally, ANA, but not OLE, can block Ca^{2+} wave propagation in astrocytes, which has to be taken into consideration in the interpretation of the results (142, 143).

In summary, astroglial networks contribute to the imbalance of neural excitation/inhibition through K^+ and neurotransmitter (glutamate but also GABA) clearance under physiological conditions, thus counteracting network priming through aberrant shifts in the E/I balance possibly leading to network

synchronization. Astrocytes rely on their extensive GJ coupling enabling effective spatial ionic, osmotic, and functional buffering. GJ hemichannels as well as pannexin-1 channels may be responsible for augmented synchronous activity through ATP and glutamate release and following Ca^{2+} spreading throughout the astroglial network. So far, we are still missing evidence for linking the astroglial fine-tuning of the extracellular ion and transmitter homeostasis to SWDs. However, as it is the case for other kinds of epileptiform activity, their role in regulating such network excitability is very likely.

Astrocytes Are Actively Involved in Network Dynamics and E/I Balance Through Neurometabolic Coupling, Neurotransmission Modulation and Gliotransmission

Astrocytes do not only contribute to neural excitability and functioning by responding to neurotransmitter release and modification of extracellular ionic composition, they are also actively involved in neurotransmitter uptake and release, thus having a direct control of E/I balance (Figure 3) (86, 156–158). One of the key features of absence epilepsy are altered GABA levels (72, 159) and GABAergic tonic and phasic inhibition in the cortico-thalamo-cortical network (25, 73). In both GAERS rats and *stargazer* mice, astroglial GABA transporter GAT-1 malfunction leads to increased GABA levels in the thalamus resulting in altered tonic inhibition of GABA_A receptors on the thalamo-cortical neurons (72, 74, 75, 77). Notably, a number of human mutations in *SLC6A1* encoding GAT-1 leads to reduced GABA transport activity, and some of the mutations are associated with CAE or clinical conditions associated with absence seizures (160–164). Moreover, GABA released by astrocytes was proven to activate GABA_A receptors on the membrane of thalamocortical neurons in rodents (165) and blocking astroglial GATs increased extrasynaptic GABA_A receptor-mediated tonic inhibition (166). On the other hand, thalamic astrocytes express GABA_A receptors themselves (167), whose specific role has not been fully resolved yet. Neuronal presynaptic GABA_B receptor expression and function is impaired in the neocortex of WAG/Rij rats, possibly contributing to network hyperexcitability (168, 169). There is plenty of evidence that GABA_B receptors contribute to network priming in absence seizures facilitating thalamo-cortical burst firing, as supported by the exacerbation of SWDs after baclofen or GHB treatment (170–176). Interestingly, the activation of extrasynaptic GABA_B receptors require GABA spillover resulting from an intense GABAergic stimulation, which is in accordance with a predominant role of astrocytic GAT-1 in regulating SWDs, given its expression in close proximity of neuronal

SSp-cx	<ul style="list-style-type: none"> - impaired pre-synaptic GABA_AR function - reduced expression of EAAT1/2 - increased astroglial TCA and glutamine-glutamate-GABA cycle resulting in increased glutamate/glutamine and decreased GABA levels - increased astroglial glutamate dehydrogenase expression 	Merlo <i>et al.</i> , 2007; Inaba <i>et al.</i> , 2009 Dutuit <i>et al.</i> , 2002 Melø <i>et al.</i> , 2006	+	increased glutamatergic and decreased GABA-ergic signalling resulting in enhanced network excitability and synchronization
	<ul style="list-style-type: none"> - reduced GABA uptake - positive allosteric modulation of mGluR1 and mGluR5 - GLAST mRNA overexpression (?) - neuropeptide Y receptor type 2 (Y2R) activation 	Richards <i>et al.</i> , 1995 D'Amore <i>et al.</i> , 2015 Ingram <i>et al.</i> , 2000 Stroud <i>et al.</i> , 2005; Morris <i>et al.</i> , 2007; van Raay <i>et al.</i> , 2012	-	
NRT	<ul style="list-style-type: none"> - impaired CB1-mediated suppression of inhibition - reduced levels of A1Rs 	van Rijn <i>et al.</i> , 2010 Ekonomou <i>et al.</i> , 1998	+	increased neuronal burst firing activity
Thalamic Nuclei	<ul style="list-style-type: none"> - altered astrocytic GAT-1 function resulting in increased GABA levels and excessive tonic inhibition of TC neurons - increased GABA_AR signalling in TC neurons - decreased function of mGluR1/5 in TC neurons - increased glutamine levels - increased astroglial glutamate dehydrogenase expression - impaired CB1-mediated suppression of inhibition 	Richards <i>et al.</i> , 1995; Cope <i>et al.</i> , 2009; Errington <i>et al.</i> , 2011; Pirttimaki <i>et al.</i> , 2013 Beenhakker & Huguenard, 2010 Ngomba <i>et al.</i> , 2011; Celli <i>et al.</i> , 2019 Melø <i>et al.</i> , 2006 Dutuit <i>et al.</i> , 2000 van Rijn <i>et al.</i> , 2010	+	increased tonic and phasic GABAergic inhibition resulting in reduced network activity but increased neuronal burst firing
	<ul style="list-style-type: none"> - positive allosteric modulation of mGluR1/5 - neuropeptide Y and Y2R overexpression 	D'Amore <i>et al.</i> , 2015 Sun <i>et al.</i> , 2001	-	

FIGURE 3 | Regional specific imbalance of E/I at the basis of absence seizures. The main components of the cortico-thalamo-cortical network (SSp-cx, primary somatosensory cortex; NRT, nucleus reticularis thalami; thalamic nuclei) display regional specific shifts toward either excitation or inhibition associated with absence seizures. The figure summarizes the pro- (+) and anti- (-) epileptic effects of specific alterations of the regional E/I balance in the pathological phenotype of absence seizures. A1R, adenosine receptor type 1; EAAT1/2, excitatory amino acid transporters 1/2; CB1, cannabinoid receptor type 1; GABA, γ -aminobutyric acid; GABA_AR, metabotropic GABA_A receptor; GAT-1, GABA transporter 1; mGluR1/5, metabotropic glutamate receptors 1/5; TC, thalamo-cortical; TCA, tricarboxylic acid cycle; Y2R, neuropeptide Y receptor type 2.

synapses compared to a more distal location of GAT-3 (175). A further level of complexity is given by the fact that astrocytes themselves express GABA_B receptors and their activation leads to downstream Ca²⁺ signaling and possibly gliotransmission as shown in the thalamus upon local *ex vivo* baclofen and GHB application (177).

As expected, the injection of the GAT inhibitor tiagabine in the thalamus enhances SWDs (178), while its injection in the somatosensory cortex suppresses SWDs, as does the injection of positive allosteric modulators of glutamate metabotropic receptors mGluR1 and mGluR5 in both somatosensory cortex and thalamus (178). A line of experimental evidence suggests that possibly all metabotropic glutamate receptors, including the mGluR2/3 and mGluR5 expressed on the astroglial membrane, are involved in SWDs through modulation of NMDA receptors and GABA uptake (178–182). Indeed, a subpopulation of astrocytes in the thalamus expresses mGluR5 and respond to cortico-thalamic glutamatergic afferents *via* intracellular Ca²⁺ oscillations (183). Therefore, it is very likely that astrocytes contribute to SWD phenotype by processing glutamate signaling. Astroglial glutamate transporters EAAT1 (GLutamate ASpartate Transporter, GLAST) and EAAT2 (GLutamate Transporter-1, GLT-1) (184, 185) as well as astroglial glutamine-glutamate-GABA cycle impairment (186, 187) have already been associated with the development of various forms of epileptic activities. GAERS rats display decreased protein expression of both

astroglial GLT-1 and GLAST proteins before the development of absence seizures (188). Notably, GLAST is overexpressed at the mRNA level, possibly due to a compensatory mechanism of gene transcription (189). Moreover, excessive neuronal firing is known to induce astroglial swelling and subsequent glutamate release (190). This may add a further level of complexity in the already complex temporal firing dynamics of the thalamo-cortical neurons and NRT neurons both ictally and at interictal-to-ictal transitions (25). Although not yet proven in the context of SWDs, astrocytes possess the extraordinary capability of converting intensive glutamatergic neuronal activity into tonic inhibition, by coupling the glutamate/Na⁺ symport with the glutamine and GABA/Na⁺ symport (191). Notably, the only ATP expenditure associated with this process relies on the replenishment of the intracellular GABA storage since the driving force of the glutamine and GABA release is the re-establishment of the physiological Na⁺ homeostasis altered by the glutamate/Na⁺ symport. Finally, a comprehensive study of metabolic alterations in GAERS rats provides further insight into the cortical and thalamic astroglial contribution to the pathology of SWDs. Most strikingly, cortical astroglial metabolism and glutamine-glutamate-GABA cycle are enhanced in GAERS rats, leading to increased glutamate and glutamine levels and decreased GABA labeling (192). Interestingly, the expression of astroglial glutamate dehydrogenase is increased, in the cortex before the development of absence seizures

and in the thalamus before and after the development of absence seizures, thus possibly leading to a decreased glutamate availability and a shift to the thalamic GABAergic inhibition fundamental for the generalization of SWDs (193). In line with this hypothesis, the intraperitoneal injection of branched-chain amino acids and α -ketoisocaproate pushing the chemical equilibrium toward the synthesis of glutamine led to decreased thalamic glutamate levels and the worsening of absence seizures (194). Moreover, a gain-of-function mutation of the glutamate dehydrogenase gene leading to aberrant glutamate availability and hyperammonemia has been associated with myoclonic absence epilepsy (195). Although further research in the field of absence epilepsy is still required, this evidence supports the role of astrocytic metabolism and glutamine-glutamate-GABA cycle in providing adequate energy supply and network homeostasis required for epileptic activity generation and propagation (94, 196).

In situ hybridization and Western blot analysis showed reduced levels of CB1 receptor mRNA and protein in the NRT and of the CB1 receptor in the thalamus of WAG/Rij rats at the protein level, thereby suggesting an impaired depolarization-induced CB1-mediated suppression of inhibition (197). Indeed, acute systemic injection of the synthetic CB1 receptor agonist WIN55,212-2 resulted in a transient reduction in SWDs frequency, however surprisingly followed by an increase in SWD duration in subchronic treatment (144, 197–199). Since the beneficial effects of the endocannabinoid ANA, previously described, last longer than the transient reduction in SWD frequency induced by the synthetic CB1 agonist and since ANA does indeed shorten SWDs, its mechanism of action is likely not only dependent on CB1 activation but a more complex molecular process (144).

The release of ATP through connexin and pannexin-1 hemichannels and the resulting spread of Ca^{2+} waves largely contribute to the astrocyte-mediated purinergic signaling in epilepsy (200). However, the net impact on the neural network is often context-dependent and may include the conversion of ATP into adenosine. Adenosine levels depend on extracellular ectonucleotidases as well as on the astroglial adenosine kinase (ADK) and its contribution encompasses antiepileptic A1 receptor-mediated as well as proepileptic A2 and A3 receptor-mediated effects (200–203). Once again, most research results have been derived from the analysis of convulsive seizures. Nevertheless, there is a number of evidence suggesting that purinergic signaling is altered in SWDs, too. To which extent this is related to astroglial contribution is still elusive. With respect to SWDs, GAERS rats show lower expression of A1 receptors in the NRT (204) and WAG/Rij rats are characterized by altered expression of A2A receptors in the somatosensory cortex, NRT and thalamus (205). Absence epileptic activity in WAG/Rij rats increases after activation of A2A receptors directly by the specific synthetic agonist 2-[4-(-2-carboxyethyl)-phenylamino]-5'-N-ethylcarboxamido-adenosine (CGS21680) (205) or indirectly after intraperitoneal injection of guanosine (206) as well as of adenosine (207). Conversely, acute caffeine administration, which is a mixed non-specific A1 and A2A receptor antagonist, reduced both amplitude and duration of SWDs in GAERS rats

(208). However, the administration of the specific A1 antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) in WAG/Rij rats had a proepileptic effect on SWDs (209). Notably, a duplication in the chromosomal region containing the gene coding for the extracellular catabolic enzyme adenosine deaminase was associated with a case of early-onset absence epilepsy, possibly leading to an impairment in adenosine homeostasis (210, 211).

The neuropeptide Y (NPY) released by thalamic neurons promotes phase-specific long-term depression of neuronal excitability in the NRT as well as in the thalamus itself and thus possibly contributing to thalamocortical synchronization and the altered dynamics of T-type Ca^{2+} channel-mediated bursting activity in the thalamic nuclei (212). Interestingly, valproic acid treatment increases thalamic levels of NPY mRNA in GAERS rats (213). Moreover, NPY intracerebroventricular injection as well as focal administration of NPY in the somatosensory cortex of GAERS rats had a strong antiepileptic effect mediated by the NPY receptor Y2 (214–216). This was confirmed by the analysis of specific NPY receptor knock-out mice (217, 218) and injection of the specific Y2 receptor agonist Ac[Leu (28, 31)] NPY24-36 and the specific Y2 receptor antagonist BIIE0246 in GAERS rats (215). Notably, viral overexpression of NPY as well as the mRNA of its receptor Y2, both in thalamus and somatosensory cortex of GAERS rats, reduced the number of seizures and the time spent in seizure activity (219). Since astrocytes produce (220) and release (221) NPY and express NPY receptors, including Y2 receptor (222, 223), one can imagine that astrocytes may play a role in NPY signaling in the pathophysiology of cortico-thalamo-cortical networks.

Alterations of astroglial neurometabolic coupling and contribution to the glutamine-glutamate-GABA cycle may be at the basis of SWDs, possibly through enhanced metabolism and glutamate presentation to cortical neurons. Moreover, astroglial control of extracellular neurotransmitter level, based on the expression of glutamate and GABA transporters (EAATs and GATs, respectively) and receptors (both metabotropic and ionotropic) and direct and indirect release of glutamate and GABA, plays a fundamental role in maintaining the E/I balance in the cortex, thalamus and NRT. Astroglial ATP release and subsequent adenosine production seem to have context-dependent effects on neural excitability, but generally in line with observations derived from convulsive seizures pointing at an antiepileptic and proepileptic role of A1 and A2 receptors, respectively. Shifts in the E/I toward inhibition in the thalamus (possibly through altered endocannabinoid signaling) and toward excitation in the NRT and cortex have a pro-epileptic effect on SWDs. Unexpected net outcomes of pharmacological or genetic manipulation may be due to differential impact on different key nodes of the cortico-thalamo-cortical network and/or to astrocytic ability to both preserve and reverse the sign of the input signal.

The Classic Chicken and Egg Situation. Which Comes First: Astroglial Ca^{2+} Or Seizures?

Intracellular Ca^{2+} oscillations are one of the most studied indicators of astroglial activity and information coding

mechanism at the core of the astroglial signaling cascade resulting, among others, in gliotransmission (86). In the context of convulsive epilepsy, excitotoxic spilling of glutamate, GABA and ATP resulting from excessive network activity as well as dying cells induce perturbation in astroglial Ca^{2+} signals (224, 225). Conversely, spontaneous as well as induced Ca^{2+} oscillations lead to gliotransmission thus influencing neuronal synchrony and E/I balance (226–234). Notably, astroglial Ca^{2+} elevations precede temporally neuronal engagement and their attenuation results in reduction of the epileptic activity in an *in vivo* model of temporal lobe epilepsy (TLE) (235). Moreover, astroglial Ca^{2+} activity is associated with spreading depolarization-mediated seizure termination (236). However, current research is far from understanding astroglial Ca^{2+} contribution to seizure generation, propagation, severity, and termination both in mechanistic and logical (sufficiency and/or necessity) terms. In particular, research on the contribution of astroglial Ca^{2+} signaling in seizure phenotype has not yet provided causative links to the SWD pathophysiology. Nevertheless, in the following paragraph we include some observations that encourage further research on the topic.

Thalamic astroglial networks display multi-cellular Ca^{2+} oscillations in absence of neuronal input and induce glutamate release and NMDA-receptor mediated long lasting inward currents in thalamocortical neurons as studied in acute brain slice preparations (226, 237). Thalamic astrocytes segregate into two groups: a first group with mGluR5-dependent and no voltage-dependent Ca^{2+} oscillations in response to cortico-thalamic activation, and a second group with no mGluR5- but voltage-dependent Ca^{2+} responses (183). Moreover, thalamic astroglial Ca^{2+} responses were recorded after acute *ex vivo* application of the weak GABA_B receptor agonist GHB (177), thus suggesting a putative role of astrocytes in the regulation of GABAergic signaling in the thalamus and possible in the phenomenology of SWDs. Notably, sustained GABA_B receptor activation led to a decrease in glutamate release from astrocytes (177). In addition, Ca^{2+} signaling and GABA seem to be connected since artificial inhibition of Ca^{2+} oscillation in striatal astrocytes leads to GAT3 functional upregulation and increased GABA uptake (238). Further evidence suggesting an integrative role of thalamic astrocytes in cortico-thalamic interactions comes from the observation that astroglial glutamate- and NMDA receptor-mediated slow inward currents (SICs) in the thalamo-cortical neurons are largely resistant to afferent cortico-thalamic inputs in their emergence but not in their frequency upon sustained input (239, 240). Moreover, cortico-thalamic glutamatergic input induced disinhibition of thalamo-cortical neurons through astroglial mGluR2 activation, Ca^{2+} -dependent glutamate release and inhibition of presynaptic GABAergic projections from the NRT (241). In the NRT astrocytes also enhance GABA_A receptor signaling (242). Astrocyte-induced glutamate-mediated SICs of thalamo-cortical neurons seem to be dependent on extracellular glutamate levels, since exogenous exposure to the glutamate-mimetic D-aspartate increased the frequency of SICs (243). Although it is still unclear if abnormal or hypersynchronous astroglial Ca^{2+} signals could promote epileptiform network activity by itself, this evidence further supports an astroglial

contribution to the propagation and self-sustain of seizure-like activity (244, 245).

The role of astrocytic Ca^{2+} signaling in epilepsy, and particularly in SWD-displaying epilepsies, is far from being understood. Yet, association studies on CAE and other idiopathic epileptic forms displaying SWDs as well as the evaluation of the genetic etiology of rodent absence epilepsy models point to a plethora of genes involved in voltage-gated Ca^{2+} channel signaling and G protein-coupled receptor signaling that is worth further assessment (7).

Astroglia display spontaneous Ca^{2+} oscillations responsible for gliotransmission and homeostatic control of the E/I balance as well as network synchronicity. Moreover, astrocytes respond to physiological network activity and pathological neurotransmitter spilling and release from dying cells by Ca^{2+} elevations, typically further contributing to network priming, seizure initiation and progression. Conversely, Ca^{2+} signaling-induced gliotransmitter release and modulation of astroglial neurotransmitter receptors and transporters may underlie putative (or potential) anti-epileptic roles of Ca^{2+} signaling. Notably, astroglial Ca^{2+} signaling may also contribute to seizure suppression. To which extent this applies to SWDs is still unclear.

Reactive Astrogliosis and the Astrocyte-Derived Inflammatory Response May Contribute to the Pathology of SWDs

Astroglial proliferation and morphological, biochemical, and functional changes associated with epilepsy as well as with other neurodegenerative diseases are commonly referred to as reactive astrogliosis (246–248). The term is misleading since it implies that the pathological phenotype of astrocytes results from the epileptiform activity and oversees the possible causative role of astrocyte modifications in its genesis (249–251). In GAERS rats, cortical as well as thalamic astrocytes display enhanced expression of the glial fibrillary acidic protein (GFAP) even before the onset of absence seizures (193). Similarly, increased levels of GFAP expression can be found in adult WAG/Rij rats, though to a lesser extent than in GAERS rats (252). Astonishingly, the number of glial cells in the somatosensory cortex is significantly decreased (253). This suggests that biochemical and functional changes may contribute to a greater extent to the pathology of absence seizures than morphological alteration or that the latter involves qualitative astroglial reorganization, e.g., overlap of the astroglial processes, astroglial domain reorganization, structural and quantitative alteration of synaptic contacts or blood-brain barrier dysfunction. Notably, valproic acid diminishes the overlap of astroglial processes observed in correspondence of epileptic foci in several pathological models of convulsive seizures (254). Nevertheless, it is not clear if the same is happening in the pharmacodynamics of valproic acid in the context of SWDs. The same is true for the alterations of the blood-brain barrier (BBB) which have been associated with many pathological scenarios, including epilepsy (255), but whose role in SWDs has not been extensively addressed yet.

Pathological stimulation of astrocytes during convulsive epileptiform activity leads to astrocytic upregulation and release of proinflammatory cytokines, with IL-1 β , IL-6, and TNF α as the most prominent ones. These factors, in turn, can induce astroglial dysfunction leading to, among others, increased glutamate release, decreased glutamate uptake, down-regulation of K_{ir}4.1, AQP4, connexins, and glutamine synthetase as well as upregulation of adenosine kinase (256–258). IL-1 β is induced in reactive astroglia in the somatosensory cortex (and not in other regions of the cortex) in adult GAERS rats with mature SWDs and interestingly also in some young GAERS in association with immature forms of SWDs (259). Furthermore, inhibition of IL-1 β biosynthesis in adult GAERS reduced both the number as well as the duration of SWDs. Conversely, IL-1 β intraperitoneal administration in WAG/Rij rats induced a significant increase in SWDs and worsened the proepileptic effects of the GABA reuptake inhibitor tiagabine (260). TNF α administration also aggravates SWDs but with kinetics incompatible with a direct effect and therefore possibly through *de novo* production of IL-1 β itself. Moreover, before the onset of SWDs, young WAG/Rij rats showed increased TNF α blood levels, which gradually decreased with age and returned to physiological levels in adult rats displaying mature SWDs, thus possibly suggesting a neuroprotective role of TNF α (260). The precise mechanism of TNF α action in this scenario is not clear, although it is known that TNF α reduces astroglial glutamate uptake and decreases neuronal GABA_A receptor expression (261, 262). Notably, IL-1 β -, TNF α -, and IL-6-inducing lipopolysaccharide (LPS) injection in WAG/Rij also promoted SWDs and the increase in the latter was prevented by blocking the inflammatory response with indomethacin (263, 264) as well as blockers of the mTOR pathway (265, 266). Similarly, LPS effects on SWDs were later confirmed in GAERS rats (267). Although IL-1 β is believed to increase the levels of glutamate, co-administration of LPS and the NMDA receptor antagonist D-(-)-2-Amino-5-phosphonopentanoic acid (AP-5) did not counteract LPS effects as expected, but conversely prolonged them (264). Recently, it has been reported that IL-6 receptor (IL-6R) blockade *via* tocilizumab (a humanized monoclonal antibody against IL-6R) reduces SWDs in WAG/Rij rats and inhibits their LPS-induced worsening (268). In line with that, human CAE is known to be associated with detectable levels of IL-6 and IL-8 in the cerebrospinal fluid (269) and treatment with valproic acid reduces IL-6 serum levels in children with tonic-clonic generalized seizures (270).

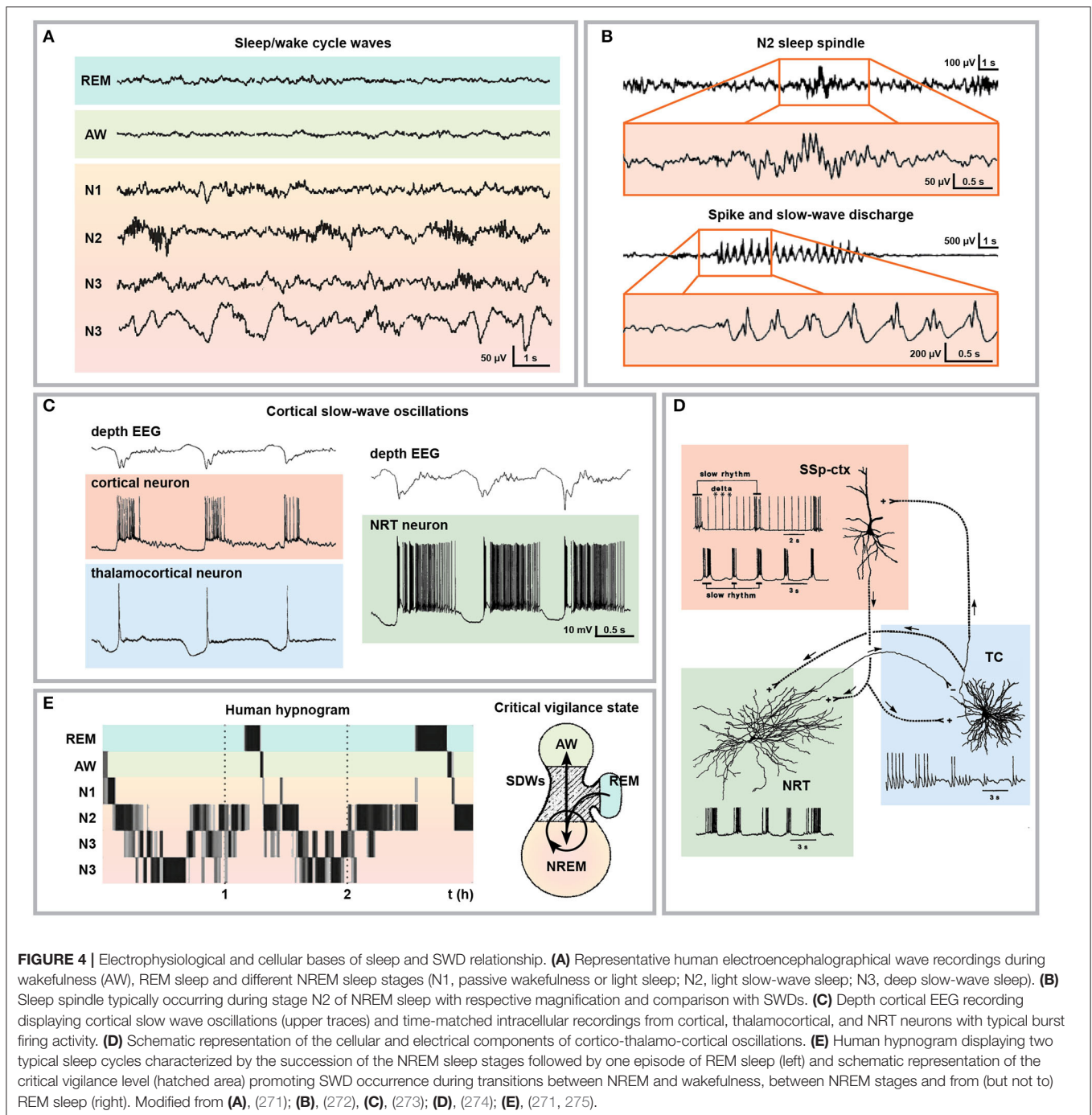
Several lines of evidence support a role for a direct contribution of pro-inflammatory cytokines in the genesis and worsening of SWDs. Notably, astroglial alterations and cytokine release precede SWD onset, although it cannot be excluded that these cell responses may be due to subclinical epileptiform activities or genetic predispositions. IL-1 β , IL-6 and TNF α may contribute to the pathology of SWDs, possibly through impaired K⁺ clearance, glutamine-glutamate-GABA cycle, adenosine metabolism, gliotransmission, and neurotransmitter reuptake.

Other morphological alterations, such as astroglial overlap, connectivity, and synaptic coverage, may play a role as well.

ABSENCE SEIZURES AND NREM SLEEP: TWO SIDES OF THE SAME COIN?

The cortico-thalamo-cortical network processes behaviourally relevant internal and external information and determines vigilance states as well as neuronal network oscillation during sleep (**Figure 4A**), thus playing a fundamental role in both physiology and pathology (25, 276–281). Several lines of evidence suggest that epilepsy and sleep are strongly related (282). Notably, various forms of epilepsy display different incidences across the 24 h sleep/wake cycle and among different sleep stages, possibly due to specific seizure susceptibility dependent on brain excitability and network engagement (283–285).

Till recently, SWDs were considered the pathological transformation of sleep spindles (also known also thalamocortical spindles) occurring during stage II NREM sleep (**Figure 4B**) (272, 286, 287). This concept was mainly supported by studies on the temporal coincidence of sleep spindles and SWDs (288, 289) and on the progressive transformation of sleep spindles into SWDs observed after intramuscular injection of penicillin in cats (24, 290). Indeed, to some extent both sleep spindles and SWDs share some anatomical, cellular and molecular mechanisms (291) and they are functionally correlated (292, 293). However, the identification of SWDs as pathological transitions from sleep spindles has been recently challenged (294–296), in favor of a predominant role of cortical slow (<1 Hz) oscillations alternating active (Up) and silent (Down) cortical activity and concomitantly occurring during NREM sleep (**Figures 4C,D**) (273, 274, 297–301). SWDs largely arise in a specific critical vigilance window in correspondence with passive wakefulness, transitions to NREM slow-wave sleep as well as during transitions between internal substages of NREM sleep (stage I to III; N1: light sleep or passive wakefulness, N2: light slow-wave sleep and N3: deep slow-wave sleep, respectively) (**Figure 4E**). Moreover, SWDs are disrupted by arousing stimuli and do not transition to REM sleep directly (38, 275, 302–308), thus suggesting that absence seizures prefer low and shifting-vigilance periods during superficial slow-wave NREM sleep (282). With respect to the incidence of seizures across the 24 h cycle, the distribution of generalized SWDs is still under debate. Seizures originating in the frontal lobe (as absence seizures are currently believed to be) are more frequent at night and in sleep (309, 310). Conversely though, dialeptic and atonic seizures occur more often during daytime (310). Generalized pediatric seizures, including absence seizures, were reported to occur predominantly during wakefulness (311, 312) but were restricted to NREM sleep stages I and II when occurring during the night and were almost absent during REM sleep (313, 314). Moreover, a study on idiopathic generalized epilepsies including CAE and other SWD-displaying epilepsies showed that interictal epileptic discharges are more frequent during NREM sleep and occur mainly at sleep onset (315). In WAG/Rij rats, SWDs are most



frequent in the beginning of the dark phase and are at their minimum frequency at the onset of the light phase (316, 317). If rats are artificially kept in dim light (thus disrupting the 12:12 light-dark cycle), SWDs still display 24 h cyclicity, proving its endogenous rhythmicity, but the cycle is desynchronized with respect to the rhythm of the general motor activity, thus suggesting that the mechanism governing SWDs and sleep/wake cycles are different (317, 318). Interestingly, after an artificial shifting in the light-dark cycle, SWDs resynchronized at the same speed of light slow-wave speed in comparison with both

REM and deep slow-wave sleep (319), pointing at the existence of a common circadian mechanism governing SWDs and light slow-wave sleep. Taken together, it seems that conditions associated with highly desynchronized (active wakefulness and REM sleep) and highly synchronized (deep slow-wave sleep) cortical activity tend to inhibit SWDs. In line with this hypothesis, the anti-absence molecule uridine (320) impacts sleep architecture by fragmenting sleep, thus increasing the frequency of NREM-REM transitions and by inducing preferentially REM sleep (321).

With respect to the putative interdependency of SWDs and NREM sleep waves, it was reported that sleep deprivation has a proepileptic effect on both humans (322–325) and rodents (304, 305, 326, 327). On the other side, epilepsy is associated with sleep alterations, including sleep fragmentation, day-time drowsiness and difficulties in sleep initiation (328). To date, the field still lacks a systematic clinical study on the effect of absence epilepsy on sleep. Nevertheless, it was shown in WAG/Rij rats that SWDs disrupt NREM sleep and sleep architecture (329). Moreover, epilepsy-induced sleep alterations depend on the timing of the epileptiform activity. In a time-controlled kindling epileptic model in rats, seizure induction at the transition from light to dark (*zeitgeber* time (ZT) 0) and from dark to light (ZT13) altered both NREM and REM duration without affecting sleep/wake cycles and the sole seizure induction at ZT13 induced increased levels of IL-1 and increased NREM sleep specifically (330). Interestingly, both IL-1 β and TNF α increase the amount of NREM sleep (331), which could contribute to the increase of SWD number after LPS injection (263, 264) by an increased state of passive awareness and slow-wave sleep. Indeed, *in silico* meta-analysis of differentially expressed proteins from the fronto-parietal cortex and thalamus of LPS-treated WAG/Rij rats supports this scenario, given the overrepresentation of proteins associated with sleep regulation (332). Moreover, the pathological activation of the mTOR pathway involved in LPS-induced increase in SWDs (265, 266) is responsible for the upregulation of the core clock gene product aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL), also known as brain and muscle ARNT-Like 1 (BMAL1), as observed in a model of tuberous sclerosis complex, a neurological disorder displaying epileptic activity (333). BMAL1 not only is a key component of both circadian and sleep/wake cycles (334) as well as susceptibility to seizures and epilepsy (335), but it is also at the basis of cell-autonomous circadian clock of astrocytes (336, 337).

SWD occurrence varies during the sleep/wake cycle with respect to both sleep and vigilance states. Notably, SWDs peak in correspondence of low and shifting-vigilance periods during superficial slow-wave NREM sleep and are underrepresented during active wakefulness and REM sleep. Resynchronization studies after shifting in the light-dark cycle suggest a common circadian mechanism governing SWDs and NREM sleep. Moreover, even though the nature and the causative link between the two are far from being clearly understood, SWDs and NREM sleep are similarly and consistently altered by a number of pathological and pharmacological alterations.

Both Sleep Architecture and Sleep/Wake Cycle Are Shaped by Astroglial Activity

Given the fact that both SWDs and NREM recruit the cortico-thalamo-cortical network, further insights into the role of astrocytes in the pathophysiology of SWDs may derive from evidence in their contribution to sleep (particularly sleep architecture and sleep/wake cycle) (Figure 5) as well as the circadian cycle. Astroglial impact on circadian clock mechanisms generated in deep structures may contribute to epilepsy in non-intuitive ways (335). In the hypothalamic

primary timekeeping center, the suprachiasmatic nucleus (SCN), astrocyte-derived glutamate inhibits neuronal firing through presynaptic NMDA receptors specifically during the night (338). Moreover, astrocytes release adenosine in a CB1 receptor- and intracellular Ca²⁺ signaling-dependent manner and induce the disinhibition of SCN neurons (339). WAG/Rij rats are also characterized by astrogliosis and impaired GABAergic transmission in the thalamic intergeniculate leaflet, which coordinates inputs from the retina and outputs to the SCN (340). The research on the role of astrocytes on timekeeping is still at its early days, but several lines of evidence support astroglial contribution to sleep, namely the modulation of sleep homeostasis, sleep pressure, vigilance states and sleep-dependent cognitive function, brain energetics and network metabolic supply, network excitability and sleep-associated waste clearance (341, 342).

The sleep/wake cycle is associated with changes in interstitial fluid and of the ionic composition with increased extracellular space and decreased interstitial K⁺ concentration during sleep (343–345), a process that involves norepinephrine-mediated inhibition of the astroglial Na⁺/K⁺ pump during wakefulness (346). This process is responsible for widespread neuronal hyperpolarization and decreased firing rate particularly during NREM sleep (347, 348). In parallel, it was recently reported that children with an autism-associated epilepsy phenotype carrying a gain-of-function mutation in the K_{ir}4.1 coding KCHJ10 gene display abnormal slow-wave sleep with a significantly longer slow-wave period (349). Norepinephrine induces astroglial process elongation and astroglial synaptic coverage during wakefulness (345, 350). Conversely, decreased levels of norepinephrine may be responsible for reduction of direct and indirect astroglial release of ATP/adenosine and D-serine, thus contributing to the overall decreased synaptic failure and increased release probability during sleep. Interestingly, norepinephrine level is particularly low during NREM sleep, due to suppression of noradrenergic neuronal firing (351).

Astroglial-dependent cerebrospinal fluid (CSF) flow is responsible for waste and interstitial fluid clearance during sleep (352) and inward flow of CSF through astroglial AQP4 occurs mainly during NREM sleep (343, 353). The CSF flow is under circadian control mediated by changes of AQP4 polarization (354). Recently, a haplotype of AQP4 carrying several single nucleotide polymorphisms (SNPs), among which some associated with reduced AQP4 expression, has been linked to altered slow-wave NREM sleep modulation (355). Moreover, astroglial gap junction coupling is likely to contribute to the regulation of the sleep/wake by means of modulation of both CSF flow and waste clearance. To date, most studies addressing GJ coupling in astrocytes are focused on the altered metabolite trafficking (namely glucose and lactate) resulting from GJ manipulation that impairs the fundamental role of astrocytes in synaptic energy support and brain energy metabolism (356). Astrocyte-specific conditional knock-out of Cx43 in mice resulted in enhanced sleepiness, fragmented wakefulness, and impaired neuromodulation of the sleep/wake cycle (357). Conversely,

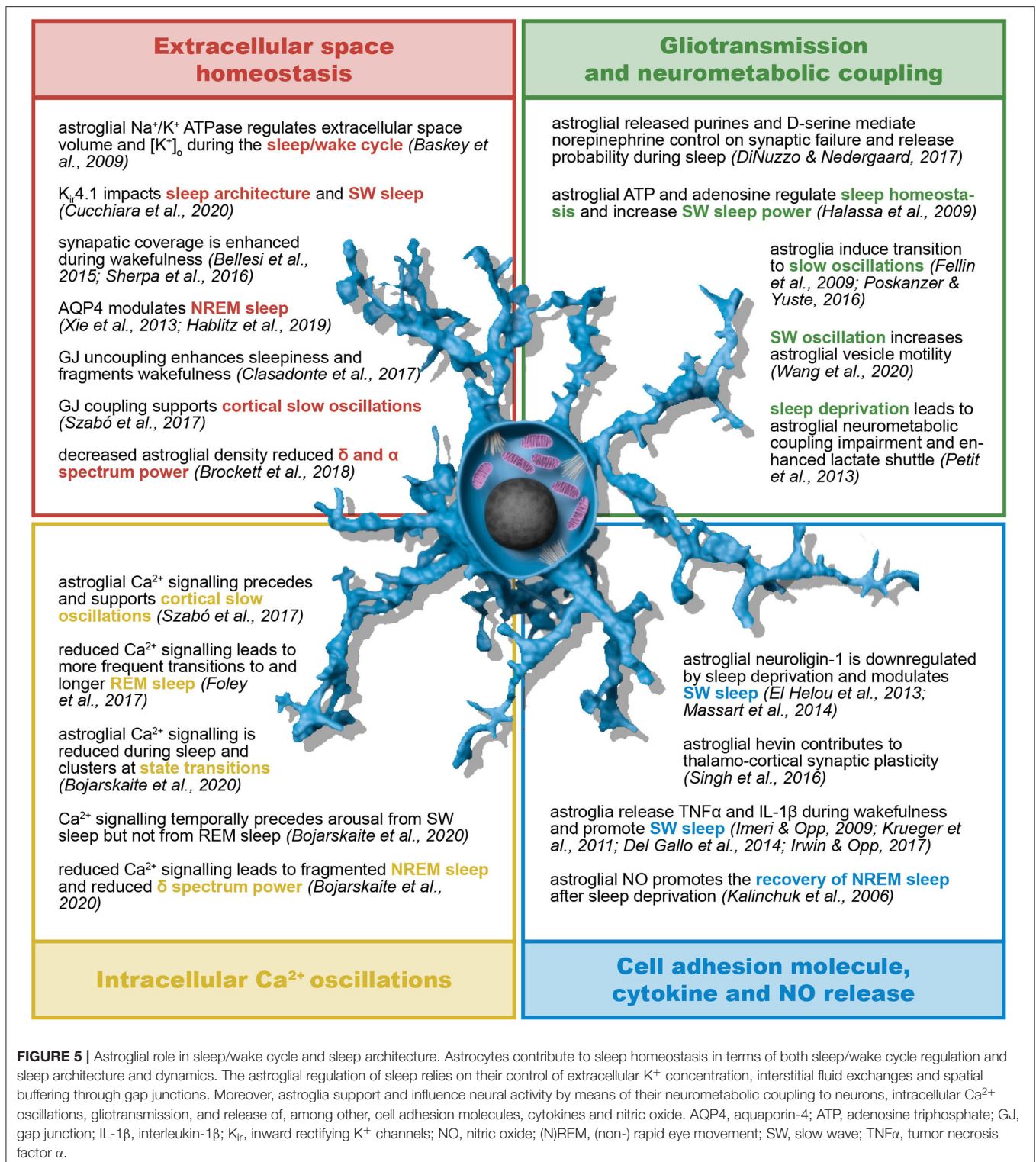


FIGURE 5 | Astroglial role in sleep/wake cycle and sleep architecture. Astrocytes contribute to sleep homeostasis in terms of both sleep/wake cycle regulation and sleep architecture and dynamics. The astroglial regulation of sleep relies on their control of extracellular K^+ concentration, interstitial fluid exchanges and spatial buffering through gap junctions. Moreover, astroglia support and influence neural activity by means of their neurometabolic coupling to neurons, intracellular Ca^{2+} oscillations, gliotransmission, and release of, among other, cell adhesion molecules, cytokines and nitric oxide. AQP4, aquaporin-4; ATP, adenosine triphosphate; GJ, gap junction; $\text{IL-1}\beta$, interleukin-1 β ; K_v , inward rectifying K^+ channels; NO, nitric oxide; (N)REM, (non-) rapid eye movement; SW, slow wave; $\text{TNF}\alpha$, tumor necrosis factor α .

astroglial neurometabolic coupling impairment results from sleep deprivation that leads to astroglial upregulation of the transporters GLUT1, GLT1, the Na^+/K^+ pump as well as other components of the astrocyte-neuron lactate shuttle (358). Sleep deprivation could therefore possibly contribute to increased

network activity also through enhanced lactate delivery to neurons as suggested by the fact that the anticonvulsant stiripentol is a lactate dehydrogenase inhibitor (359) in addition to being a positive allosteric modulator of GABA_A receptors (360).

Impairment of astroglial exocytosis and gliotransmission using cell-specific expression of dnSNARE results in reduced tonic A1R adenosinergic signaling, altered sleep homeostasis and reduced slow-wave power, and reduced sleep pressure in mice (361), as confirmed by previous evidence suggesting the role of A1 receptors in augmented sleep pressure (362–364). The same genetic manipulation suppressed the LPS-induced increase in slow-wave power during NREM sleep, proving the astroglial contribution to inflammatory-derived increased sleep pressure (365). Although the role of A2 receptor (A2R) activation by astroglial adenosine is still controversial, A2Rs may play a role in sleep homeostasis through activation of A2AR-expressing neurons in the nucleus accumbens core involved in the induction of slow-wave sleep (366). In the cortex, altered gliotransmission resulted in reduced neuronal NMDA receptor activity and reduced slow oscillations (367), whereas astroglial specific activation induced neuronal transition to slow oscillations (368). *In vivo* characterization of Ca^{2+} signaling in both rat cortical astrocytes and neurons revealed that astroglial synchronized activity reliably precedes neuronal oscillations and that both astrocyte uncoupling and intracellular Ca^{2+} chelation reduced the fraction of astrocytes and neurons involved in the cortical slow waves. Remarkably, neurons closer to active astrocytes were more likely involved in the oscillations (369). Recently, simultaneously recording of BOLD fMRI and astroglial Ca^{2+} signaling in anesthetized rats revealed that a fraction of intrinsic cortical Ca^{2+} signals were associated with reduced EEG power and negative fMRI signal throughout the cortex (correlated with decreased neuronal activity) and that increased activity in the thalamus specifically preceded these signals (370). Conversely, reduction in the density of cortical astrocytes in the medial prefrontal cortex (and therefore putatively in their connectivity) has been linked to a decrease in δ (0.5–4 Hz) and α (8–12 Hz) spectrum power (371). Moreover, mice overexpressing an astrocyte-specific inositol triphosphate (IP_3) phosphatase, and therefore displaying reduced IP_3 -dependent Ca^{2+} activity, spent more time in REM sleep and revealed more transitions to REM sleep from passive wakefulness (372). In line with that, mice lacking the inositol 1,4,5-triphosphate receptor type 2 exhibit reduced Ca^{2+} signaling, a more fragmented and shorter NREM sleep associated with decreased δ spectrum power and more frequent microarousals (373). Remarkably, astroglial intracellular Ca^{2+} increases precede the transition from NREM sleep to wakefulness but follow arousal from REM sleep (373), thus suggesting that astroglia could mediate norepinephrine-induced arousal from NREM sleep (374). Furthermore, it has been recently shown that *in vitro* application of an oscillatory electric field specifically in the slow-wave range (and not at higher frequencies) increased astroglial synaptic vesicle mobility (375), thus suggesting a positive feedback mechanism for slow-wave state perpetuation. Taken together, these data suggest that astroglial connectivity, astroglial Ca^{2+} waves and gliotransmitter release may initiate and/or support the initiation of cortical slow wave oscillations or favor this transition over others (e.g., passive wakefulness-REM).

Another piece of evidence supporting the contribution of astroglial synaptic plasticity in the modulation of sleep

derives from studies focused on the extracellular matrix components in the synaptic cleft. In the mouse forebrain, sleep pressure after sleep deprivation decreased the expression of astroglial neuroligin-1 (376), a cell adhesion molecule binding to presynaptic neurexins (377, 378). Conversely, neuroligin-1 knock-out mice have increased slow-wave sleep and enhanced synchrony during sleep (379). Astrocytes contribute to glutamatergic synaptic plasticity of thalamo-cortical synapses through secretion of hevin, a synaptogenic protein inducing the interaction between non-canonical synaptic partners including neuroligin-1 (380). Knock-out mice lacking another member of the neuroligin family, neuroligin-2, develop SWDs and behavioral arrests, a phenotype blocked by ethosuximide and attenuated by expression of neuroligin-2 selectively in the thalamic neurons or optogenetic activation of GABAergic projections from the NRT (381). This could be due to an interaction with GABA_A receptors as suggested by previous studies on sleep-deprived mice (382). Mice with a missense mutation in neuroligin-3 exhibit an altered EEG power spectrum (383). Moreover, variations in the copy number of the gene encoding the postsynaptic scaffolding protein Shank3, which interacts with both neuroligin and glutamate receptors thus regulating synaptic plasticity (384, 385), have been linked to epileptiform activity specifically arising during slow-wave sleep (386). Shank3 loss-of-function mutations have been associated with several different epileptic forms but most commonly with atypical absence seizures (387).

Finally, as mentioned already above, inflammation and sleep are tightly intertwined. $\text{TNF}\alpha$ and $\text{IL-1}\beta$ increase during wakefulness and decrease during sleep both at mRNA and protein level (388–390) and their systemic injection selectively increase slow-wave sleep (389, 391). Mice lacking $\text{IL-1}\beta$ and $\text{TNF}\alpha$ receptors are characterized by less slow-wave and REM sleep (392, 393). Notably, agonists of both P2X- and P2Y-type purinergic receptors are known to activate the astroglial release of $\text{TNF}\alpha$ and $\text{IL-1}\beta$ (394) and pannexin-1 knock-out mice with impaired ATP release display altered slow-wave sleep (395). Interestingly, unilateral cortical $\text{TNF}\alpha$ injection induces state-specific EEG asymmetries during NREM sleep (396) and ipsilateral increase in the number of $\text{IL-1}\beta$ positive cells (mainly astrocytes) in the cortex, the NRT and in the thalamic nuclei (397). Along with $\text{TNF}\alpha$ and $\text{IL-1}\beta$, reactive astroglia also produce nitric oxide (NO) *via* inducible NO synthetase (iNOS) (398, 399) and NO has been linked to the pathology of epilepsy (400, 401). NO affects both NREM and REM sleep (402, 403) but inhibiting iNOS in sleep-deprived mice specifically impairs NREM recovery, whereas inhibiting neuronal NOS (nNOS) impairs the recovery of REM sleep (404), thus suggesting a specific role of astrocyte in NREM physiology.

Astroglial homeostatic control of the extracellular space and synaptic transmission through K^+ clearance mediates widespread neuronal hyperpolarization and decreased firing activity during sleep and impacts NREM sleep architecture. Astroglial regulation of the extracellular volume controls both waste and cerebrospinal

fluid clearance essential for correct functioning of the brain and relies on AQP4-mediated water influx and GJ coupling. Adenosine released by astrocytes governs sleep homeostasis, sleep pressure and slow-wave power and astroglial gliotransmission contributes to neuronal slow oscillations in the cortex. Moreover, artificial lowering of astroglial Ca^{2+} oscillations and connectivity leads to reduced slow-wave power and relative shortening and fragmentation of NREM sleep. Finally, astroglial $TNF\alpha$, $IL-1\beta$, and NO are likely to impact sleep architecture by selective increase of slow-wave sleep. These findings support the fact that astroglia play a fundamental role in the physiology of NREM sleep and therefore represent a promising target to study pathophysiological alterations inducing or sustaining the abnormal recruitment of the cortico-thalamo-cortical network during SWDs.

CONCLUSION

From a clinical, social and human point of view, epilepsy is probably one of the most heterogeneous neurological diseases. This variability partially relies on the fact that epilepsy may originate from a plethora of different conditions, among others traumatic injury, stroke, CNS infections or inflammation, brain tumor, genetic predisposition, and drug or alcohol abuse. In addition, in six out of 10 epilepsy cases the pathological origin is unknown. Yet, from a scientific point of view, epilepsy can ultimately be reduced to a local imbalance of excitation and inhibition and altered synchrony and functioning of neural networks in the brain. The heterogeneity of pathological outcomes associated with epilepsy arises from the variety and complexity of functions carried out by the human brain and the multiple layers of fine-tuning that each of them requires for reliable physiological functioning of the electrical activity in neural circuits. Given the existence of common molecular and cellular mechanisms at the basis of epilepsy and their nature as pathological transitions of altered physiological processes, both epilepsy research and clinical treatment benefit from the understanding of the inner functioning of neural networks.

Since spike and slow-wave discharges (SWDs) share some key anatomical and functional physiological brain oscillations naturally occurring during slow-wave sleep, absence seizure research could advance our understanding of both epilepsy and healthy brain mechanisms. In this review, we collected evidence supporting the functional and mechanistic relationship between slow-wave sleep and SWDs, thus providing insights into network alterations that contribute to the pathology of SWDs. Moreover, proving and characterizing the interdependency between epilepsy, sleep architecture and sleep/wake cycles possess an undeniable therapeutic value, since sleep is a pre-existing condition affecting any treatment outcome and efficacy.

We focused our attention on the role of astrocytes in the physiology of sleep and in their putative pathophysiological contribution to SWDs. Astroglial control on extracellular

homeostasis in terms of ionic composition, volume regulation and transmitter clearance, astroglial connectivity, Ca^{2+} signaling and gliotransmission as well as cytokine release are hallmarks of astroglial function for physiological brain performance and were addressed in the context of SWDs and sleep research. Please note that it is insufficient and underestimating of the system complexity to label the astrocytic contribution to neural homeostasis as exclusively anti- or pro-epileptic. Many astroglial mechanisms may be beneficial or detrimental with respect to different forms of epilepsy, not to mention different network connectivities and states. Current research on astroglial contribution to epileptic brain functioning mostly relies on studies focused on convulsive seizures, possibly due to their lower remission rate and their clinical symptoms which appear more obvious and life threatening. Nevertheless, some clues suggest the mechanisms governing network excitability and synchrony may have a role in SWDs, too. This work was not intended to be and is far from being comprehensive neither of the role of astroglia in epilepsy nor of their contribution to sleep homeostasis and architecture but provides with significant associations in the tripartite synapse engaging astroglia, epilepsy and sleep in the context of the pathophysiology of cortico-thalamo-cortical oscillations. Understanding how astroglia contribute to the mechanisms underlying slow-wave sleep and how these are altered in pathology could possibly shine light on new therapeutic targets for a plethora of epileptic forms displaying SWDs, among which absence epilepsy, a condition that still affects 50 million people worldwide and is pharmaco-resistant in almost one third of those.

AUTHOR CONTRIBUTIONS

DG screened the literature, conceptualized the review focus, wrote the first draft, designed and realized the figures, and finalized the manuscript. AS and FK contributed to figure conceptualization, reviewed and finalized the manuscript. All authors approved on the final version of the manuscript.

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

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