From sleep spindles of natural sleep to spike and wave discharges of typical absence seizures: is the hypothesis still valid?

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Abstract The temporal coincidence of sleep spindles and spike-and-wave discharges (SWDs) in patients with idiopathic generalized epilepsies, together with the transformation of spindles into SWDs following intramuscular injection of the weak GABAA receptor (GABAAR) antagonist, penicillin, in an experimental model, brought about the view that SWDs may represent ‘perverted’ sleep spindles. Over the last 20 years, this hypothesis has received considerable support, in particular by in vitro studies of thalamic oscillations following pharmacological/genetic manipulations of GABAARs. However, from a critical appraisal of the evidence in absence epilepsy patients and well-established models of absence epilepsy it emerges that SWDs can occur as frequently during wakefulness as during sleep, with their preferential occurrence in either one of these behavioural states often being patient dependent. Moreover, whereas the EEG expression of both SWDs and sleep spindles requires the integrity of the entire cortico-thalamo-cortical network, SWDs initiates in cortex while sleep spindles in thalamus. Furthermore, the hypothesis of a reduction in GABAAR function across the entire cortico-thalamo-cortical network as the basis for the transformation of sleep spindles into SWDs is no longer tenable. In fact, while a decreased GABAAR function may be present in some cortical layers and in the reticular

thalamic nucleus, both phasic and tonic GABAAR inhibitions of thalamo-cortical neurons are either unchanged or increased in this epileptic phenotype. In summary, these differences between SWDs and sleep spindles question the view that the EEG hallmark of absence seizures results from a transformation of this EEG oscillation of natural sleep.

Keywords Epilepsy · Cortex · Thalamus · Nucleus reticularis thalami · GABA receptors

Numerous clinical observations indicate the presence of complex bidirectional interactions between sleep and epilepsy [10, 19, 57]. In particular, spike and wave discharges (SWDs), the electrographic hallmark of typical absence seizures¹ [26], which are an integral component of several idiopathic generalized epilepsies, have been reported to occur preferentially during the light stages of non-rapid eye movement sleep (NREM) where the majority of sleep spindles are observed (Fig. 1A) [49–51]. This high temporal coincidence between sleep spindles and SWDs, together with the transformation of sleep spindles into SWDs following intramuscular injection of penicillin (a weak GABAA antagonist) in the cat [2, 31, 33, 55, 56] and other experimental evidence following manipulations of GABAA receptors (GABAARs) [6, 20, 43, 105], has brought about and consolidated the view of SWDs as ‘perverted’ sleep spindles [12, 33, 50, 54, 68].

However, absence seizures can occur as frequently during wakefulness as during light NREM sleep, and the issue of why and how SWDs are also generated during the former behavioural state has not received the necessary critical

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¹ Typical absence seizures are non-convulsive epileptic attacks that are characterized by a sudden and relatively brief impairment of consciousness which is invariably accompanied by generalized and synchronous 2.5–4 Hz SWDs in the EEG.

exacerbated in those with (idiopathic) epilepsy [9, 11, 17, 19, 109]. Overall, therefore, the conclusions on the preferential occurrence of SWDs during different components of the sleep–wake cycle in humans should be considered with some caution.

Though clear indications of an association between light sleep and SWDs had previously been reported [55, 56], it was the seminal work of Kellaway and co-workers [51] that, using continuous long-term recordings in 13 drug-free and six treated patients with different idiopathic generalized epilepsies, fully highlighted the tight temporal association between SWDs and sleep spindles and the prevalent occurrence of these epileptic paroxysms during NREM sleep. It is unfortunate, however, that one finding of this study has systematically been overlooked by old and recent reviews of this research field [34, 42, 54, 68], i.e. that ‘rare’ cases were identified of patients who showed an exclusive appearance of absence seizures during wakefulness (see page S22 and figure 12 in [50]). Niedermeyer’s work, while confirming these observations also highlighted the occurrence of SWDs at times of behavioural state transition, i.e. at sleep onset and at time of awakening [74]. Many more recent studies have confirmed the preferential presence of SWDs at transitional states and in light NREM sleep and the modifications in the morphology and frequency of SWDs during sleep stages 3 and 4 [37], but have also clearly indicated their occurrence during (mostly quiet) wakefulness [8, 37, 40]. It is interesting to note that in these studies, as previously reported by Kellaway [49, 50], the difference between wake and sleep state occurrence of SWDs is very often patient dependent more than related to subsequent day–night cycles in the same patient. Finally, a recent large study on 77 children (mean age 6.4 ± 5.4 years) with different types of idiopathic generalized epilepsy has shown that SWDs preferentially (91%) occur during wakefulness, with a large peak between 9 a.m. and noon, though a much smaller peak is also evident between 6 p.m. and midnight which is independent from the patient being awake or asleep [110]. In another study, in three drug-free children with SWDs there were fewer sleep spindles in stage 2 sleep but a similar total amount of spindles during the entire night compared to the control age-matched group [73]. However, in children that responded to pharmacological treatment there was no difference in the amount of sleep spindles in stage 2 compared to the control group [73]. Although these data may suggest that spindles in stage 2 are being ‘replaced’ by SWDs, thus indirectly supporting the spindle-SWDs transformation hypothesis, confirmation of these results in a larger untreated patient cohort is needed. In conclusion, therefore, the human studies strongly support the view that SWDs are present during both wakefulness and NREM sleep, and that sleep spindles

are not entirely suppressed in patients with absence seizures.

As far as experimental absence epilepsy is concerned, meaningful data on the temporal correlation of spindles and SWDs can only be gathered from genetic models. No data are available on the temporal distribution of SWDs across the wake–sleep cycle of monogenic mutant models of absence seizures (e.g. *st*, *lh*, *tg*). In the Wistar Albino Glaxo (WAG) rats, 56% of SWDs occur during the wake state (15% and 39% during active and quiet wakefulness, respectively) and 46% during sleep (35% in non-REM and 11% in REM sleep) [88]. In Fisher 344 rats, SWDs (or High Voltage Spindles as they used to be called in this model) are observed only during awake immobility and are quite distinct from sleep spindles, which are of lower amplitude and rarely observed in the immobile awake condition [46]. In the genetic absence epilepsy rats from Strasbourg (GAERS) rats, 66% of SWDs starts and ends during quiet immobile wakefulness, 27% during transition between wakefulness and slow-wave sleep (20% from wakefulness to slow-wave sleep and 7% from slow-wave sleep to arousal) and less than 7% is entirely contained within slow-wave sleep [59, 66]. The majority of SWDs in this rat model emerge from a short episode (0.5 to 3 s) of medium-voltage 5–9 Hz oscillations [80, 81]. Interestingly, such oscillations in the theta frequency band, which should not be confused with the classical theta rhythm of limbic regions, are also recorded in control non-epileptic rats during quiet immobile wakefulness, but not before sleep spindles, suggesting marked differences in the initial conditions of the underlying neuronal network prior to the expression of either sleep spindles or SWDs. An increased power in the theta frequency band which occurs just before the development of a SWD has also been observed in local field potential recordings in cortex and thalamus of WAG rats [86, 102]. Differently from the GAERS model, however, in WAG rats this increase in theta power is accompanied by an enhanced alpha and delta band power [86, 102], suggesting that the potential increase in theta oscillations prior to the appearance of a SWD in absence models may not be selective for this low frequency band.

Within the context of sleep and absence seizures, other recent key observations have been the deficiency in sleep-promoting mechanisms in WAG rats and the ability of partial activation of a sleep-promoting area (ventrolateral and median preoptic nuclei) to elicit absence-like paroxysms in normal rats [95]. Although the effect of anti-absence drugs against these absence-like EEG activity were not tested, these results point to an insufficiency/inefficiency in sleep-promoting mechanisms as one of the underlying causes of absence seizures. Indeed, WAG rats show fewer SWDs at the start of the light phase of sleep, when sleep

pressure is at its highest, whereas they occurrence increases towards the end of the light phase [101].

In summary, these human and experimental results strongly indicate that far from being strictly associated with a defined behavioural state, and in particular with stage 2 sleep where the vast majority of sleep spindles are observed, SWDs do occur as frequently during quiet wakefulness as during (the light stages of) NREM sleep. Moreover, the preferential occurrence of SWDs either in the wake or sleep state is strongly patient dependent. Therefore, any proposed pathophysiological mechanism of absence seizures should fully account for their development during both the wake and sleep states and be able to explain how both in humans and genetic animal models sleep spindles and SWDs can co-exists side-by-side during certain behavioural stages. Indeed, the proposed deficiency in sleep-promoting mechanisms may well account for these observations. Lastly, the question remains of whether the lack of consciousness in a sleeping patient during SWDs is similar to the temporary loss of consciousness that is experienced by awake patients during typical absence seizures, particularly in view of the fact that in the latter condition some subjects can recollect events linked to some (though not all) sensory modalities [77].

Sleep spindles and SWDs generation: a common neuronal network but a different initiation site

The initial proposal that SWDs may represent a paroxysmal transformation of sleep spindles originated from the experimental observation that intramuscularly injected penicillin can transform the 10–15 Hz sleep spindle oscillations into 4–5 Hz SWDs in felines (FPGE) [33, 34, 56, 83], though evidence in support of an origin from cortico-thalamo-cortical networks were evident in earlier studies, in particular from Jasper's group [44]. As mentioned above, at about the same time Kellaway's work [49–51] was providing support to this view by showing a tight temporal association between sleep spindles and SWDs. These findings, therefore, led to the proposition that both electrographic signatures arise from the same neuronal circuit [34, 67, 92], and Beenhakker and Huguenard [12] have recently re-branded the thesis that the normal spindle-generating circuitry, i.e. the cortico-thalamo-cortical network, is hijacked to generate SWDs. However, we will here argue that while the original idea that the cortico-thalamo-cortical network is responsible for the generation of both sleep spindles and SWDs is still valid, the recent proposals of (a) a cortical initiation of sleep spindles and (b) a compromised thalamic GABAAR function as a necessary condition for SWDs generation [12] are not defensible,

since they are based on a selective choice interpretation of the available evidence, as explained in this and the following section, respectively.

The expression of human typical absence seizures requires coordinated activity in reciprocally connected thalamic and cortical territories, as revealed by some old invasive studies and modern non-invasive imaging investigations, with some of the latter focusing on childhood absence epilepsy patients where, as mentioned before, these seizures represent the only pathological phenotype [4, 35, 52, 72, 100, 108]. These studies have also confirmed the lack of involvement of other brain areas, including hippocampus, cerebellum and limbic regions, though the anterior thalamus and the precuneate nucleus have recently been highlighted as regions of potential interest [100, 103]. Importantly, the almost exclusive involvement of cortico-thalamo-cortical networks in the generation of typical absence seizures has also been widely confirmed in experimental absence models [69, 104].

Against the common belief that absence seizures are generalized from their very start, one of the most important recent discoveries in the field has been the identification of a cortical 'initiation site' of SWDs. Thus, in agreement with some old data using standard EEG configurations, recent high density EEG studies in patients with different idiopathic generalized epilepsy have shown the presence of SWDs in discrete, mainly frontal and parietal cortical regions before they appear over the rest of the cortical mantle [39]. These findings have been confirmed in MEG and fMRI studies of children with a pure typical absence seizure phenotype [4, 72, 107]. In particular, an increased BOLD signal can be detected in frontal and parietal cortex more than 5 s before any clinical signs of the seizure are manifested, and then spreads to other cortical sites and to the thalamus [4].

Interestingly, the cortical site of initiation can be different among various patients, but in a given patient it is maintained in successive seizures and across days [72]. The presence of a putative cortical 'initiation site' for typical absence seizures has also been shown in the WAG and GAERS models where, differently from human absence epilepsy however, it is consistently located in the perioral region of the primary somatosensory cortex [65, 69, 82]. Whether a similar site is present in the monogenic mutant models *st*, *lh* and *tg* as well as in different KO mice with an absence epilepsy phenotype remains to be determined.

The only study that has systematically compared sleep spindles and SWDs using current source density analysis and large neuronal ensemble recordings in the neocortex has shown that these two brain rhythms possess a similar pattern of cortical sinks, sources and unit firing, which only differ in their relative strength and timing, as well as in a spatially more restricted cortical spread of spindles com-

pared to SWDs [48]. In contrast to SWDs, however, the essential network that is currently believed to initiate sleep spindles consists of two groups of mutually connected thalamic neurons, the glutamatergic thalamocortical (TC) neurons and the GABAergic inhibitory neurons of the nucleus reticularis thalami (NRT; Fig. 1B), as indicated by several key experimental *in vivo* and *in vitro* studies [42, 43, 93]. Of course, because of the extensive thalamocortical and corticothalamic projections, it is the entire cortico-thalamo-cortical network that ultimately determines the expression and spatio-temporal coherence of sleep spindle oscillations over the cortical mantle as measured from EEG electrodes [16, 21, 23].

As mentioned before, it has recently been suggested that sleep spindle waves are initiated by a cortical input/volley to thalamic regions [12]. This argument stems from the fact that since sleep spindles are most commonly observed during the UP states of the slow (<1 Hz) sleep oscillation of NREM sleep, which is considered to be of cortical origin [36, 38, 71, 99], then sleep spindles too are initiated by a neocortical drive to the thalamus. However, the generally accepted and simplistic explanation of the slow (<1 Hz) sleep oscillation as being entirely of cortical origin has recently been challenged [25], since it does not take into account the finding that both TC and NRT neurons are capable of eliciting the slow (<1 Hz) sleep oscillations in the absence of a cortical drive [14, 27, 29, 41]. In agreement with this view, recent *in vivo* data from Timofeev's group have now conclusively demonstrated that the slow (<1 Hz) sleep oscillation in the neocortex is abolished following temporary inactivation of the somatotopic thalamic region [61]. Thus, the proposed cortical initiation of sleep spindles is not supported by currently available evidence, and the more solid explanation for sleep spindle generation does still remain the one that considers the NRT-TC network as the driver/initiator of this EEG signature of sleep.

Another interesting difference between spindles and SWDs has come from a recent investigation that analysed cortical EEG and thalamic local field potentials in freely moving, naturally sleeping WAG rats following unilateral ibotenic acid lesions of the NRT [70]. This study shows that only the rostral part of the NRT plays a role in the generation and spreading of SWDs, whereas the entire NRT is critically involved in sleep spindles. Notwithstanding the technical difficulties of selectively delivering a neurotoxin to a localized region within the peculiarly narrow and elongated shape of the NRT, these results suggest that although generated in the same cortico-thalamo-cortical network genetically determined SWDs and naturally occurring sleep spindles in a well-established model of absence epilepsy may be governed by different thalamic subcircuits.

In summary, the cortico-thalamo-cortical circuit is the main neuronal network that underlies the EEG expression of both sleep spindles and SWDs, but a major difference exists between sleep spindles and SWDs initiating mechanisms, with the former being of thalamic origin and the latter possessing a cortical 'initiation site', the location of which is often patient selective.

Does a decreased GABAAR function underlie the transformation of sleep spindles in SWDs?

As mentioned earlier, the hypothesis that SWDs result from aberrations of sleep spindle-generating mechanisms has mainly evolved from, and been putatively consolidated by two sets of data. Firstly, the old *in vivo* results from the intramuscular injection of penicillin in cats (the FPGE model) [33, 34, 56], and secondly, the results of more recent electrophysiological *in vitro* studies performed in ferret thalamic slices, where the block of thalamic GABAARs was shown to transform spindle-like 10–14 Hz oscillations into a rhythmic activity at a frequency (3 Hz) similar to that of SWDs in humans [6, 105] (Fig. 2B). Because of the similarity in frequency, and because the fact that (a) penicillin is a GABAAR antagonist, (b) a number of mutations in GABAAR have been identified in families with different idiopathic epilepsies with absence seizures [47, 58, 63, 64, 98, 106] and (c) a decreased GABAergic inhibition is intuitively assumed to underlie epileptic paroxysms, the firing patterns and underlying ionic mechanisms observed in thalamic slices of different species during block of GABAARs have been heralded as the series of events that occur in thalamic neurons during absence seizures [6, 43, 45, 53, 105]. However, the overall intracellular voltage waveform recorded from TC neurons in thalamic slices where GABAARs had been blocked bears no resemblance to that observed *in vivo* in TC neurons from two well-established models (compare TC neurons activities *in vitro* and *in vivo* in cat and GAERS in Fig. 2B). Nor could these differences be explained by differences in spindle intracellular waveform or generating mechanisms since they look very similar across species (cat and rats) and conditions (*in vitro* and *in vivo*; Fig. 1A).

More worryingly, the thalamic *in vitro* data have been used to support the view that absence epilepsy is characterized by a reduced GABAAR activity in the major cellular components of the cortico-thalamo-cortical network, i.e. cortical, TC and NRT neurons. However, as far as TC neurons are concerned, all findings from the well-established *in vitro* and *in vivo* absence epilepsy models do not support this view, since as indicated by the following pieces of independent evidence phasic and tonic GABAAR function in TC neurons is neither abolished nor decreased:

- As clearly demonstrated and thoroughly reviewed by Massimo Avoli, Pierre Gloor and George Kostopoulos, the intramuscular injection of penicillin has no apparent effect on GABAergic function in TC neurons [1, 3, 34, 54]
- The direct intrathalamic injection of either penicillin [54] or the more potent GABAAR antagonist bicuculline [91] fails to elicit SWDs in the cat
- During spontaneous SWDs the vast majority (60% and 90% in cat and GAERS, respectively) of TC neurons *in vivo* shows rhythmic sequences of composite GABA_A IPSPs which occur in synchrony with each spike and wave complex, indicating that these receptors are operational during absence seizures (Fig. 2B) [79, 90]
- Strong repetitive stimulation of the corticothalamic afferents in ferret thalamic slices with intact GABAAR

Fig. 2 Intracellular membrane potential correlates of cortical, TC and NRT neuron activity during sleep spindles and spontaneous SWDs. **A** Intracellular recordings in vivo during sleep spindles and in vitro during spindle-like oscillations. The cat neuron (in motor precruciate cortex) shows rhythmic EPSPs at about 6 Hz with occasional action potentials. The NRT neuron firing is similar in the three preparations and consists of repetitive high-frequency (200–400 Hz) bursts of action potentials. The underlying membrane potential envelope in NRT neurons, however, is depolarizing in vivo but hyperpolarizing in vitro (*blue box*). The TC neuron activity is characterized by rhythmic IPSPs with occasional single, or doublets of, action potentials, some of which are generated by low threshold Ca^{2+} potential (LTCPs). In vivo spindles were recorded under barbiturate anaesthesia. *n.m.p.* membrane potential not reported in the original traces (reproduced with permission from Refs [94] and [105] © Science, Refs [80] and [7] © Wiley). **B** Intracellular or extracellular recordings in vivo during SWDs and intracellular recordings in vitro in the presence of bicuculline or during cortico-thalamic (CT) stimulations. Cortical neurons were in layer V/VI of the motor precruciate area (for cat, under ketamine xylazine) and somatosensory cortex (for GAERS, under neurolept anaesthesia). The two GAERS neurons were located outside (*top trace*) or within the cortical initiation site (*bottom trace*). In both cat and GAERS, the cortical neurons show rhythmic depolarizations underlying action potentials discharges, which occur at the characteristic SWD frequency of each model (cat, 2–2.5 Hz; GAERS, 7–9 Hz). In GAERS, note the strong firing of the neuron located in the initiation site compared to that of the neuron in an adjacent region. The activity of NRT neurons during SWDs is similar across models (cat and rat) and conditions (in vivo and in vitro), and consists of rhythmic LTCPs, each crowned by a strong high-frequency burst of action potentials. In thalamic slices, the frequency of the spindle-like oscillation (*blue box in A*) is slowed down from 5 to 3 Hz while the duration of the action potential burst is markedly increased in the presence of bicuculline (*green box*). The activity of TC neurons in vivo and in the presence of bicuculline in vitro is drastically different. TC neurons recorded in cat and GAERS show rhythmic sequences of composite IPSPs with the occasional firing of (usually) one or two action potentials. In striking contrast, the activity recorded in the presence of bicuculline (*green box*) consists of regular and rhythmic LTCPs, each crowned by a high-frequency burst of action potentials. In the absence of bicuculline; however, TC neurons can express an activity similar to that of SWDs recorded in vivo when strong repetitive stimulation of corticothalamic fibres is applied in a thalamic ferret slice (*yellow box*). All traces are intracellular recordings except the extracellular recording from a cat NRT neuron during a SWD. Action potentials were truncated in some original traces (reproduced with permission from [15, 78, 82, 87, 90] © Society for Neuroscience; [7, 80] © Wiley)

function [5, 15] leads to an activity pattern in TC neurons (see yellow box in Fig. 2B) that is similar to that recorded in vivo during SWDs in absence models

- Localized microiontophoretic application of bicuculline during SWDs drastically increases the firing of TC neurons in WAG rats in vivo, indicating that GABAARs are functional during this epileptic activity in an inbred model [89]
- The overwhelming majority of data from in vivo models indicates either no change or an increase in phasic GABAAR-mediated inhibition (i.e. IPSPs or IPSCs) in TC neurons of sensory thalamic nuclei

compared to their respective non-epileptic control strains (Fig. 3A) [13, 24, 96]

- Tonic GABAA inhibition is enhanced in TC neurons of GAERS rats, of *st*, *lh* and succinic semialdehyde dehydrogenase (SSADH)^{−/−} mice as well as by GHB (Fig. 3B) [24, 30]
- Systemic and intrathalamic (i.e. in the ventrobasal thalamic nucleus) injection of drugs that selectively increase tonic GABAA inhibition elicit typical absence seizures in normal animals [24], demonstrating the necessity of this form of GABAA inhibition in TC neurons for the expression of SWDs
- GABA-transporter-1 knockout mice, which express a prominent absence seizure phenotype, have an enhanced tonic GABAA current in TC neurones compared to wild-type littermates [24]
- GABAA IPSPs in TC neurons of GABAAR- $\beta 3$ subunit KO mice, which have absence seizures, are unchanged compared to wild-type littermates [45]
- The unitary conductance of GABAA IPSCs in TC neurons of an intralaminar thalamic nucleus in WAG rats is increased compared to non-epileptic rats [18]
- Mice with the human GABAA- $\gamma 2$ (R43Q) mutation, which has been identified in a large Australian family [106], express spontaneous absence seizures but no change in miniature IPSCs in TC neurons [97]

Against this overwhelming set of data stands the ability of microdialysis application of bicuculline into the rat ventrobasal thalamic complex to elicit continuous 3 Hz waves in the somatotopic cortical area in vivo [20], a finding that has been used to support the importance of a reduced GABAAR function in the generation of SWDs [12]. This claim, however, is fully ill-founded at present, since the effect of anti-absence drugs was not tested on these 3 Hz cortical oscillations, and therefore we do not know whether they are SWDs. Moreover, we have known for some years that no SWDs are induced by thalamic injection of bicuculline in the cat in vivo [91].

As far as GABAAR function in NRT neurons is concerned, in an inbred rat model (GAERS) [13], in mice carrying the human GABAA- $\gamma 2$ (R43Q) mutation [97] and in mice with spontaneous mutations (DBA/2J) [96], there is either no change or an increase in intra-NRT phasic GABAA inhibition. In contrast, in GABAAR- $\beta 3$ subunit KO mice, which show absence seizures as part of a much complex phenotype, GABAA IPSCs in NRT neurons are abolished [45], and in $\alpha 3$ KO mice, which show an unexpected decrease in GHB-induced seizures, GABAA IPSCs in the NRT are increased [85]. Thus, it remains unclear which type of changes (if any) in intra-NRT phasic GABAA inhibition is a necessary condition for the expression of typical absence seizures.

Fig. 3 Phasic and tonic GABA_A inhibition in TC neurons in genetic and pharmacological models of typical absence seizures. **A1** Phasic GABA_A inhibition is not decreased in GAERS TC neurons. GABA_A mIPSCs in TC neurons of ventrobasal nucleus slices from non-epileptic control (NEC) and GAERS rats. **a** Upper traces show mIPSCs, depicted at a faster time base in the lower traces. **b** Decay kinetics measured on averaged mIPSCs from the neurons is best fitted by two exponentials and shows no difference between NEC and GAERS. **A2** Paired-pulse depression of IPSCs recorded in ventrobasal TC neurons in vitro is similar between NEC and GAERS. **B** Tonic GABA_A current is enhanced in TC neurons of rat and mouse models of typical absence seizures. **B1** Current traces from ventrobasal TC neurons in vitro show a larger tonic current in GAERS rats and

SSADH^{-/-} mice than in respective non-epileptic control animals. Tonic current is revealed as a shift in baseline current following the focal application of the GABA_A receptor antagonist (100 μ M gabazine, white bars). **B2** Summary histogram depicts the percentage increase of tonic GABA_A current in TC neurons of GAERS, stargazer (*stg*), lethargic (*lh*) and SSADH^{-/-} mice compared with their respective age-matched control littermates. An increased tonic GABA_A current is also observed in vitro in ventrobasal TC neurons of normal Wistar rats following the application of the pro-absence drug γ -hydroxybutyric acid (GHB, 3 mM); reproduced with permission from [13] © American Physiological Society; [24] © Nature Publishing Group

As far as the neocortex is concerned, a decreased cortical GABAergic inhibition has been suggested to occur in layer 2/3 regular spiking neurons [62] and in layer 5 pyramidal neurons [28] of adult WAG rats. Moreover, a slight reduction in GABA_A IPSPs/IPSPs in layer 2/3 has been reported in mice carrying the human GABA_A- γ 2(R43Q) mutation [97]. However, no change is observed in mIPSCs in pyramidal cells and interneurons of cortical layer 2/3 of

young, pre-seizure GAERS [13], and cortical GABAergic inhibition is apparently intact in the FEPG model [32].

In summary, human and experimental evidence strongly support the view that the changes in GABAAR function in absence epilepsy are brain area selective, with a potential layer- and model-specific decrease in neocortical GABAAR function, a reduction or an increase in NRT neurons but either no change or an increase in TC neurons. Thus, the TC neuron

mechanisms observed in thalamic slices during block of GABAARs carry no relevance to the pathophysiological mechanism of absence seizures: this, in turn, weakens the hypothesis that SWDs originate from a transformation of sleep spindles via an overall decrease in GABAAR function across the entire cortico-thalamo-cortical network.

Conclusions

The picture that emerges from the available human and experimental evidence is that SWDs occur both in the wake and sleep state and are therefore not restricted to behavioural states with a high incidence of sleep spindles. Whereas both sleep spindles and SWDs do emerge from the same neuronal circuit, i.e. the cortico-thalamo-cortical network, the initiation site of the two activities is different: thalamic for spindles and cortical for SWDs. Moreover, the majority of SWDs in experimental models appears to evolve from EEG periods with an increased power in the theta frequency band, whereas sleep spindles do not. A decreased GABAAR function, which has often been suggested to be associated with absence seizures, may be present in some neocortical layer of some absence models and possibly among NRT neurons, while in TC neurons both phasic and tonic GABAAR-mediated inhibition is either unchanged or increased in both genetic and pharmacological models. Whether these substantial differences could still be construed as to satisfy the hypothesis that sleep spindles are transformed in SWDs now appears highly doubtful.

More likely is the scenario where absence seizures arise in a discrete cortical initiation site due to paroxysmal development of normal 5–9 Hz oscillations which is likely to involve a cortical layer-selective reduction in GABAAR function and a potential deficiency in sleep-promoting mechanism. The resulting synchronised cortical discharge potently excites NRT neurons which respond by generating T-type Ca^{2+} channel-mediated high-frequency bursts of action potentials on every cycle of the SWD. The resulting strong barrages of IPSPs in TC neurons easily override cortical excitation, while the concomitant increase of ambient GABA levels, due to reduced GABA uptake by GABA transporter 1, enhances tonic inhibition and thus membrane conductance in these neurons. This, in turn, reduces the action potential output of the TC neurons, with T-type Ca^{2+} channel-mediated high-frequency bursts of action potentials rarely occurring. Importantly, the rhythmic IPSP barrages entrain TC neuron output to cycles of the SWD, providing a sparse but synchronised input to the cortex and maintaining paroxysmal activity within the cortico-thalamo-cortical network.

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