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Thalamic synchrony and dynamic regulation of global forebrain oscillations

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The circuitry within the thalamus creates an intrinsic oscillatory unit whose function depends critically on reciprocal synaptic connectivity between excitatory thalamocortical relay neurons and inhibitory thalamic reticular neurons along with a robust post-inhibitory rebound mechanism in relay neurons. Feedforward and feedback connections between cortex and thalamus reinforce the thalamic oscillatory activity into larger thalamocortical networks to generate sleep spindles and spike-wave discharge of generalized absence epilepsy. The degree of synchrony within the thalamic network seems to be crucial in determining whether normal (spindle) or pathological (spike-wave) oscillations occur, and recent studies show that regulation of excitability in the reticular nucleus leads to dynamical modulation of the state of the thalamic circuit and provide a basis for explaining how a variety of unrelated genetic alterations might lead to the spike-wave phenotype. In addition, given the central role of the reticular nucleus in generating spike-wave discharge, these studies have suggested specific interventions that would prevent seizures while still allowing normal spindle generation to occur. This review is part of the *INMED/TINS* special issue *Physiogenic and pathogenic oscillations: the beauty and the beast*, based on presentations at the annual INMED/TINS symposium (http://inmednet.com).

Introduction

The thalamus is a major subcortical structure with primary roles in sensory processing and motor output. Reciprocal excitatory connectivity between sensory, motor, and associational cortical areas and related thalamic nuclei forms an extensive thalamocortical (TC) network in which coordinated activity can be generated, especially during sleep. The role of the thalamus in modulating sensory throughput, which occurs through state-dependent changes in thalamic relay function, has been reviewed elsewhere [1], and an overview of some of the intrinsic cellular features that are associated with different TC rhythms has recently been discussed [2,3]. Here, we focus on dynamic changes in thalamic circuitry that can regulate synchrony. This occurs in such a way as to allow physiological rhythm generating circuits to be co-opted under pathological conditions such that they instead generate hypersynchronous epileptic discharges associated with generalized absence epilepsy. Recent findings regarding circuit regulatory mechanisms in thalamus are leading to a better understanding of the larger TC network in which it is embedded. Mechanistic studies of thalamic synchronization should lead to improved therapies for absence seizures.

The thalamic oscillatory circuit

The neuronal elements of the thalamic network are composed of three basic types, excitatory TC relay neurons and two classes of inhibitory cells, neurons of the thalamic reticular and perigeniculate nuclei (RT/PGN cells) and local circuit interneurons. As detailed below, TC and RT/PGN neurons have extensive synaptic connections between them and together create a recurrent intrathalamic circuit (Figure 1). By contrast, local circuit neurons have a primary role in sculpting sensory inputs [4]. Because of limited synaptic connectivity with other thalamic elements (i.e. they receive little input from either TC or RT/PGN cells), the local circuit neurons seem to have no major role in generating recurrent TC oscillations in slice preparations and will not be further discussed here.

Relay neurons

TC cells are a population of excitatory neurons that are organized into thalamic nuclei, each associated with a specific sensory, motor or higher order associational role. Relay neurons have a relatively unique ability to switch their mode of responsiveness in a way as to promote network oscillations. John Eccles and coworkers [5] described a post-anodal exaltation in relay neurons, in which neural inhibition was followed by an exuberant rebound spiking response. Llinás and Jahnsen [6] later identified an underlying Ca^{2+}-dependent low-threshold spike (LTS) whose activation required a conditioning membrane hyperpolarization. The LTS is a long lasting generator potential that triggers a burst of action potentials and is a form of post-inhibitory rebound (PIR) that can drive reentrant activity

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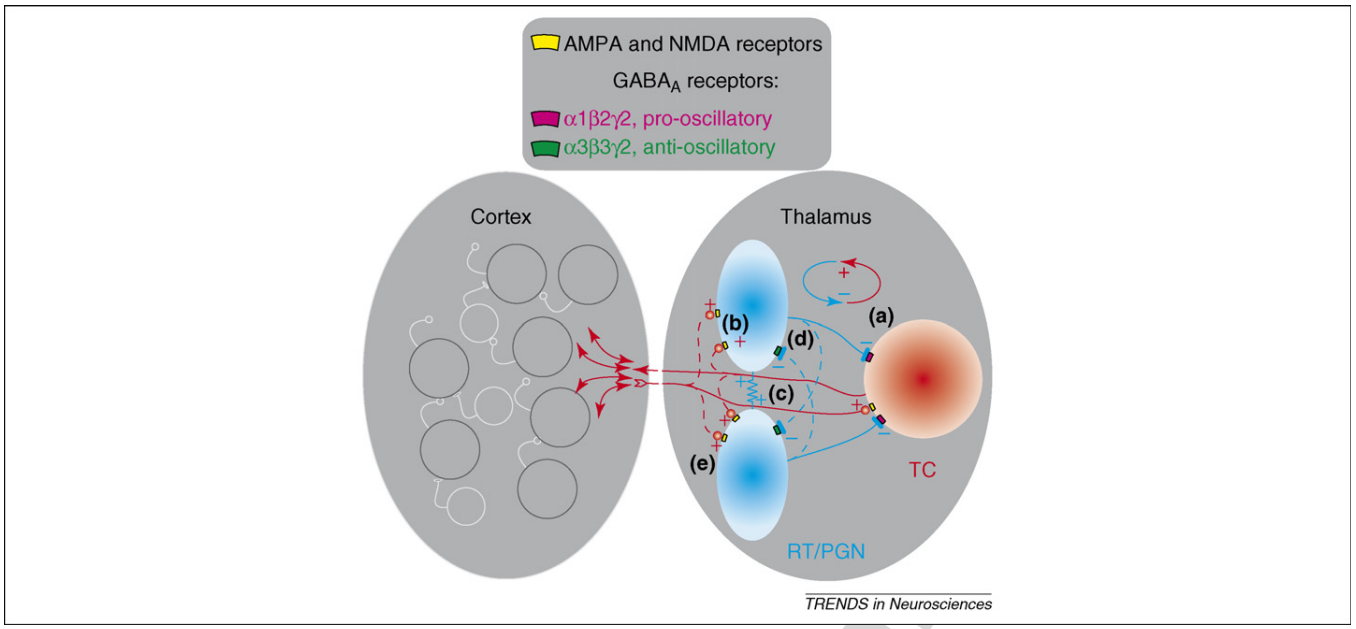

Figure 1. Thalamocortical oscillations driven by an intrathalamic circuit. Reciprocal connectivity between excitatory and inhibitory neurons of the thalamus creates an oscillatory circuit. **(a)** Inhibitory neurons (blue) of the reticular (RT) and perigeniculate (PGN) nuclei make strong inhibitory connections (thick blue lines) with excitatory thalamocortical neurons (TC, red). Thalamocortical cells, which have an essential role in the relay of sensory information from the periphery to the cerebral cortex, send a major excitatory projection (thick red line) to the appropriate neocortical areas. **(b)** Thalamocortical axons emit collateral projections (red dashed lines) within RT/PGN where excitatory connections are made onto the inhibitory neurons therein. Thus, the inhibitory and excitatory neurons are coupled in a reciprocal synaptic loop. Because TC neurons express a powerful post-inhibitory rebound response, synaptic inhibition arising from RT/PGN activity results in a rebound burst of action potentials that transmit excitatory synaptic responses back to RT/PGN, leading to recurrent activation of the circuit (red and blue arrows). Widespread synchronization of the thalamic network is promoted by synaptic convergence and divergence of the major excitatory (b) and inhibitory (a) intrathalamic pathways. **(c)** Concerted network activity would also be promoted through gap-junction mediated electrical synapses, which can couple excitation between nearby RT/PGN cells. **(d)** Countering these synchronizing influences are chemical inhibitory synapses mediated by axon collaterals (blue dashed lines) of RT/PGN cells. These desynchronizing, anti-oscillatory connections are mediated by $GABA_A$ receptors composed of α3, β3 and γ2 subunits, whereas the pro-oscillatory output connection from RT/PGN to TC cells contain $GABA_A$ receptors composed of α1, β2 and γ2 subunits. Although this intrathalamic circuit is an intrinsic oscillator in itself, both spindle oscillations and spike-wave seizures involve activation of widespread corticothalamic circuits, which can be reinforced through bidirectional communication between thalamus and cortex. **(e)** Cortical output provides a powerful excitatory drive onto RT/PGN neurons, which, if properly timed, can reinforce the thalamic oscillatory network. In this scenario, the ability of RT/PGN neurons to synchronize their firing will depend on the balance of synaptic inhibition (d) and excitation (b,c,e). Not included in this simplified scheme, which focuses on the basic intrathalamic rhythm generator, are local circuit interneurons, $GABA_B$ receptors, which are highly expressed in TC cells and can be activated especially during spike-wave seizures, and extensive intracortical recurrent circuitry.

in neuronal networks [7]. Perez-Reyes and colleagues [8] later identified genes for three members of a family of voltage-gated T-type calcium ion channels, α1G, α1H, α1I (subsequently renamed CaV3.1, CaV3.2 and CaV3.3) [9]. CaV3.1 is highly and uniformly expressed in all thalamic relay neurons [10], and CaV3.1 null mutants fail to show PIR, demonstrating that the TC cell LTS depends critically on this ion channel.

Thalamic reticular neurons

The second neuronal population involved in thalamic rhythm generation is RT/PGN neurons, which are contained in a shell-like nucleus that surrounds mainly anterior and lateral aspects of the dorsal thalamus [11]. RT/PGN is composed entirely of inhibitory neurons [12] that express T channels CaV3.2 and CaV3.3 [10]. The properties of the RT/PGN T channels are subtly different [13,14] from those expressed in TC cells and allow burst firing under resting conditions. The T channels in RT/PGN neurons seem to be primarily localized in dendrites (sites of incoming excitatory synaptic activity) [15], and thus can boost efferent signals to these cells, including those arriving from TC or cortical neurons. Knockout mice for CaV3.2 and CaV3.3 have not yet been reported, so the primary mediator of burst firing in RT/PGN cells remains unknown.

The intrathalamic reciprocal excitatory-inhibitory loop

Excitatory TC cells are reciprocally connected with inhibitory RT/PGN neurons [4] in a loop that can sustain network oscillations. The basis of the oscillations has been extensively reviewed [1], but a brief overview of the essential components follows. Inhibitory output resulting from spiking in RT/PGN cells leads to activation of $GABA_A$ and/or $GABA_B$ receptors on relay neurons (Figure 1a) and generation of a post-synaptic inhibitory potential (IPSP) [16–18]. The membrane hyperpolarization of the IPSP primes CaV3.1 T channels, and upon termination of the IPSP a T-channel dependent rebound burst of action potentials ensues. Reciprocal connectivity in the circuit ensures that the burst output of relay neurons is transmitted back to RT/PGN (Figure 1b) as synaptic excitation [16,18], with both AMPA and NMDA receptor mediated components [18,19], thus renewing the recurrent network activity. Burst firing in both cell types ensures robust synaptic output at each stage. The network oscillation, which can occur spontaneously in an isolated thalamic network [18,19], thus depends on reciprocal connectivity between excitatory and inhibitory cells and a PIR mechanism in the excitatory cells. Accordingly, pharmacological manipulations that block synaptic excitation, inhibition [16,18] or T channels [16,20] completely abolish *in vitro* intrathalamic

oscillations. The oscillation period is determined mostly by the duration of the IPSP, which controls the timing of the PIR response [17]. Network oscillations that are predominantly mediated by ionotropic $GABA_A$ receptors have shorter periods ($\sim$100 ms $\geq$ 10 Hz) than those driven by metabotropic $GABA_B$ receptors ($\sim$300 ms $\geq$ 3Hz), and manipulations that increase $GABA_A$ receptor mediated IPSP duration, such as pentobarbital treatment, can slow the network response [19].

Mechanisms of network generalization

The thalamus is thus capable of initiating and sustaining network oscillations, yet the intrathalamic network is considerably more intricate than the simple inhibitory–excitatory point-to-point connectivity suggested in the circuit description above. There is synaptic convergence and divergence at each stage, such that individual RT/PGN neurons inhibit multiple relay neurons [21–23] and receive inputs from several relay neurons [17] and vice versa. With this extensive lateral connectivity a small local network oscillatory response can recruit neighboring cells leading to generation of widespread thalamic synchronous oscillations *in vitro*.

Synchronized oscillatory electrical activity of groups of neurons occurs *in vivo* during various behavioral states, especially during sleep and seizures. It can be detected with scalp electrode electroencephalograph (EEG) recordings. Two EEG rhythms that reflect activity of TC networks [24] are sleep spindles (8–14 Hz) and the 3-Hz spike and wave pattern of generalized absence epilepsy. Sleep spindles are characterized by a sparse TC network oscillation in which on any given cycle of the oscillation only a small percentage of the neurons participate [18,25], and thus individual spindle sequences are variable in their duration and amplitude and in their recruitment of diverse cortical areas. By contrast, spike and wave seizures and related activities are characterized by spiking in the underlying cellular networks that is much more highly synchronized within a given cycle of the rhythm [17] and across multiple cortical areas [26]. Thus, bilaterally synchronous 3-Hz high amplitude spike and wave discharge reflecting widespread TC synchrony is the hallmark of generalized absence epilepsy.

Desynchronizing mechanisms in the thalamic circuit

The ability of the TC network to generate both forms of network oscillations has led us to the hypothesis that regulatory mechanisms exist within the network that normally function to prevent the development of hypersynchronous epileptic oscillations. The remainder of this review focuses on neural circuit features within the thalamus, and especially the RT/PGN, that lead to desynchronization of the network. In addition, where possible the underlying molecular mechanisms are described.

Functional recurrent connectivity within RT/PGN

Steriade, Deschênes and coworkers identified structures in cat PGN that might support intranuclear inhibitory signaling – dendrodendritic synapses [27] – and these workers [28] also reported spindle-related IPSPs in PGN neurons. These and other studies have demonstrated that RT/PGN neurons also emit recurrent axon collaterals within the nucleus to mediate axo-dendritic inhibition (Figure 1d) [28,29]. Evoked and spontaneously occurring $GABA_A$ receptor ($GABA_AR$)-mediated synaptic responses are clearly evident in rat RT neurons [30], and spindle related $GABA_AR$ events were reported in ferret PGN [31]. Although these events probably arise from within RT/PGN, inhibitory projections from other GABAergic structures such as substantia nigra [32], basal forebrain [33] and the zona incerta [34] could account in part for the inhibitory signaling observed within the nucleus. The most definitive method for demonstrating intra-RT/PGN connectivity is paired simultaneous intracellular recording, yet such recordings from nearby RT cell pairs failed to provide such evidence [35]. Although slightly less direct, neuronal activation by either electrical stimulation of cortical efferents [36] or glutamate activation (which will not activate fibers of passage) [31,37] have each demonstrated that synaptic inhibition can be invoked from within RT/PGN.

Recently it has been shown that neighboring RT neurons are also connected by electrical synapses (Figure 1c) that are dependent on connexin 36 [35]. This gap-junction protein is highly expressed in RT [38] and molecules are localized at opposed membranes, where they are well positioned to form functional gap junctions. However, these authors [38] found no morphological evidence for gap junctions themselves. Pannexins, a recently identified gene family related to the connexins, are a candidate for the gap junctions, and pannexin 1 is highly expressed in RT [39]. If this molecule is involved in electrotonic coupling in RT, it must also depend in some manner on connexin 36, as mice with null mutations of this gene fail to demonstrate any coupling between RT neurons [35]. As expected for the low-pass electrical characteristics of electrical synapses, LTS burst responses are more faithfully transmitted through gap junctions than single action potentials [40], and thus activities that depend on bursting such as spindles [18,41] and spike-wave discharge [42] would be strongly synchronized by electrical coupling. Consistent with this, neighboring RT neurons were shown to be highly synchronized during spike-wave seizures [42] and during slow oscillations induced *in vitro* by the mGluR agonist *trans*-ACPD [40]. A potential role for gap junctions in dynamic modulation of thalamic network activities come from the finding that the strength of electrical coupling between RT neurons is regulated in a use-dependent fashion through activation of mGluRs [43].

How extensive are the chemical and electrical recurrent networks within RT/PGN? This issue has recently been addressed using laser scanning photostimulation (LSPS) [44,45], whereby groups of neurons are focally activated by photolytic release of glutamate that can evoke action potentials in affected cells [46]. Intracellular recordings from post-synaptic cells capture evoked synaptic signals reflecting LSPS-induced spiking activity in presynaptic neurons. LSPS studies in RT slices obtained from juvenile rats [44,45] demonstrated extensive chemical connectivity among RT neurons that was organized along the long axis of the nucleus in the same orientation as the major dendrites. There was a somewhat lower incidence of electrical

synapses. Both types of responses were blocked by TTX, indicating that they depend on spiking in presynaptic neurons. Furthermore, blockade of the events by TTX was taken as evidence that both electrical and chemical connectivity were largely mediated by axodendritic rather than dendrodendritic connections [45]. Chemical and electrical connectivities were differentially favored in coronal versus horizontal planes, and there was little evidence for combined electrical and chemical connections from any given presynaptic neuron [44]. This result suggests exclusivity of the two forms of connectivity that would form internal RT/PGN networks, acting together to synchronize local activity through electrical connections [40] but to prevent longer range synchrony through chemical inhibitory connections [31,47,48]. Although this hypothesis will require validation *in vivo*, supporting evidence is provided by the finding that localized infusion into RT of either the gap-junction blocker carbenoloxone or 18-α-glycyrrhetinic acid reduced spike-wave seizures in an animal model of acquired epilepsy [49].

Recurrent RT/PGN inhibition desynchronizes thalamic oscillations

There is some controversy regarding whether recurrent inhibitory connectivity would promote or suppress thalamic oscillatory phenomena such as spindles [24]. It was proposed that recurrent synaptic connectivity along with a PIR mechanism within RT/PGN forms a self-contained oscillatory network [27], and the retention of spindle-like rhythms in a semi-isolated RT network *in vivo* supported this idea [50]. On the other hand, *in vitro* studies have shown that spindle-like rhythms are completely abolished by blockers of ionotropic excitatory neurotransmission [16,18,19], indicating that excitatory feedback from relay neurons is necessary for recurrent oscillatory activity in this network. Furthermore, the efficacy of $GABA_A$R-dependent inhibition in triggering PIR is highly dependent on the equilibrium potential for chloride ions (E_{Cl}). In RT neurons E_{Cl} (~ -70 mV) is very near resting membrane potential [51] and thus, unlike in relay neurons, $GABA_A$R IPSPs in RT/PGN cells are unlikely to produce PIR. The difference in E_{Cl} in relay versus RT/PGN neurons seems to result from a much higher expression of the KCl ion cotransporter KCC2 in RT cells [52].

A powerful role for intra-RT/PGN chemical connectivity (Figure 1d) in desynchronizing thalamic oscillations has been shown in experiments using mice with mutated $GABA_A$R subunits. $GABA_A$Rs are heteropentamers with a stoichometry of two αs, two βs and a single γ subunit [53]. The reticular nucleus is striking in its restricted expression of $GABA_A$R subunits – only α3, β3 and γ2 subunits are present – whereas relay nuclei mainly express α1, β2, γ2, α4 and δ [54,55]. (The α4 and δ subunits mediate tonic inhibition through extrasynaptic receptors [56–59]). A null mutation of the β3 subunit results in recurrent seizures [60] and highly compromised synaptic inhibition within RT [61]. Synchronization of oscillatory activity was essentially complete in $\beta3^{-/-}$ thalamic slices, indicating that loss of chemical connectivity was associated with a defective desynchronizing mechanism.

Other $GABA_A$R mutants have been useful in analyzing synchronizing versus desynchronizing roles for synaptic inhibition in the thalamic circuit. Single point mutations (knock-ins) have been targeted to extracellular domains that determine sensitivity to the allosteric modulators that interact with $GABA_A$Rs at the benzodiazepine binding site. *α3(H126R)* and *α1(H101R)* mice were generated that have little or no outward phenotype [62,63]. In such mice, benzodiazepines will be rendered ineffective in influencing pathways using α3- or α1-containing $GABA_A$Rs, respectively. Given the nearly exclusive expression in the thalamus of α1 in TC neurons and of α3 in RT/PGN cells, slices from such mice can be used to test whether specific augmentation of either inhibitory pathway by benzodiazepines enhances or suppresses network oscillations. The antiepileptic benzodiazepine clonazepam had no effect on $GABA_A$R-mediated synaptic responses in RT neurons from *α3(H126R)* mice, whereas benzodiazepine sensitivity of IPSCs in relay neurons was unaffected. By contrast slices from *α1(H101R)* mice confirmed a specific defect in benzodiazepine sensitivity in TC synaptic $GABA_A$Rs (D.M. Porcello, M.M. Huntsman and J.R.H., personal communication). Thus α1 is the primary α subunit at TC synapses, whereas α3 occupies this role for intra-RT/PGN synapses. Thalamic spindle like oscillations were suppressed by clonazepam in slices from wild type mice and *α1(H101R)* mutants, whereas the suppressive effect of clonazepam was completely eliminated in slices from *α1(H126R)* mice [64]. This demonstrated that enhancement of intra-RT/PGN inhibition was necessary and sufficient to produce the antioscillatory (putative antiepileptic) effects of clonazepam. In *α3(H126R)* slices, benzodiazepines tended to produce the opposite effect – an enhancement of the network responses consistent with a role of synaptic inhibition of relay neurons in promoting the oscillation (Figure 1).

A role for $GABA_B$ receptors in overcoming desynchronizing mechanisms

In thalamic slices, blockade of $GABA_A$ receptors does not obliterate the oscillations, but instead strengthens the responses and produces a marked slowing [16,18]. This occurs for at least three reasons: (i) because $GABA_B$ receptors are highly expressed in thalamus [65] and produce long lasting inhibition [16,18]; (ii) recurrent inhibitory connections between RT/PGN cells are blocked, leading to increased synchronous firing and/or prolonged burst duration [18,48]; and (iii) some $GABA_A$R antagonists, especially bicuculline derivatives, are also antagonists of small conductance Ca^{2+} activated K^+ (SK) channels and therefore increase intrinsic excitability of RT/PGN neurons [66]. This SK channel block is not required, because epileptiform thalamic network responses can also be obtained with $GABA_A$R antagonists that do not block SK channels, such as picrotoxin [19] or penicillin [29].

$GABA_B$ mediated IPSPs, because they are long-lasting and strongly hyperpolarizing [16,18], are especially powerful in recruiting rebound bursts and therefore network activity. In addition, strong activation of RT/PGN neurons can lead to a relative uniform recruitment of rebound firing in relay neurons. This is because $GABA_B$ mediated IPSPs have relatively homogeneous durations among different relay neurons, which contrasts with $GABA_A$R mediated responses, which can be highly variable and thus suppress

synchrony [67]. $GABA_BR$ responses are of the appropriate duration (~300 ms) to promote 3 Hz spike-wave discharge, although the frequency of this epileptic response can be higher in rodents (4–10 Hz) than in humans. A computational study [68] has suggested that at least some of the species-dependence of spike-wave frequency might be explained by differential activation of $GABA_A$ versus $GABA_B$ receptors in relay neurons.

Extrinsic factors influencing thalamic $GABA_B$ receptor activation

As indicated above, global blockade of $GABA_AR$s in thalamic slices leads to activation of $GABA_BR$-dependent hypersynchronous network oscillations. Yet, except in the case of the $GABA_AR$ β3 knockout (which largely abolishes intra-RT/PGN inhibition), such a complete block of $GABA_AR$s is unlikely to occur *in vivo*. Are there other mechanisms that could produce a functional override of intranuclear inhibition, a resultant increase in RT/PGN neuron burst duration and/or recruitment? Recent evidence supports the following model, in which network excitation of RT/PGN cells becomes so powerful that the feedforward $GABA_AR$ mediated inhibition is rendered ineffective in producing its desynchronizing effect. Excitation of RT/PGN arises from both TC (Figure 1a) and corticothalamic (Figure 1e) pathways, through activation of AMPA and NMDA receptors [69,70]. TC cell output produces very powerful unitary excitatory responses, with prominent NMDA receptor mediated components, even at rest [69], whereas cortical activation evokes weaker responses [70]. However, anatomical studies indicate that cortical inputs onto reticular neurons are more numerous [71] and more powerful than those onto relay neurons [72]. Thus, during activation of the TC loop, RT/PGN neurons are effectively recruited to produce feedforward inhibition onto relay neurons, which fire rebound bursts leading to recurrent activation of cortical areas. Activity in the cortical network would then feed back to the thalamus, mainly resulting RT/PGN activation and feedforward inhibition.

Evidence that intra-RT/PGN inhibition can be overridden comes from two studies that combined *in vitro* thalamic slice models with an artificial cortical network [73,74]. Spindle activity was detected on thalamic electrodes and used to trigger activation of an artificial cortical circuit that reactivated the thalamic network through stimulation of corticothalamic fibers. Both studies showed that simple cortical feedback (a single evoked response triggered on each wave of a spindle sequence) produced modest augmentation of the thalamic spindle response. By contrast, when the sensitivity of the cortical circuit was turned up, such that brief bursts of cortical activity were fed back to the thalamic network, very striking results occurred – the thalamic oscillations were transformed into slow, synchronous $GABA_BR$ dependent oscillations. This occurred without $GABA_AR$ blockade and was associated with an increased duration of PGN cell bursting. Thus repetitive synaptic excitatory responses in PGN cells can powerfully summate in such a way as to promote prolonged burst firing, even in the presence of an extensive intra-RT/PGN inhibitory network.

These results then give rise to the following question: under what conditions might cortical network activity be sensitized to produce the necessary feedback to synchronize the thalamic circuit? A modest localized or global increase in cortical excitability might be one factor. Studies in the feline penicillin model of absence seizures demonstrated that diffuse increases in neocortical excitability could lead to induction of spike wave episodes [75]. Association studies of EEG activity in an inbred rat strain have suggested that the earliest activity occurs in perioral neocortical areas before being generalized into a larger TC network [76]. In this scenario, a localized increased activity in a particular cortical region would lead to localized recruitment of the associated portion of RT/PGN, where prolonged burst discharges would occur, followed by robust inhibition of relay cells and recurrent activity that would reinforce the neocortical network. This model would require that the neocortical network be receptive to the feedback excitatory TC activity, that is, that it not produce destructive interference that would destabilize the overall development of a global oscillation. This hypothesis remains to be tested.

Peptidergic influences on thalamic synchrony

In addition to the thalamic recurrent network loops mediated by classical neurotransmitters (GABA and glutamate), RT/PGN and relay neurons both express cotransmitters, mainly neuropeptides, that influence overall network activity. Neuropeptides are differentially packaged and released than classical transmitters. They are contained in dense core vesicles, located distal to synaptic release zones and require repetitive electrical activity to trigger vesicular release [77]. Neuropeptides that are expressed in thalamus can have both excitatory [78,79] and inhibitory [80] actions, and it has been proposed that some neuropeptides such as neuropeptide tyrosine (NPY) and galanin might act as endogenous antiepileptic compounds [81,82]. Of these, NPY is expressed in thalamus; it uniformly expressed throughout RT [83], where it might serve an antiepileptic role. NPY application results in inhibitory actions including activation of K^+ channels in relay and reticular neurons and suppression of Ca^{2+} currents and neurotransmitter release [84]. Repetitive activation of the excitatory afferents results in a long-lasting (several seconds) synaptic inhibition in RT that is blocked by Y1 receptor antagonists [80]. Y1 agonists suppress thalamic oscillations *in vitro* [80,85] and *in vivo* [86]. Evidence for an endogenous antiepileptic role comes from antagonist studies. The specific Y1 receptor antagonist BIBP3226 induces an enhancement of thalamic epileptiform activity *in vitro* [80,87], suggesting that repetitive oscillatory activity triggers NPY release from RT neurons, which then exerts an autoinhibitory effect. This hypothesis is consistent with the finding that chronic treatment of rats with valproic acid (an antiepileptic drug) induces an increased expression of NPY in RT neurons and an increased sensitivity of thalamic oscillations to BIBP3226 treatment. Thus, similar to the effects of clonazepam in the thalamus, valproic acid might be exerting its seizure-suppressing effects through enhancement of an endogenous antiepileptic mechanism.

Concluding remarks

We conclude that, as in other forms of epilepsy, a balance between synaptic inhibition and excitation is important in

regulating seizures. In contrast to cortical epilepsies, where it is crucial to maintaining synaptic balance within recurrent excitatory networks, in the case of absence (TC) networks the balance of synaptic signals in inhibitory RT/PGN must be appropriate to ensure that regions within RT/PGN can act in a semi-autonomous manner so that spontaneously occurring, but sparsely populated, spindle sequences will be generated. When the balance shifts too strongly towards excitation, recurrent inhibition fails catastrophically and the circuit becomes entrained into a generalized epileptic oscillation. An understanding of the synaptic mechanisms ($GABA_AR$, AMPAR and NMDAR) regulating synchrony will lead to development of interventions that prevent the development of TC seizures.

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