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Neuronal Circuitry of Thalamocortical Epilepsy and Mechanisms of Anti-absence Drug Action

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Powerful mechanisms exist within the thalamus that lead to the promotion of synchronous and phasic 3 Hz neuronal activity. These mechanisms include robust burst-firing capability of thalamic neurons, recurrent excitatory/inhibitory synaptic connectivity, and long lasting and powerful inhibitory synaptic responses arising from activity in thalamic reticular neurons and mediated by (-aminobutyric acid receptors. The 3 Hz thalamic synchronization appears to arise from a perturbation of a physiological, higher frequency spindle oscillation. Two currently available anti-absence medications interact with this circuitry with the net result of decreased synchronization, largely through reduction in inhibitory output from the thalamic reticular nucleus. Ethosuximide blocks T-type calcium channels and thus reduces the ability of thalamic neurons to fire bursts of spikes, thereby reducing inhibitory (and excitatory) output within the circuit. By contrast clonazepam enhances recurrent inhibitory strength within the reticular nucleus. This results in a decreased ability of neighboring inhibitory neurons to fire synchronously and produce the powerful inhibitory synaptic responses that are required for network synchronization.

INTRODUCTION

Typical absence epilepsy of childhood is a nonconvulsive form of epilepsy that is characterized by frequent "absences" and bilaterally synchronous 3 / s spike and wave electroencephalographic features (1-4). The disease appears to have a genetic component, and occurs predominately in girls. Age of onset is most commonly around 6 to 7 years, and the seizures spontaneously resolve in most cases by the time of pubescence. Juvenile onset absence epilepsy has a somewhat later onset, and is a more severe disorder in that it is persistent and somewhat more resistant to pharmacotherapy (5). While pure absences are generally not convulsive, they can occur hundreds of times per day are associated with significant cognitive affects (6,7), and can lead to increased risk of injury (8). Some antiepileptic drugs demonstrate specific efficacy in the treatment of this disorder (e.g. ethosuximide, ref. 9), especially the childhood onset form. Others drugs are broad spectrum, showing efficacy in both absence and other epilepsies (e.g. valproate), while still others either show no effect or actually exacerbate the absences (10). These data suggest a wide variety of seizure causes and antiepileptic drug mechanisms (11). Although simple absences are well controlled by currently available medications, more severe forms of the disease are resistant to therapy (2,4), indicating the need for continued development of improved anti-absence drugs.

Recent work from several of laboratories have built upon a large body of evidence obtained in the feline penicillin model (12,13) and provided overwhelming evidence that a reverberant thalamocortical discharge underlies the seizures. In this chapter we will review thalamocortical involvement in absence epilepsy, aspects of the intrathalamic circuitry that seem to be critical for the generation of 3 Hz synchronous network activity, and how this intrathalamic circuit might interact with the global corticothalamic system to produce the spike-wave discharge (SWD) that is the hallmark of absences. In addition we will describe the putative mechanisms of action for two anti-absence drugs. These compounds, ethosuximide and clonazepam, have specific actions on thalamic circuitry that result in desynchronization of slow (2-4 Hz) reverberant neuronal network activities. As will

be shown below, the cellular actions of these two agents are quite distinct, but they share a final common pathway for their antiepileptic actions, which is down-regulation of thalamic inhibitory synaptic pathways.

THALAMOCORTICAL INVOLVEMENT IN GENERALIZED ABSENCE EPILEPSY

Simultaneous participation of both cortex and thalamus is an essential feature of absence seizures. In humans (14-16) and in several experimental animal models of absence, including mutant mice (17), inbred strains of rat (18-20), systemic penicillin in cat (21,22), and in photosensitive baboon (23), depth electrode recordings revealed massively synchronous discharges in thalamus that coincide with the surface EEG.

The variety of absence animal models have been very useful in the study of both epileptic and antiepileptic mechanisms and the underlying thalamocortical circuitry. Most of the models share a number of similarities with human absence epilepsy (but see ref. 24), including most importantly a spike and wave electroencephalographic pattern, which in most cases is associated with behavior absences, and appropriate responsivity to antiepileptic medications (25-30). Model specific features include age of onset and persistence (31-33), characteristic frequency of the spike wave activity, which is quite variable amongst different models and normally higher (4-12 Hz) in rodents (19,28,34) than in humans (3 Hz), the presence (28,35) or absence (19,36) of concomitant motor defects, and direct involvement of non-thalamocortical circuits (37). the common occurrence of spike-wave phenotype in this variety of genetic as well as chemically- and electrically-evoked models suggests that recurrent synchronous activity may be evoked with relatively little perturbation of the thalamocortical circuit. For example, there is evidence that within the thalamocortical loop *either* cortical (15,38) or thalamic activity (14,28,39,40) may be responsible for *initiation* of the seizure discharge in humans and in different animal models.

If it is postulated that the thalamocortical loop includes the necessary synaptic connections and cellular excitability patterns to enable synchronous network activity, then it may be suggested that initial "pacemaking" of SWD could occur at a number of independent sites in the cortex or thalamus and that absence seizures would result from an emergent network response (41). As the initial pacemaking events may be difficult to resolve with surface EEG (42) absence seizures are designated as a form of primary generalized epilepsy. This hypothesis of multiple potential initiating sites is suggested by the finding that chemical or electrical stimulation of the thalamus (43-47) or cortex (15,38) in different species can initiate the seizures. It is important to note that while electrical activity resembling spike-waves has be observed in athalamic preparations (48), more recent studies suggest that an intact thalamocortical loop is required for complete expression of the seizures (13,49).

With regard to cortical mechanisms that might promote and/or exacerbate SWD, several animal models have provided interesting clues. Cortical excitability appears to be enhanced in the feline generalized penicillin model because excitatory synaptic potentials within spindle sequences are more likely to evoke action potentials (50). In the Strasbourg rat model, changes in both N-methyl-D-aspartate (NMDA), and non-NMDA excitatory responses have been reported. Application of NMDA to neocortical slices resulted in enhanced extracellular calcium removal and the NMDA receptor-dependent field potential responses were longer lasting and more extensively distributed than in non-epileptic controls (51). Similarly, increases were seen in cortical glutamate receptor immunoreactivity, electrically-evoked excitatory synaptic responses displayed a reduced sensitivity to the non-NMDA receptor antagonist CNQX, and the non-NMDA receptor agonist quisqualate increased membrane input resistance in the epileptic rats (52).

In addition to direct cortical and thalamic involvement, other structures have been shown to influence spike wave discharge. For example, activation or inactivation of mesopontine cholinergic nuclei (53), nucleus basalis (19), substantia nigra (54,55), locus coeruleus (56), superior colliculus (57), can all dramatically alter or even block the expression of epileptic discharges, even though synchronous electrical activity is not normally observed in these regions during absences (29). Further, systemic injection of cholinergic, noradrenergic, dopaminergic or GABAergic agonists can mimic many of these results (58-60), and the tottering mouse genetic model is associated with dramatic proliferation of noradrenergic fibers in the forebrain (35). This suggests that these regions modulate excitability within the thalamocortical loop (see below) but do not directly participate in seizure generation.

Much of what we know about the corticothalamic involvement in absence epilepsy arises from studies of

thalamocortical synchronization during sleep, and it has even been suggested that spike wave discharge may arise from an aberration of the neuronal networks that generate sleep spindles, which originate in the thalamus (61). Evidence for a connections between spindles and SWD arises from both human and animal studies. In absence patients the highest incidence of spike wave activity can occur at the transitions between wakefulness and sleep (62,63), periods when spindle activity is high, but not during REM sleep when spindles are largely absent (63). Evoked single spindles in cats are transformed in a progressive fashion to longer lasting epileptiform neocortical rhythms following systemic injection of penicillin (50,64). In addition several rodent models have an increased incidence of seizure discharge upon sleep or during quiet wakefulness/immobility (19,65,66).

In summary, thalamic and cortical activity are central to the genesis of SWD. While other brain structures can influence the seizure activity, there is little evidence for direct participation of these areas in the phasing or synchronization of the seizures. The critical role of the thalamus as an pacemaker in absence epilepsy is suggest by the finding that SWD appears to be an aberrant manifestation of sleep spindles, and the latter have been shown to originate in the thalamus.

IN VITRO ANALYSIS OF THALAMOCORTICAL SYNCHRONIZING MECHANISMS

Recent experimental work has proven the powerful utility of *in vitro* models of spike wave activity. These thalamic or thalamocortical slice preparations have been developed with the specific goal of retaining critical circuit connectivities in reduced preparations where quantitative physiological and pharmacological studies may be performed (67-69). It is clear that these preparations, by their very nature, do not retain comprehensive connectivity and therefore only provide incomplete information. For example, little yet has been learned from slice preparation regarding the critical contribution of midline thalamic structures (43) to thalamocortical synchronization. Nevertheless, results from *in vitro* studies have provided clear evidence regarding some basic mechanisms of intrathalamic and thalamocortical synchronization.

There appear to be 3 major factors that are critical for the synchronization of slow thalamic network activity — reciprocal connectivity, specific synaptic mechanisms, and intrinsic burst-firing ability. The anatomical basis for synchronized thalamic discharge is the topographically-organized (70) reciprocal connections between thalamic reticular nucleus (or nucleus reticularis thalami; nRt) and thalamic relay nuclei (71). nRt consists of a shell-like nucleus that surrounds mainly lateral and anterior aspects of dorsal thalamus, is composed entirely of (-amino-butyric acid (GABA) containing neurons (72), and is a critical site for generation of sleep spindles (73) and regulating sensory receptive fields (74). nRt receives a collateral projection from the major thalamocortical radiation (71). In turn nRt neurons send an inhibitory projection back to the appropriate dorsal thalamic sector. Recent evidence suggests a heterogeneity of nRt cell axonal projection patterns, ranging from extremely focal to quite diffuse (75). Thus a heterogeneous reciprocal excitatory-inhibitory connectivity exists within the thalamic circuit. In the case of focal nRt projections the reciprocal connectivity would lead to regionally-restricted recurrent activity, while the diffuse projections would lead to more global activity. The divergence of the intrathalamic circuit provided by the diffuse output nRt cells is postulated to promote the eventual spread and/or synchronization of synchronous activities such as SWD (75,76).

A second factor that underlies the ability of the thalamic circuit to become self-synchronizing is the essential ability of nearly all relay and nRt neurons to fire phasic, Ca^{2+}-dependent bursts of action potentials (61). This feature was first clearly demonstrated by Jahnsen and Llinás (77) in an *in vitro* slice preparation of guinea pig thalamus. They showed that upon appropriate conditioning, which amounted to membrane potential hyperpolarization, thalamic neurons would fire in a burst pattern, and this pattern was dependent on extracellular Ca^{2+}. Subsequent voltage-clamp studies (e.g. refs. 78,79) have identified the ion channel responsible for burst firing in these neurons as the T-type calcium channel. These biophysical studies have provided a complete characterization of kinetic properties of the T channel, such that burst firing behavior can be accurately reconstructed via computer simulations (80,81). As a result of a high level of T channel expression, thalamic neurons fire action potentials in high-frequency, short-duration bursts after membrane hyperpolarizations, as opposed to the regular firing pattern obtained in the absence of hyperpolarization. Thus because burst-firing depends on membrane potential and bursting is critical for synchronous network discharge (see below), membrane

polarization is a powerful means to regulate the network. A number of neuromodulators, including for example acetylcholine, norepinephrine, and serotonin, have been shown to depolarize thalamic neurons mainly via reductions in K+ channel activity (82), and thus reduce their burst-firing capacity. Thus, alteration of resting membrane potentials is likely to contribute to the neuromodulatory influences on SWD described above.

Given the reciprocal connectivity within the intrathalamic loop, and the powerful ability of both relay and nRt neurons to fire Ca^{2+}-dependent bursts in a membrane potential-dependent manner, it becomes relatively straightforward to understand the network synchronization. Burst-firing in nRt cells results in high frequency GABA-dependent inhibitory synaptic potentials(IPSPs) in the downstream relay neurons (68,69,83). These IPSPs summate and produce large synaptic potentials mediated by $GABA_A$ (68,69,83) and $GABA_B$ (68,84) receptors. The hyperpolarization associated with the IPSP is an effective "repriming" (79) mechanism for the T channels in relay cells so that upon decay of the IPSP a rebound Ca^{2+}-dependent burst can be evoked (68,85). The $GABA_B$ component of the IPSP is especially powerful in evoking rebound bursts because it is long lasting and K^+ mediated, which makes it strongly hyperpolarizing (68,84,85). The rebound bursts in relay neurons result in nRt cell activation via excitatory collaterals of the thalamocortical projection (68,69,83). If the resting membrane potential of nRt neurons is sufficiently hyperpolarized, as is the case with *in vitro* slices (68), then the incoming excitatory synaptic potentials (EPSPs) evoke Ca^{2+}-dependent bursts, and this can lead to reentrant activation of the circuit (68,69,83). Thus, it appears that specific resting conditions are required for the recurrent activity to be enabled. Relay neurons must be sufficiently depolarized at rest such that the nRt-evoked IPSP will result in a rebound burst response. In contrast, nRt cells must be sufficiently hyperpolarized at rest so that incoming EPSPs can directly evoke a burst response (68). It is interesting to note that acetylcholine receptor activation might be pro-oscillatory in this circuit, because it can result in hyperpolarization of nRt cells (86) and depolarization of relay cells (87). The exact conditions *in vivo* that would lead to appropriate membrane potentials in relay and nRt cells remain to be determined.

The duration of the IPSP in relay neurons appears to be the central factor that controls the timing of the circuit oscillation (88). In ferret visual thalamic slices the IPSP is mainly mediated by relatively brief chloride-dependent $GABA_A$ receptors and the resultant network frequency is around 8 Hz, similar to sleep spindles (69), while in rat somatosensory thalamus slices, there is a prominent $GABA_B$ component to the IPSP and network activity is characterized by 3Hz oscillations that are more characteristic of SWD (68). This is a pertinent finding because $GABA_B$ antagonists have been shown to have anti-absence effects in several animal models (28,89-91). It is interesting to note that the ferret slice preparation can be made to oscillate at lower frequencies, and in a $GABA_B$ receptor-dependent manner, through blockade of $GABA_A$ receptors (69). The relative prominence of $GABA_B$ IPSPs in rat vs. ferret remains unexplained and deserves further consideration. If it can be demonstrated what conditions lead to powerful recurrent IPSPs in thalamus we may begin to understand the transition between physiological and pathophysiological rhythm generation.

In this section we have discussed circuit mechanisms that may lead to synchronous, phasic discharges in the thalamus. These findings have identified the underlying intrinsic and synaptic mechanisms that promote such activity, and it may be proposed that thalamic synchronization could be responsible for recruiting the cortical network into a global synchronization. However, it must again be stressed that SWD is a thalamocortical oscillation, that can be triggered by chemical or electrical stimuli applied to the cortex (see above). Furthermore, recordings of seizure-like activity in cats suggest that large portions of the thalamic circuitry can in fact be silent during cortical synchrony (92). A critical issue that must be explored in detail is how corticothalamic output, which interacts monosynaptically with both relay and nRt neurons, will influence and/or control the larger thalamocortical loop. Studies in thalamocortical slices (67) are beginning to address these critical issues.

CELLULAR MECHANISMS OF DRUGS USED IN TREATMENT OF ABSENCE SEIZURES

In this section we will discuss cellular actions of two commonly used anti-absence drugs, ethosuximide and clonazepam. Both compounds have the net effect of reduced GABAergic inhibition in the thalamus, but these effects come about through very different mechanisms. As outlined above, thalamic involvement is a central feature of absence epilepsy. Given that Ca^{2+}-dependent burst

firing is such a prominent feature of thalamic neurons, we hypothesized that the specific anti-absence agent ethosuximide may exert its action through alteration in thalamic cellular excitability. We found that clinically relevant concentration of ethosuximide reduced the burst potential of thalamic relay neurons and that it did so by blocking the T-type calcium current (93-95). In addition, the active metabolites of the structurally- and clinically-similar antiepileptic drugs tridione and methsuximide also blocked the T current (95,96). By contrast, the unsubstituted ring structure succinimide (which lacks therapeutic actions), the convulsant tetramethylsuccinimde, and the antiepileptic drug phenytoin (which lacks anti-absence activity) all had no effect (94,96). The blockade of Ca^{2+}currents by ethosuximide was specific for T current, however metabolites of tridione and methsuximide also blocked other voltage-gated Ca^{2+}currents (95,96). The mechanism of channel antagonism appears to be open channel block (97). It should be noted that valproic acid is one of the primary medications used in the treatment of absence and other forms of epilepsy, yet it has little, if any, effect on T-current (94,98). Thus *specific* anti-absence compounds seem to be effective blockers of T current, while other compounds, exert their antiepileptic actions through different mechanisms (11). In other words, T channel blockade is not likely to be the sole anti-absence drug mechanism.

Within the thalamic circuit T channel blockade would be expected to have profound effects. As the intrathalamic oscillations depend on Ca^{2+}-dependent burst firing in both nRt and relay neurons, ethosuximide would be a powerful down regulator of the seizure-like activity. Indeed, ethosuximide causes dramatic reductions in the *probability* of obtaining burst responses in thalamic neurons. Clinically effective concentrations of ethosuximide (600 -700 ：M) do not alter the basic excitability of neurons or even the basic morphology of a burst response. Instead, for a given stimulus the likelihood of obtaining a burst is decreased (68). Thus the network oscillation, which depends on the ability of the recurrent circuitry to continue to evoke burst output at each temporal phase of the reentrant activity, is powerfully and reversibly dampened by the drug (68) as it progressively reduces the late recurrent IPSPs arising from nRt activity. In support of the hypothesis that T channel blockade is the mechanism of anti-absence actions is the finding that an experimental compound U-92032 also blocks thalamic T currents and has effects on thalamic network activity that are equivalent to those of ethosuximide (99).

Another therapeutic agent for which we have gained insight regarding the mechanism of action is clonazepam. This benzodiazepine drug has the seemingly paradoxical ability to ameliorate absence epilepsy (100). Other compounds that enhance inhibition can have proconvulsant activity in humans and in animal absence models (29,45,47,101). Yet clonazepam was able to dampen intrathalamic oscillations (102). Intracellular analysis of synaptic responses during the network activity revealed that clonazepam had very little effect on the $GABA_A$ component of the IPSP recorded in relay neurons, but diminished the $GABA_B$ component (102). The $GABA_A$ antagonist bicuculline caused an increase in the $GABA_B$ IPSP, an effect opposite from that obtained with the pro-$GABA_A$ benzodiazepine compound. This suggested that the effects of clonazepam were due to network effects, and not a direct interaction with the $GABA_B$ receptor. It was postulated that the recurrent intranuclear inhibitory fibers within nRt normally provide an “anti-oscillatory” braking mechanism on the thalamic circuit. Local perfusion of bicuculline into nRt supported this finding. Recurrent network responses were more closely synchronized and longer lasting after disinhibition of nRt (102). Similarly, spindle-like activity in ferret thalamic slices was transformed into hypersynchronous absence-like activity by bath application of bicuculline (69). Thus modulation of GABAergic receptors, especially within nRt, seems to be particularly effective means of regulating synchronous thalamic activity, although GABA-modulatory effects in cortex may also prove to be important (103).

The approach of indirectly modulating thalamic and thalamocortical circuits will prove to be useful in future antiepileptic drug development. This may come about through a number of different approaches. For example, given the heterogeneity of GABA receptors throughout the brain (e.g. ref. 104), it may be possible to target specific brain nuclei with neuromodulatory agents, in order to produce a desired final network modification. Synaptic responses in thalamic relay and reticular neurons are differentially modulated by the broad spectrum benzodiazepine compound midazolam (105) and there are nucleus specific differences in benzodiazepine potency within the thalamus (106), suggesting the potential utility of such an approach. Another possible target is the

synaptic release machinery. A number of neurotransmitters/neuromodulators are known to alter synaptic release through interaction with presynaptic receptors (107), and activation of receptors for endogenous neuromodulators in the thalamus has been shown to alter synaptic release. Adenosine, acting at purinergic A1 receptors (108), and baclofen acting at $GABA_B$ receptors (109) both dramatically reduce IPSPs and EPSPs, and dampen thalamic network activities. If presynaptic receptors can be selectively targeted it may be possible to exploit a use-dependent down regulation of synaptic release. Thus endogenous hypersynchronous activity such as that occurring during the onset of SWD might be rapidly quenched, and the seizure averted.

CONCLUSIONS

Absence epilepsy represents a hypersynchronous thalamocortical discharge that relies heavily on phasic activity in the thalamic reticular nucleus. Reduction in either the phasic output or modulation of the net inhibitory response are two mechanisms of action for known antiepileptic drugs. In this way, forebrain networks can be modulated in subtle ways to alter their ability to sustain certain activities. This suggests that various specific sites within thalamic and thalamocortical circuitry might be further exploited in the development of new antiepileptic drugs. Continued research focused on key modulatory sites, and especially those that are invoked selectively during pathological circuit discharges, will ultimately provide important information regarding the control of seizure activity.

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