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Anatomical and physiological considerations in thalamic rhythm generation

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SUMMARY The thalamus, known as the pacemaker for spindle rhythms in sleep, has several enabling features that promote such pacemaking. These include a circuitry that interconnects large groups of excitatory and inhibitory neurons, all of which are essentially capable of firing high-frequency 'bursts' of discharges. Bursts in thalamic reticular neurons produce powerful inhibition in thalamic relay neurons, which leads to rebound excitation. The timing properties of the inhibition regulate the network activity by controlling rebound burst latency. Anatomical features within thalamus such as convergence and divergence determine the spread and synchronization of pacemaking activity. The anatomical basis of divergence, i.e. the degree of axonal arborization of elements within the thalamic circuit, can be functionally modified in a dynamic fashion by biochemical pathways that regulate the properties of synaptic release. These data suggest that it will be possible to therapeutically regulate the thalamus to modify not only the propensity to sleep but also forms of epilepsy that rely on similar thalamic circuitry.

KEYWORDS GABA, nRt, rebound-burst, recurrent circuitry, spindle.

INTRODUCTION

It has long been known that thalamic circuitry is key to the generation of certain sleep rhythms, especially delta oscillations and sleep spindles. Studies in the cat especially have shown that decorticate animals still produce thalamic spindles (Morison and Basset 1945), whereas isolated cortical slabs are devoid of such activity (Burns 1950). These initial findings have been refined over the years by Steriade and Deschênes and colleagues (Steriade and Deschênes 1984). This group has elegantly demonstrated with intracellular recordings *in vivo*, that a key element in spindle generation is the generation of inhibitory synaptic potentials in thalamocortical (TC) relay neurons. These inhibitory responses arise from activity in neurons of the thalamic reticular nucleus (RE or nRt), and result in a paradoxical, rebound excitation in the TC cells. Here, phasic inhibitory drive can be converted through such paradoxical responses into net excitatory thalamocortical activity. It appears that nRt can sustain the pacemaker through recurrent inhibitory connections (Deschênes *et al.* 1985), although *in vitro* in ferret geniculate slices, an intact excitatory/inhibitory feedback loop was necessary for generation of spindle-like oscillations (von Krosigk *et al.* 1993). Thus from *in vivo* studies it we know that thalamus, and especially nRt is critical for spindle generation.

A number of *in vitro* investigations have recently demonstrated the biophysical and synaptic components in thalamic neurons that are required for spindle oscillations, and the results provide an important framework on which it will be possible to manipulate the circuit with molecular tools. From this we can expect development of therapeutic agents that will modify sleep as well as some forms of epilepsy that appear to be an aberrant form of sleep oscillation (Kellaway 1985; Kostopoulos *et al.* 1981a; Kostopoulos *et al.* 1981b).

This report will review some recent progress in our understanding of intrathalamic circuitry and its relationship to spindle generating mechanisms. Specifically, the report will focus on the biophysical properties of thalamic neurons, the characteristics of both inhibitory and excitatory synaptic responses within the intrathalamic circuit, and some features of connectivity (anatomy) of the circuit that govern the synchronization of thalamic network activity. Together, these features enable recruitment of a recurrent network oscillation and suggest several points of intervention that might disrupt the synchrony.

METHODS

Results from this laboratory include studies in brain slices of somatosensory thalamus of young rat, and computer simula-

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tions that incorporate the known morphological, synaptic and intrinsic excitability properties of thalamic neurons.

Tissue preparation

Thalamic slices were prepared as described (Huguenard and Prince 1994b; Ulrich and Huguenard 1996a). Briefly, 9–15-day-old rat pups (Sprague–Dawley) of either sex were anesthetized (50 mg/kg pentobarbital, i.p.) and decapitated. The brain was removed and transferred into 5°C cold slicing solution containing (in mM): 234 sucrose, 11 glucose, 24 $NaHCO_3$, 2.5 KCl, 1.25 NaH_2PO_4, 10 $MgSO_4$, and 0.5 $CaCl_2$, equilibrated with 95% O_2 and 5% CO_2. Horizontal slices (200–300 μm) were cut with a vibratome (TPI, St. Louis, MO, USA), and thalamus with parts of the adjacent striatum were dissected out and kept in an incubator containing standard artificial cerebrospinal fluid (ACSF; see below) at 32°C for at least 1 h prior to recording.

Electrophysiology

Whole-cell patch-clamp recordings were performed under visualized control (Edwards *et al.* 1989). Brain slices were transferred into a recording chamber and superfused (2 mL/min. 21–23°C) with standard ACSF containing (in mM): 126 NaCl, 26 $NaHCO_3$, 2.5 KCl, 1.25 NaH_2PO_4, 2 $MgCl_2$, 2 $CaCl_2$, and 10 glucose, equilibrated with 95% O_2, 5% CO_2. Patch pipettes were pulled from borosilicate glass (Garner Glass, Claremont, CA, USA) and filled with a solution containing (in mM): 120 Cs-gluconate, 11 CsCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 HEPES, and 11 EGTA (pH adjusted to 7.3 with CsOH, 290 mosm.). Postsynaptic studies of $GABA_B$ responses were done at a temperature of 29–31°C with K-gluconate and GTP (0.4 mM) in the pipette. Whole-cell configuration was established by application of short pulses of suction generated by a vacuum valve. A liquid-junction potential of 10 mV was subtracted on line. Continuous voltage-clamp recordings were performed with a List EPC 7 amplifier (List, Darmstadt, Germany). Access resistance (5–15 MΩ) was monitored throughout the experiment and unstable recordings were rejected. Composite IPSCs were evoked by constant current (200–500 μA) or voltage (60–80 V) pulses through patch electrodes filled with normal saline or 150 mM NaCl. Triggered sweeps were low pass filtered at 1 kHz (3 pole Bessel filter), digitized on line at 3 kHz by a Labmaster TM-100 A/D converter at a 12 bit resolution (Scientific Solutions, Solon, OH, USA) controlled by the software package pClamp (Axon Instruments, Foster City, CA, USA).

RESULTS

Intrinsic excitability of thalamic neurons

Early intracellular studies both *in vitro* and *in vivo* (Deschênes *et al.* 1984; Jahnsen and Llinás 1984) suggested that thalamic neurons are endowed with the special intrinsic ability to fire calcium dependent bursts of action potentials. Subsequent voltage clamp studies mainly in isolated thalamic neurons (Coulter *et al.* 1989; Crunelli *et al.* 1989; Hernandez-Cruz and Pape 1989; Suzuki and Rogawski 1989; Huguenard and Prince 1992) indeed confirmed that these cells contain high densities of the T-type calcium current. The biophysical properties of the T current (Huguenard 1996) result give rise to the paradoxical excitability referred to in the introduction. T channels are normally inactivated when neurons are in their resting state, and it is only after either transient or sustained negative movements in the membrane potential (i.e. hyperpolarizations), such as occur during inhibitory synaptic responses (see next section, below), that a T channel-dependent response can be activated. The resulting calcium-dependent response can have a duration of tens to hundreds of milliseconds, and as it depolarizes the membrane potential above the threshold for sodium action potential generation, a train, or burst of fast sodium spikes rides on the crest of the calcium response.

It is interesting to note that the known heterogeneity of burst responses in various thalamic nuclei may be mediated by region-specific differences in the molecular properties of T channels. For example, nRt neurons, which can fire very prolonged bursts of spikes (Domich *et al.* 1986), contain a specialized form of T channel which has slow inactivation kinetics (Huguenard and Prince 1992). While the kinetic properties of various T channels are of course interesting from biophysical point of view, their heterogeneity strongly indicates a molecular heterogeneity of ion channels in different thalamic nuclie. This suggests the interesting possibility that therapeutic agents could be developed based on the targeting of properties of specific subclasses of neurons.

Overall, the abundance of T channels endows thalamic neurons with the ability to respond with a unit response that is composed of a stereotyped burst of action potentials. Burst responses occur either upon the termination of an inhibitory synaptic response, or during periods of sustained hyperpolarized membrane potentials in which excitatory synaptic responses can directly elicit burst responses, because T channels are available for activation in such a state (see below). Each burst consists of somewhere between a few to tens of action potentials, and to the extent that each individual action potential is propagated throughout the neuron's axonal terminal arborization, the burst will evoke a compound synaptic response resulting from the summation of multiple unitary responses. Theoretical and experimental evidence suggests that the qualitative nature of the synaptic response can be influenced by presynaptic spike firing pattern (Destexhe and Sejnowski 1995; Kim *et al.* 1997).

In summary, thalamic neurons have the special ability to fire rebound bursts of action potentials, i.e. they can fire upon the termination of a transient inhibition. This is one feature that enables recurrent circuit activation in the thalamus. The second feature, which results from burst firing in thalamic neurons and especially nRt cells, is a powerful and long-lasting form of synaptic responsiveness, which will be discussed in the next section.

Synaptic responses in the intrathalamic circuit

A major technical advance in the study of intrathalamic rhythm generation was the development of *in vitro* brain slices that retained functional connectivity amongst critical thalamic regions. Early experiments utilizing coronal rat slices were able to demonstrate intact synaptic pathways in anterior thalamus (Thomson 1988), but for our studies we used a horizontal slice orientation that retained a high degree of intact functional connectivity between nRt and adjacent somatosensory relay nuclei in ventroposterior thalamus (Huguenard and Prince 1994b; Huguenard and Prince 1994a). Other laboratories have used slices cut at different angles to retain connectivity within the entire mouse thalamocortical axis (Warren *et al.* 1994), or in the ferret lateral geniculate nucleus (von Krosigk et al. 1993).

The immense experimental advantage of these preparations is that complex network interactions can be readily elicited and manipulated. For example, in our rat somatosensory preparation recurrent network activity could be sustained for several seconds (Huguenard and Prince 1994b; Ulrich and Huguenard 1995). Thus after an initial extrinsic perturbation the neuronal circuitry became self-activating, and sustained itself through intrinsic mechanisms. Therefore these preparations have provided the opportunity to study network activity in a carefully controlled *in vitro* environment in which modern techniques, such as voltage-clamp, could be applied to directly identify the ionic channels responsible for the complex network activities.

These results proved, as had been suggested from the results of *in vivo* studies (Steriade and Deschênes 1984), that activation of nRt results in strong inhibitory responses termed 'post-synaptic ihibitory potentials' (IPSPs; or currents IPSCs) in relay neurons. These responses are produced by the synaptic release of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) from nRt axon terminals. A number of pre and post-synaptic factors combine to produce powerful post-synaptic inhibition. The first factor, as mentioned above, is the burst firing ability of nRt neurons, which leads to a rapid succession of individual IPSPs (Huguenard and Prince 1994b; Sanchez-Vives *et al.* 1997a), each corresponding to individual action potentials in nRt cells. Under these conditions, individual IPSPs summate to produce large compound responses mediated by two types of GABA receptors. The first type, $GABA_A$ receptors, are chloride ionophores, while $GABA_B$ receptors mediate metabotropic responses that indirectly operate potassium ionophores through activation of G-protein intermediates.

The relative contributions of the two types of receptors ($GABA_A$ and $GABA_B$) to the total IPSP seems to be somewhat dependent on the preparation, with prominent $GABA_B$ responses commonly observed under control or baseline conditions in rat somatosensory thalamic slices (Huguenard and Prince 1994b), less frequently observed in mouse (Warren *et al.* 1994; Warren *et al.* 1997), and rarely observed in ferret (Kim *et al.* 1997). It remains to be determined what factors are responsible for these species and/or preparation differences, but it is clear that in each case $GABA_B$ dependent IPSPs can be produced with sufficient stimulation. $GABA_B$ synaptic responses have been hypothesized to depend on cooperativity, and may thus be preferentially activated by high frequency action potential bursts (Destexhe and Sejnowski 1995). Indeed, Kim *et al.* (1997) found that in ferret $GABA_B$ IPSPs were only produced by high frequency (> 100 Hz) firing of nRt cells, such as can occur for example in calcium-dependent burst responses, and this group further suggested that concurrent activity in multiple nRt cells was necessary for robust $GABA_B$ responses (Sanchez-Vives and McCormick 1997b), suggesting that a very high degree of co-operativity was necessary in the ferret. This contrasts with results in the rat, where $GABA_B$ responses are readily obtained, even with very weak stimuli that are likely to only activate a few nRt cells (Huguenard and Prince 1994b). One possible explanation for this discrepancy is a difference in anatomy–rat somatosensory relay nuclei are essential devoid of local inhibitory neurons while interneurons are present at significant levels in ferret lateral geniculate nucleus. The presence of such interneurons does not appear to be an absolute requirement for spindle generation, however, as interneurons are essential silent during spindle-like oscillations in ferret (von Krosigk et al. 1993) and spindles occur in rodents in which many thalamic relay nuclei contain no interneurons (Jones 1985). Because the presence of a $GABA_B$ component can greatly prolong the IPSC, intrinsic oscillatory responses tend to be slower in rat, where $GABA_B$ is prominent and rebound excitation occurs after delays of several hundred milliseconds (Huguenard and Prince 1994b), compared to ferret, where $GABA_B$ responses are largely absent and rebound excitation occurs after the brief $GABA_A$ response and a burst latency of about 100 milliseconds von Krosigk et al. 1993).

Thus powerful inhibition in relay neurons can be produced by nRt burst responses which lead to high levels of GABA release. Several additional postsynaptic factors serve to promote rebound calcium-dependent burst responses by moving the relay neurons membrane potential to very negative levels during IPSPs. As mentioned above, this negative movement, or hyperpolarization, is very efficient at repriming the T-type calcium channels (Huguenard 1996), and thus ensuring rebound burst generation. One important factor is the strong hyperpolarization produced by opening $GABA_A$-receptor-dependent chloride channels. Studies in mouse, rat and ferret (Huguenard and Prince 1994b; Warren *et al.* 1994; Sanchez-Vives and McCormick 1997b; Ulrich and Huguenard 1997b) have all demonstrated that the electrochemical driving force for negative chloride ions in relay neurons is very negative, between –80 and–90 mV, probably due to low set point for intracellular chloride concentration. The second post-synaptic factor is the nature of the $GABA_B$ response, which is both very hyperpolarizing, with a driving force near–100 mV, and very long lasting, presumably due to the metabotropic and cooperative nature of the G-protein coupled potassium channels (Ulrich and Huguenard 1996a; Otis *et al.* 1993; Destexhe and Sejnowski 1995). Thus combined $GABA_A$

and $GABA_B$ responses can be very effective in evoking rebound bursts in relay cells (Huguenard and Prince 1994b), and a reciprocal circuit that connects the inhibitory neurons of nRt with excitatory cells in relay nuclei will be able to sustain recurrent activity, especially if nRt cells are in a relatively hyperpolarized state, as they are in the rat somatosensory thalamic slice. Recurrent excitatory synaptic responses, mediated by both NMDA and nonNMDA type glutamate receptors, can directly trigger calcium-dependent burst responses in hyperpolarized nRt cells because T channels are primed and ready to open, even in the resting state (Huguenard and Prince 1994b).

Another point to mention here is that the resting state of the neurons in deafferented and 'sleepy' slices *in vitro* may provide clues regarding the necessary conditions for spindle generation *in vivo*. Simply stated, nRt cells must be hyperpolarized to sufficient levels such that incoming excitatory synaptic responses can elicit calcium-dependent bursts, and relay neurons must be depolarized enough such that upon the termination of a transient IPSP the membrane potential will arrive at the threshold for rebound calcium-dependent burst generation. The state-dependent neuromodulatory mechanisms that can regulate membrane potential in these cells types have been recently reviewed (McCormick and Bal 1997).

Recent evidence from our laboratory indicates that the functional synaptic connectivity within the thalamus can be dynamically modulated via the mechanism of pre-synaptic inhibition (Thompson *et al*. 1993). Two endogenous substances (GABA and adenosine), whose extracellular levels can be increased in a use-dependent manner, have been shown to decrease the probability of synaptic release at both excitatory and inhibitory synapses in thalamus (Ulrich and Huguenard 1995; Ulrich and Huguenard 1996a). This indicates that neuronal activity associated with spindle generation may lead to biochemical changes that serve to self-regulate the activity, and suggests the possibility that pre-synaptic mechanisms might be pharmacological manipulated to either increase or decrease spindle stage sleep.

Finally, it should be pointed out that several lines of evidence indicate that recurrent inhibitory connections in nRt are incapable of supporting spindle generation, at least in rat and ferret thalamus *in vitro*. First of all, recurrent inhibitory connections are rather weak for $GABA_A$ (Zhang *et al*. 1997), and especially for $GABA_B$ (Ulrich and Huguenard 1996a; Sanchez-Vives and McCormick 1997b) responses. Therefore recurrent IPSPs are unlikely to produce rebound bursting in nRt cells. Furthermore, the electrochemical gradient for chloride ions is less in nRt cells than in relay neurons (Ulrich and Huguenard 1997b; Sanchez-Vives and McCormick 1997b), so that even when strongly activated, $GABA_A$-receptor-dependent IPSPs will not produce repriming hyperpolarizations, but rather 'shunting' inhibition which can influence burst firing but apparently not initiate it (Ulrich and Huguenard 1997a; Sanchez-Vives *et al*. 1997a). In addition, to fully support rebound bursts in nRt cells $GABA_B$ IPSPs would have to be much larger than is physiological reasonable, and even then would only support a very slow form of spindle activity (1–2 Hz) (Ulrich and Huguenard 1996b). Taken together these data provide very little evidence for normal spindle pacemaking activity in rat and ferret nRt.

Anatomical features

The patterns of connectivity between nRt cells and relay neurons have been recently studied in detail, and it is clear that individually labelled nRt cells can have extended axonal arborizations with numerous swellings in both nRt and relay nuclei. These swellings presumably represent synaptic boutons and indicate that single nRt cells can profoundly influence thalamic relay neurons within a region (Cox *et al*. 1996; Sanchez-Vives *et al*. 1997a; Cox *et al*. 1997a). Recent studies have indicated that nRt neurons can produce quite focal regions of inhibitory synaptic output (Cox *et al*. 1996; Pinault *et al*. 1995), as well as the diffuse (Cox *et al*. 1996) type of projections that had been commonly been reported previously (Yen *et al*. 1985; Scheibel and Scheibel 1966). Paired intracellular recordings have shown that the diffuse type nRt neurons ('tickler' cells) produce weak and variable inhibition, while the focally projecting neurons ('cluster' cells) can produce extremely potent inhibition with apparent release at least 70 synaptic boutons simultaneously (Cox *et al*. 1997a). We proposed that by producing strong inhibitory responses in relay neurons cluster-type connections would be very effective in recruiting neurons into the recurrent network response, and that the ticklers may help synchronize activity across the network. We recently examined this question from a theoretical point of view, and these results will be summarized in the next section.

Theoretical considerations

Can nRt cells with diffuse (or tickler type) connections actually help synchronize spindle-type oscillations across wide areas of thalamus? We assembled a computer-based simulation of a thalamic slice that contains either 64 or 128 interconnected nRt and relay cells to address this question (Sohal and Huguenard, unpublished observations). Using methods similar to those previously published (Golomb *et al*. 1996; Destexhe *et al*. 1996) we endowed model nRt and relay neurons with appropriate intrinsic excitability and synaptic connectivity properties. We arrived at the somewhat unexpected finding that tickler cells did not necessarily affect synchronization, at least as measured by the rate of propagation of network activity. Similar rates of propagation could be obtained in networks either with or without diffuse (tickler) connectivity from nRt to relay neurons, if other features were slightly adjusted (Fig. 1). On the other hand, other measures of synchronization were strongly influenced by the inclusion of diffuse connections. For example, while the propagation *rate* was not necessarily affected, the overall phase lag (or relative time differences between activities in different portions of the slice) was dramatically reduced (Fig. 1). Similarly, collisions

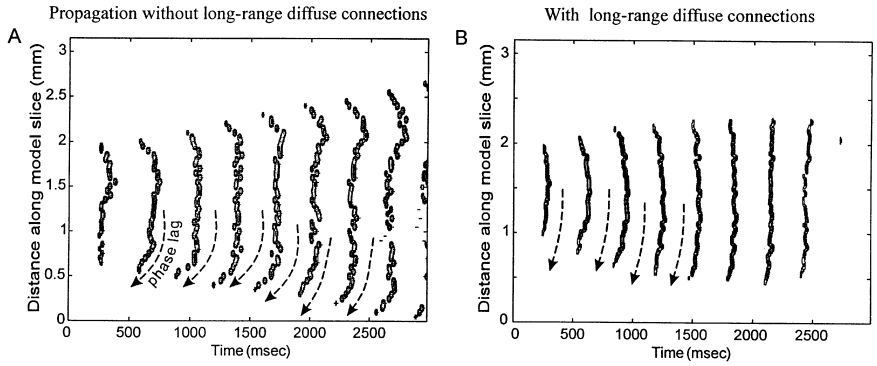

Figure 1. Diffuse axonal projections of nRt cells reduce phase lags but do not necessarily influence propagation speed in intrathalamic oscillations. Computer simulation of 64 each interconnected nRt and thalamic relay neurons. Simulation was begun at time 0 by stimulating a small set of nRt cells in the middle of the slice. Global network activity is measured by counting action potentials within fixed time windows (ratemeter). Activity across the slice is plotted as a function of time after the stimulation. **(A)** In a network without diffuse nRt axonal projections, phase lags of several hundred milliseconds (arrows) rapidly develop between the central and peripheral portions of the slice. By contrast, when diffuse nRt projections are included; **(B)** the total phase lag is nearly abolished, even though the speed of propagation is similar. Similar propagation speed could be obtained in **(B)** by increasing total $GABA_B$ conductance on each relay neuron by 30%.

between two spindle-like waves were very slow to coalesce in the absence of diffuse connections, but similar collisions rapidly became synchronous in their presence. From these results we conclude that one of the functions of diffuse inhibitory output from nRt is to restrict the intra thalamic phase differences during spindle oscillations. It is interesting to speculate that this group of nRt cells might be somehow selectively activated by cortical input, and this might contribute to the known synchronizing influence of cortical input on spindles (Contreras *et al*. 1996).

CONCLUSIONS

The primary features of thalamic spindle-like activity have been clearly identified in a number of preparations. These include calcium-dependent burst-firing in thalamic relay and reticular neurons, strong inhibitory synaptic responses in relay cells, and recurrent excitation from relay neurons onto nRt neurons. We are now beginning to examine the secondary and more subtle features of the network that modulate, regulate, synchronize and desynchronize such network activity. These features include the anatomical and functional convergence and divergence within the thalamic circuit (Cox *et al*. 1997b), the dynamic aspects of synaptic release (Ulrich and Huguenard 1995; Ulrich and Huguenard 1996a), and the use-dependent changes in intrinsic excitability that ocur within spindle sequences (Bal and McCormick 1996). The results of this work will potentially enable new therapeutic interventions in sleep disorders and epilepsy.

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