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Modeling the control of reticular thalamic oscillations by neuromodulators

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COMPARTMENTAL models of thalamic reticular (RE) neurons were investigated based on current-clamp and voltage-clamp data. Spontaneous oscillations in the model arise from the interaction between inhibitory synaptic currents and the rebound burst of RE cells. These oscillations critically depend on the level of the resting membrane potential. A network of RE neurons can be switched between silent and sustained oscillatory behavior by modulating a leak potassium current through neuromodulatory synapses. These results suggest that neuromodulators, such as noradrenaline, serotonin and glutamate, can exert a decisive control over the oscillatory activity of systems of RE cells. The model may explain why the isolated RE nucleus oscillates spontaneously *in vivo* but not *in vitro*.

Key words: Sleep; Noradrenaline; Serotonin; Glutamate metabotropic; GABA; Brain stem biophysical model; Spindle oscillations; Inhibitory networks; G-protein

Introduction

The relay and reticular nuclei of the thalamus have an important role in generating some types of sleep oscillations, such as spindle waves. The cellular origins of this rhythmicity have been investigated by *in vivo* and *in vitro* techniques (reviewed in Ref. 1). Interaction between thalamic reticular (RE) and thalamocortical (TC) cells is involved in the genesis of this rhythmic activity, but the exact mechanisms are still uncertain. The RE nucleus receives collaterals of TC axons and has a massive inhibitory projection back to the relay nuclei. The RE nucleus is critically important for the genesis of spindle rhythmicity since thalamic oscillations do not survive removal of the RE nucleus[2] but are still observed in the rostral pole of the isolated RE nucleus *in vivo*.[3] Single RE cells show rebound burst activity due to the presence of a low-threshold Ca^{2+} current (I_T).[4,5] Rodent RE neurons display a series of rhythmic rebound bursts at 7–12 Hz following injection of small (0.3–1 nA) hyperpolarizing current pulses.[5,6] It has been suggested that this behavior arises from the interaction between I_T and two Ca^{2+}-activated currents, a K^+ current ($I_{K[Ca]}$) and a non-specific cation current (I_{CAN}), both with slow kinetics.[5]

Realistic models of the rhythmic properties of single RE cells have been proposed[7–10] and used to study the rhythmic abilities of networks of RE cells interconnected with inhibitory synapses.[7,8,10] These studies have shown that RE cells having a rebound burst response oscillate robustly if they are interconnected with inhibitory synapses, as shown in previous studies on central pattern generators.[11] However, *in vitro* preparations of the isolated RE nucleus do not oscillate spontaneously,[12–14] in sharp contrast to the oscillations found in the isolated RE nucleus *in vivo*[3] and all models proposed until now. One possibility for explaining this discrepancy is the absence of neuromodulators *in vitro*.[15]

We introduce here a model for investigating how neuromodulators influence RE oscillations, using a simple kinetic model of the action of noradrenaline and serotonin. We suggest that the level of the resting membrane potential can explain why RE cells do not oscillate spontaneously in slices and predict how spontaneous oscillatory behavior could be restored *in vitro*. Some of the results presented here have appeared in abstract form.[15]

Methods

Each thalamic reticular neuron was modeled by a single compartment using kinetic equations similar to the standard Hodgkin–Huxley scheme.[16] The intrinsic currents of RE cells were based on voltage-clamp and current clamp data and were described in detail in a previous paper.[10] The general form of the equation was:

$$C_m \dot{V}_i = -g_{NaL}(V_i - E_{Na}) - g_{KL}(V_i - E_K) - I_T - I_{K[Ca]} - I_{CAN} - I_{Na} - I_K - I_{GABA} \quad [1]$$

where V_i is the membrane potential of the i^{th} RE neuron in the network, C_m (= 1 μF/cm^2) is the specific capacity of the membrane, g_{NaL} (= 0.2 ns) and g_{KL} are the maximal leakage conductances for Na^+ and K^+ respectively (E_{Na} = 50 mV and E_K = − 100 mV). I_T is the low-threshold Ca^{2+} current, based on the voltage-clamp data of Huguenard and Prince;[4] $I_{K[Ca]}$ is a Ca^{2+}-activated K^+ current and I_{CAN} is a Ca^{2+}-activated non-specific cation

current, both based on current clamp data.[5,6] I_{NA}, I_K are the fast Na^+ and K^+ currents responsible for the generation of action potentials (taken from Ref. 17). Details of the kinetics of these currents, based on estimates from physiological data, are given in Ref. 10.

The synaptic current I_{GABA} represents the intra-RE inhibitory current, mediated by γ-aminobutyric acid (GABA). The receptors on RE cells are of $GABA_A$ type with a very weak $GABA_B$ component. Only the $GABA_A$ synaptic currents were modeled here, using a kinetic scheme for the binding of neurotransmitter to postsynaptic receptors.[18] The current is described by the first-order equation:

$$I_{GABA} = g_{GABA}\, m(V - E_{Cl}) \quad [2]$$

$$\frac{dm}{dt} = \alpha\,[T]\,(1 - m) - \beta\, m \quad [3]$$

where $\bar{g}_{GABA}$ is the maximal conductance, $E_{Cl} = -80$ mV is the reversal potential, m is the fraction of postsynaptic receptors in the open state, $[T]$ is the concentration of neurotransmitter in the cleft and α (= 0.53 ms^{-1} mM^{-1}) and β (= 0.184 ms^{-1}) are forward and backward binding rates. The neurotransmitter was released as a pulse (1 ms duration, 1 mM amplitude) when a presynaptic spike occurred. This method for computing synaptic currents accurately accounts for the summation of PSPs.[19]

In network simulations, 100 RE cells were organized in a 10 × 10 lattice with 'dense proximal' connectivity, in which each model neuron connects all others within some radius. We used a radius of three neurons so that there were 25 GABAergic synapses for each RE neuron. This connectivity is the same as that used previously;[10] the behavior of this network is representative of other dense connectivities. A series of neuromodulatory pathways innervates the thalamic RE nucleus, including acetylcholine (ACh), noradrenaline (NE) and serotonin (5HT). Electrophysiological experiments have shown that ACh affects the firing pattern of RE cells by activating a leak K^+ current[20] whereas NE and 5HT depolarize thalamic cells by blocking a leak K^+ current.[21] The actions of these receptors is based on the activation of G-proteins. The most likely mechanism for these neurotransmitters is the direct activation/deactivation of a K^+ channel by the G-protein itself.[22]

In a recent paper,[19] we introduced both detailed and simplified models of the G-protein transduction mechanism mediating the action of neuromodulators such as NE and 5HT. The simplified scheme assumes that the opening of the K^+ channel is slow compared with the time course of G-protein activation, and the time course of the second messenger is a pulse of long duration (80–100 ms). This simplified model was able to fit accurately averaged $GABA_B$ currents,[19] which share a very similar G protein-based activation mechanism.

The noradrenergic or serotonergic-mediated currents regulated the conductance of the leak K^+ current in the model, according to:

$$g_{KL} = \bar{g}_{KL}\, m \quad [4]$$

$$\frac{dm}{dt} = \alpha\,[S]\, m - \beta\,(1 - m) \quad [5]$$

where $\bar{g}_{KL}$ (= 1 *nS*) is the maximal leak conductance for K^+ and $[S]$ represents the concentration of second messenger. For RE neurons, the only experiments available for noradrenergic and serotonergic depolarization are from delivery of agonists *in vitro*:[21] the response lasted up to several minutes. Comparable data are not available for electrical stimulation of noradrenergic and serotonergic receptors. Brief stimulation of peribrachial cholinergic nuclei evoked a short lasting (about 2 s) hyperpolarization in RE neurons[23] and there are many indications that these muscarinic receptors have the same G protein-based activation mechanisms as noradrenergic and serotonergic receptors.[22] Therefore, we chose kinetic parameters to obtain a slow depolarization of 2–3 s following a presynaptic spike (α = 0.01 ms^{-1} μM^{-1}, β = 0.001 ms^{-1}, pulse of $[S]$ of 85 ms duration and 1 μM amplitude). Other receptors may participate in the neuromodulatory control of RE cells, such as the glutamate metabotropic receptor.[24] In the following, we will use the generic term 'NE/5HT' to refer to the transmitter systems involved into the depolarization of RE cells via deactivation of a leak K^+ current.

All kinetic models, single cell and multiple cell models were simulated using the NEURON simulator[25] on a SUN Sparc 10 workstation. The precise values of the parameters used here were identical to those in a previous paper,[10] unless stated otherwise. The behavior shown here was robust to changes in the parameters, such as the values of the maximal conductance, the connectivity and the kinetics of currents.

Results

We first simulated the firing modes of single RE cells in which the leak K^+ current, active at rest, was under the control of NE/5HT synapses, and investigated the oscillatory behavior in networks of RE cells with GABAergic synapses. We considered three different levels of NE/5HT (Fig. 1): first, a hyperpolarized resting level, of − 65 to − 75 mV, similar to *in vitro* conditions where no NE/5HT synapses are activated (Fig. 1a). The second case was a more depolarized resting level, of − 60 to − 70 mV, for which about 20% of the leak K^+ current was blocked. This depolarized resting potential corresponds to a weak NE/5HT activity (one out of five synapses was activated in Fig. 1b). In the third case, when all NE/5HT synapses were activated, a tonic spike activity resulted from the block of virtually all leak K^+ current in the cell (Fig. 1c). These three states also correspond to different intrinsic firing properties: for both hyperpolarized and depolarized resting states, injection of hyperpolarizing current pulses resulted in a sequence of rebound bursts occurring rhythmically at a frequency of 6–10 Hz (Fig. 1a,

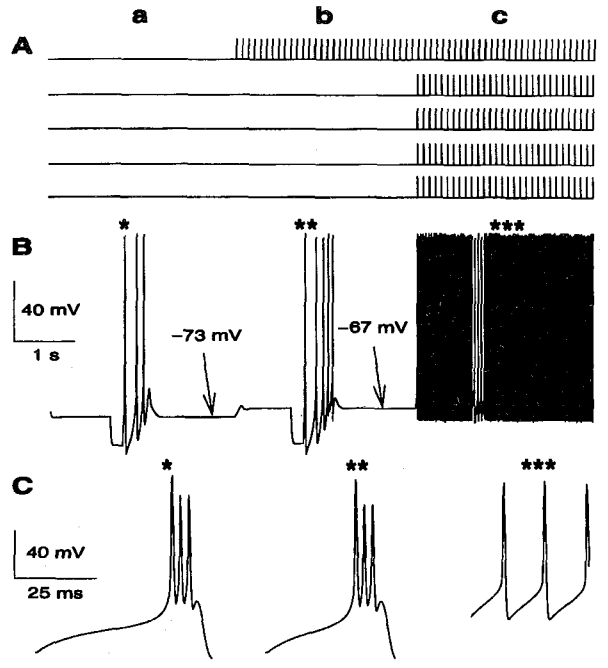

FIG. 1. Noradrenergic/serotonergic regulation of the firing mode of thalamic reticular cells. A single RE cell with five noradrenergic synapses was simulated. (**A**) Five top traces show the presynaptic activity of the NE/5HT synapses. (**B**) Membrane potential of the RE cell. (**C**) Bursts of action potentials shown at higher temporal resolution. **a.** During the first 3 s, no synapse was activated and the membrane potential was of − 73 mV as indicated. **b.** After 3 s, one NE/5HT synapse was activated for 3 s, blocking about 20% of the leak K^+ channels, bringing the cell to a more depolarized resting level of − 67 mV. **c.** In the last 3 s, all synapses were activated, leading to the block of virtually all leak K^+ channels, for which the cell was continuously spiking. A hyperpolarizing current pulse was injected during each 3 s period; the two first pulses showed repetitive bursting response whereas the third pulse only slowed the frequency of repetitive spiking.

b). This bursting activity resulted from the interaction between I_T and $I_{K[Ca]}$, as suggested by current clamp experiments on RE slices[5] on which the model was based.[10] During tonic spike activity, injection of the same current pulse only slowed down the frequency of action potentials (Fig. 1c).

Although at the single cell level there are few differences between the bursting activity of the depolarized and hyperpolarized resting states, there might be important differences at the network level. In a previous paper,[10] we described how a network of RE cells can generate synchronized oscillatory behavior in the spindle frequency range. The oscillations arose from the interaction between the rebound burst property of RE cells with the GABAergic currents arising from intra-RE collaterals. The occurrence of these oscillations depends critically on the level of the membrane potential, as shown in Figure 2. During the first 2 s all RE cells were brought to a depolarized resting state by activating 20% of the NE/5HT synapses. When the NE/5HT activity was suppressed, all RE cells ceased to participate in oscillatory behavior and relaxed to the hyperpolarized rest. Injection of hyperpolarizing or depolarizing current pulses failed to restore sustained oscillations. This behavior was extremely robust to changes in parameters such as the reversal potential of GABAergic currents (E_{Cl}), the values of the synaptic conductances or the amount of leak K^+ current affected by NE/5HT synapses. Typically, E_{Cl} and the resting level were varied in a range of 5 mV around the present values; the simulations showed that sustained oscillations arose only if there was a sufficient 'driving force', of at least several millivolts (around 10–15 mV, depending on the maximal conductance of GABAergic synapses), between the resting membrane potential and E_{Cl}. If the membrane is hyperpolarized too close to E_{Cl}, the resulting shunting inhibition between RE cells prevents them from sustaining oscillations.

Discussion

The simulations provide evidence for a duality of bursting modes in RE cells, depending on the value of the resting membrane potential. For moderate NE/5HT activity, the RE cells are slightly depolarized due to the block of some fraction of the leak K^+ current. In these conditions, GABAergic IPSPs can deinactivate I_T and generate a rebound burst. This property is the basis of self-sustained oscillations since RE cells are interconnected through GABAergic synapses. In the absence of NE/5HT activity, although the bursting properties are nearly identical, the more hyperpolarized resting level makes RE cells insensitive to the activity of GABAergic synapses, preventing networks of interconnected RE cells from oscillating (Fig. 2).

This interpretation is supported by data showing that the resting membrane potential of RE cells is relatively hyperpolarized *in vitro* (− 71.2 ± 6.0 mV in Ref. 14). Another indication is that under various anesthetics, for which spontaneous oscillations were reported in the isolated RE *in vivo*,[3] the resting membrane potential of cat RE cells was − 63.8 ± 1.2 mV.[26] The difference in membrane potential may explain why spontaneous sustained oscillations are observed in the isolated RE nucleus *in vivo*[3] but not in *in vitro*.[12–14] In *in vivo* experiments, histological examination showed that the rostral pole of the RE nucleus was perfectly isolated from the dorsal thalamus and the cerebral cortex, but projections of the most ventral fibers arising from the brain stem could reach the RE nucleus as well as the basal forebrain, which was still present in the isolated island.[3] These fibers may constitute the NE/5HT projections from the raphe nucleus and locus coeruleus, as well as glutamatergic projections from various forebrain areas. It is therefore plausible that a reduced, but not suppressed, neuromodulatory input was still present in these experiments, bringing the membrane to more depolarized level that is consistent with oscillations. This is corroborated by the relatively depolarized resting level of RE cells observed in intracellular recordings in the intact RE nucleus *in vivo* under various anesthetics.

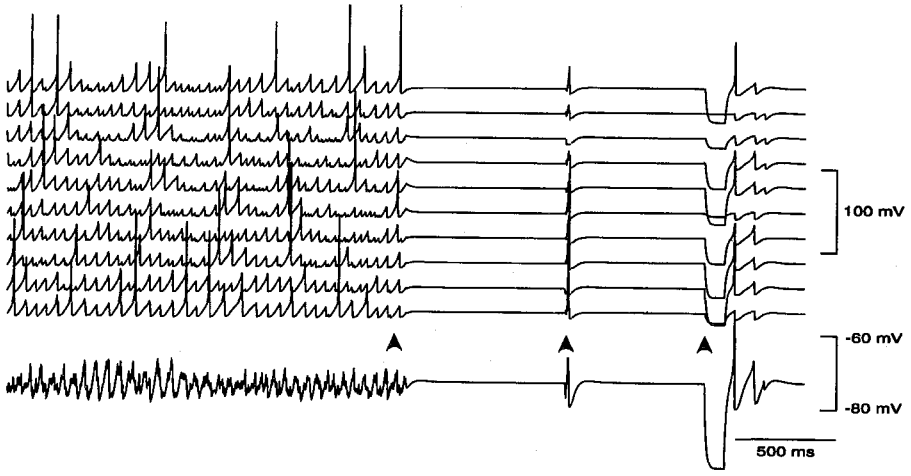

FIG. 2. Dependence of RE oscillatory behavior on the membrane potential. Simulation of a network of 100 RE cells interconnected with their neighbors through GABAergic synapses. The top 10 traces represent the activity of 10 neurons in the network and the bottom trace is the average membrane potential. 20% of NE/5HT synapses were initially activated (as in Fig. 1b). In these conditions, the network showed self-sustained oscillations at a frequency of 10–16 Hz and the average membrane potential displayed waxing and waning fluctuations of amplitude. After 2 s (first arrow), all NE/5HT synaptic activity was suppressed; the resulting hyperpolarization prevented the network from sustaining oscillations. Depolarizing (second arrow) or hyperpolarizing (third arrow) current pulses injected simultaneously in all neurons (with random amplitude) could not restore spontaneous oscillations. These conditions might correspond to the membrane potential of RE cells *in vitro*.

The model predicts that spontaneous sustained oscillations could be observed in slices of the RE nucleus if the resting level of RE cells be brought to more depolarized values. This could be achieved by using bath application of NE/5HT agonists in weak concentration such as to depolarize all RE neurons to the – 60 to – 70 mV range. Another prediction is that NE/5HT antagonists should suppress oscillatory behavior in the isolated RE nucleus *in vivo*. The same results should be found in other models of networks of inhibitory neurons displaying rebound bursts.[7,8]

Finally, we propose that the regulation of the resting level could be critical for controlling the oscillations in the RE nucleus. Since the RE nucleus occupies an important position by its extended projection to relay nuclei of the thalamus, neuromodulatory-induced oscillations in the RE might contribute to the ascending control of arousal by brain stem structures. The possibility that local regions of the RE nucleus, and associated relay nuclei, might be brought selectively to an oscillatory regimen is worth considering. Some disorders of oscillatory mechanisms, including some types of epileptic seizures, originate in the thalamic circuitry (reviewed in Ref. 1); it is possible that, through their ability to control RE oscillations, the neuromodulatory projections from the brain stem may also be involved.

Conclusion

The model proposed here suggests that spontaneous oscillatory activity depends critically on the level of the resting membrane potential relative to the chloride reversal potential in RE cells. For sufficiently negative resting levels, interconnected RE cells do not sustain oscillatory behavior. This may explain why the isolated RE nucleus *in vitro* does not exhibit spontaneous oscillations. We predict that RE cells *in vitro* may show spontaneous oscillations if their resting levels were brought to more depolarized values, such as those seen *in vivo*. Such a depolarization might be provided by noradrenergic or serotonergic agonists, or by glutamate metabotropic receptor agonists. More generally, this model suggests that neuromodulatory systems cannot only regulate the firing mode of RE cells, but they can also control the ability of interconnected cells to sustain oscillations. Investigation of this mechanism might lead to a better understanding of how sleep oscillations are controlled by brain stem structures.

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