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;
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Modeling the control of reticular thalamic oscillations by neuromodulators

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current, both based on current clamp data.\textsuperscript{5,6} \( I_{\text{Na}} \), \( I_{\text{k}} \) are the fast Na\textsuperscript{+} and K\textsuperscript{+} 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 \( I_{\text{GABA}} \) represents the intra-RE inhibitory current, mediated by \( \gamma \)-aminobutyric acid (GABA). The receptors on RE cells are of GABA\textsubscript{A} type with a very weak GABA\textsubscript{B} component. Only the GABA\textsubscript{A} synaptic currents were modeled here, using a kinetic scheme for the binding of neurotransmitter to postsynaptic receptors.\textsuperscript{18} The current is described by the first-order equation:

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

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

where \( g_{\text{GABA}} \) is the maximal conductance, \( E_{\text{Cl}} = -80 \) 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 \( \alpha (= 0.53 \) ms\textsuperscript{-1} mM\textsuperscript{-1}) and \( \beta (= 0.184 \) ms\textsuperscript{-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

\[
g_{\text{Kl}} = \tilde{g}_{\text{Kl}} m
\]

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

where \( \tilde{g}_{\text{Kl}} (= 1 \) nS) is the maximal leak conductance for K\textsuperscript{+} 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 \textit{in vitro};\textsuperscript{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\textsuperscript{23} and there are many indications that these muscarinic receptors have the same G protein-based activation mechanisms as noradrenergic and serotonergic receptors.\textsuperscript{22} Therefore, we chose kinetic parameters to obtain a slow depolarization of 2–3 s following a presynaptic spike (\( \alpha = 0.01 \) ms\textsuperscript{-1} M\textsuperscript{-1}, \( \beta = 0.001 \) ms\textsuperscript{-1}, pulse of \([S]\) of 85 ms duration and 1 \mu M amplitude). Other receptors may participate in the neuromodulatory control of RE cells, such as the glutamate metabotropic receptor.\textsuperscript{24} In the following, we will use the generic term ‘NE/S-HT’ to refer to the transmitter systems involved into the depolarization of RE cells via deactivation of a leak K\textsuperscript{+}
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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 $I$, 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
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/SHT 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/SHT 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 neu-