current, both based on current clamp data.\textsuperscript{5,6} \(I_{\text{Na}}\) \(I_{\text{K}}\) 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 \(I_{\text{GABA}}\) represents the intra-RE inhibitory current, mediated by \(\gamma\)-aminobutyric acid (GABA). The receptors on RE cells are of GABA\(_{\text{A}}\) type with a very weak GABA\(_{\text{B}}\) component. Only the GABA\(_{\text{A}}\) synaptic currents were modeled here, using a

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

where \(g_{\text{KL}} (= 1 \text{nS})\) 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 \textit{in vitro}:\textsuperscript{21} the response lasted up to several minutes. Comparable data are not available for electrical stimulation of noradre-
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/SHT 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/SHT 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
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 vitro. The same results should be found in other models of networks of inhibitory neurons displaying rebound bursts.

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 regime 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 paraventricular 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.

References
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