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SPINDLE RHYTHMICITY IN THE RETICULARIS THALAMI NUCLEUS: SYNCHRONIZATION AMONG MUTUALLY INHIBITORY NEURONS

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The sleep spindle rhythm of thalamic origin (7–14 Hz) displays widespread synchronization among thalamic nuclei and over most of the neocortex.[1] The mechanisms which mediate such global synchrony are not yet well understood. Here, we theoretically address the hypothesis of Steriade and colleagues that the reticularis thalami nucleus may be considered as a genuine pacemaker for thalamocortical spindles.[29–31] Interestingly, the reticularis consists of a population of neurons[15,25] which are GABAergic and synaptically coupled.[9,21,23,35] These cells, as do thalamic relay cells,[10,17–18] exhibit a transient depolarization following release from sustained hyperpolarization.[2,19,22,28] This postinhibitory rebound property is due to a T-type calcium ionic current which is inactivated at rest but de-inactivated by hyperpolarization. Theoretically, rebound-capable cells coupled by inhibition can generate rhythmic activity, although such oscillations are usually alternating (out-of-phase), rather than synchronous (in-phase).[24] Here, we develop and apply to Steriade's pacemaker hypothesis our earlier finding[34] that mutual inhibition can in fact synchronize cells, provided that the postsynaptic conductance decays sufficiently slowly. Indeed, postsynaptic receptors of the $GABA_B$ subtype mediate inhibition with a large decay time-constant ($\simeq$ 200 ms).[13] In contrast, chloride-dependent, $GABA_A$-mediated inhibitory postsynaptic potentials are fast and brief. Both $GABA_A$ and $GABA_B$ receptor binding sites are present in most thalamic regions, including the reticularis.[4,6] We suggest that if $GABA_B$ receptors exist postsynaptically in the reticularis, they may play a critical role in the rhythmic synchronization among reticular neurons, hence in the thalamocortical system.

We consider a minimal ionic model of coupled cells which requires only: (i) that cells interact via inhibitory synapses with a characteristic decay rate (inverse time-constant) k_r; and (ii) that they possess a T-type calcium current, $I_T = g_T m_\infty^3 h(V - V_{Ca})$, and a leakage current $I_L = g_L(V - V_L)$ (see Fig. 1 caption). Due to the T-type calcium current our model neurons exhibit postinhibitory rebound (PIR) responses, similar to those found in cells of most thalamic relay nuclei and of the reticularis thalami nucleus (RTN). These responses underlie bursts of sodium-dependent action potentials, although, for simplicity, we do not include fast spikes in the present form of the model. The synaptic current in our model has a rapid onset and slow decay analogous to the two-component time-course expected if both $GABA_A$ and $GABA_B$ receptors are activated. The reversal potential for this current can be viewed as between that for $GABA_A$-mediated Cl^- and that for $GABA_B$-mediated K^+ current, say -65 and -90 mV, respectively.

First, we discuss the behavior of a pair of mutually inhibitory cells. As expected, if the synaptic conductance is modeled as an instantaneous function of the presynaptic voltage, the two cells tend to oscillate alternately. This rhythm persists even for time-dependent but fast-decaying synaptic conductance (Fig. 1A). That is, for large k_r a cell can be inhibited only if its partner is depolarized; therefore a sustained rhythm will be out-of-phase *a fortiori*. However, when k_r is decreased sufficiently, a different behavior appears, in which the two cells are synchronized with zero phase difference (Fig. 1B). In this case, postsynaptic current decays slowly so that the I_T deactivation phase in a hyperpolarized cell does not have to coincide with the depolarization phase of its partner. Another factor contributing to the in-phase behavior is that the PIR current is strong enough to overcome the (slowly decaying) hyperpolarizing synaptic current. Consequently, a cell can escape, on its own, from a prolonged inhibition, rather than depend on being released upon repolarization of its partner.[34]

The synchronizing mechanism we propose does not depend on a conduction delay for synaptic action, or

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Abbreviations: ASS, asymmetric steady state; PIR, post-inhibitory rebound; RTN, reticularis thalami nucleus.

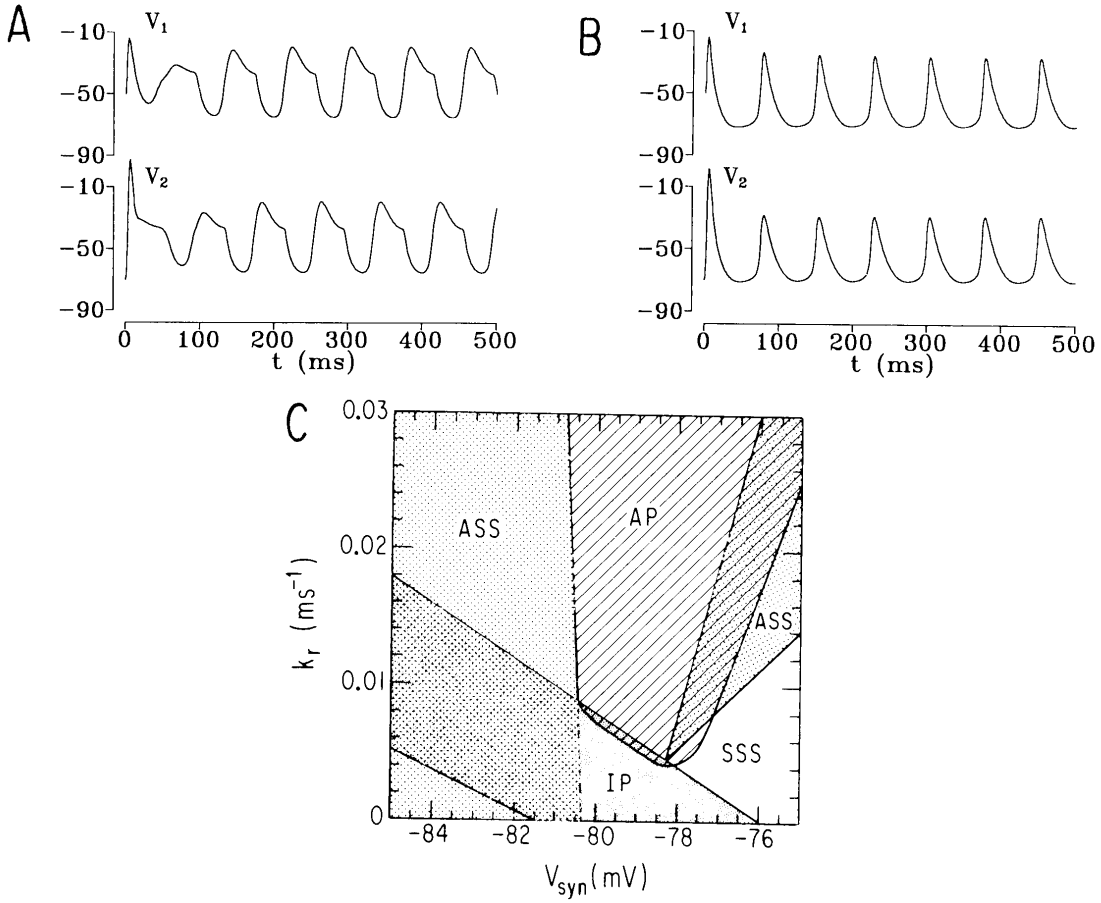

Fig. 1. A network of identical, mutually inhibitory model neurons are described by the following equations: (1) $CdV_i/dt = -g_T m_\infty^3(V_i)h_i\ (V_i - V_{Ca}) - g_L\ (V_i - V_L) - \sum_j J_{ij} s_j g_{syn}\ (V_i - V_{syn})$; (2) $dh_i/d_t = \phi[h_\infty(V_i) - h_i]/\tau_h(V_i)$; (3) $ds_i/dt = S_\infty(V_i)(1 - s_i) - k_r s_i$. J_{ij} are the elements of the connectivity matrix ($0 < J_{ij} < 1$), and s_i is the postsynaptic conductance (fraction of the maximum g_{syn}) due to activity in cell i. The synaptic function S_∞ is assumed to be a sigmoidal function of the presynaptic membrane potential, with a threshold θ_{syn}, $S_\infty(V) = 1/\{1 + \exp[-(V - \theta_{syn})]/2\}$. The expression for I_T in Eqn (1) is a simplified version of a quantitative model of the T-type calcium current,[33] derived from recent voltage-clamp data on relay cells.[7,8,14,32] The activation gating is rapid, so we set $m = m_\infty(V) = 1/\{1 + \exp[-(V + 65)]/7.8)\}$. The kinetic functions for the inactivation gate are $h_\infty(V) = 1/\{1 + \exp[(V + 81)/11)]\}$, $\tau_h(V) = h_\infty(V)\exp[(V + 162.3)/17.8]$. The time-constant, τ_h, for h, has a maximal value of 65 ms at about -70 mV. The factor ϕ scales the kinetics of h; we set $\phi = 2$. Recent data from RTN cells, reported after our computations were completed, suggest some differences between RTN and relay cells in the gating parameter values of I_T.[16] These quantitative changes should not alter qualitatively the significance of our conclusions here; a detailed model for RTN cells should await additional data on ionic currents and dendritic cable structure. For the simulations reported here, the following parameter values have been used: $g_T = 0.5$ mS/cm^2, $g_L = 0.05$ mS/cm^2; $V_{ca} = 120$ mV, and $V_L = -60$ mV. With $C = 1\ \mu$F/cm^2, the passive membrane time-constant $\tau_0 = C/g_L = 20$ ms. For the synaptic current, $g_{syn} = 0.15$ mS/cm^2, $V_{syn} = -80$ mV, and $\theta_{syn} = -45$ mV are our standard values. Equations (1–3) were integrated numerically using the fourth order Runge–Kutta method ($\Delta t = 0.01$–0.05 ms). Computed voltage time-courses shown here are for a network of two mutually inhibitory model neurons [in Eqn (1), $J_{12} = J_{21} = 1$]. (A) Anti-phase oscillation with fast synaptic decay, $k_r = 0.5$ m/s and (B) in-phase oscillation with a fast rising and slowly decaying postsynaptic conductance, $k_r = 0.005$ m/s. (C) State diagram indicating types of stable behaviors (only attractors are represented) as functions of V_{syn} and k_r. SSS, symmetric steady-state (blank); ASS, asymmetric steady-state (stippled); IP, in-phase oscillation (shaded) as in B; and AP, anti-phase oscillation (striped) as in A. The synchronous rhythmic behavior (IP) is possible only for sufficiently small k_r and sufficiently negative V_{syn}. Note various overlapping regions indicating bistability.

on a noticeable latency for the onset of synaptic current. With regard to the cellular mechanism of PIR current and synchronous oscillation in RTN cells, $GABA_A$-mediated inhibitory postsynaptic potentials appear tuned to play a more critical role than those of $GABA_A$ origin for two reasons: the deinactivation of the T-type calcium channels requires sufficiently deep hyperpolarization (since the midpoint for the inactivation equilibrum function h_∞ is at -81 mV), and this hyperpolarization must last for a sufficiently long time.[27]

For our two-cell system we have explored thoroughly how the maintained stable responses depend on two parameters, V_{syn} and k_r, that determine

the hyperpolarization depth and duration, respectively (Fig. 1C). The in-phase oscillation occurs for sufficiently negative V_{syn} and small k_r (lower-left, IP), compatible with known properties of $GABA_B$-mediated synaptic current. For $V_{syn} > -76$ mV, the T-type calcium channel cannot be adequately de-inactivated by synaptic inhibition, and the cells become effectively decoupled and remain stable at rest (lower-right region, SSS). For larger values of k_r, the system displays either an anti-phase oscillation (the classical alternating rhythm), or an asymmetric steady state (ASS). For the ASS region in the upper-right, the two cells are at slightly different membrane potential levels. For the ASS region on the left, a cell near rest provides enough inhibition to hyperpolarize the other cell. This state arises because of two features of our parsimoniously chosen model. Our neuron model has a rather high resting potential (about -35 mV), and, without sodium spikes, synaptic transmission is graded and partially activated at rest.

We have also studied emergent oscillatory behaviors in a network of n model neurons, with widespread connectivity. Since cell density[26] in the RTN of adult cats is about 15–20 cells/100 μm^3, and since the dendritic arborizations[31] extend for up to 1 mm, a limited number of cells ($n \leq 100$ for instance) can be considered as connected in an all-to-all fashion, excluding the self-coupling. Network behavior was studied as a function of synaptic strength, by fixing $k_r = 0.005$ m/s with $n = 10$, and by varying the parameter g_{syn}. If g_{syn} is small, the cells are effectively uncoupled, and the network remains in a steady resting state. For moderate values of g_{syn}, partial synchrony may occur in which cells within subgroups oscillate in-phase, but the different subgroups are out-of-phase from each other. (Similar clustering phenomena have been seen in some network models of endogenous oscillators.[12]) In some ranges of moderate g_{syn} values, we also saw total synchrony, and this

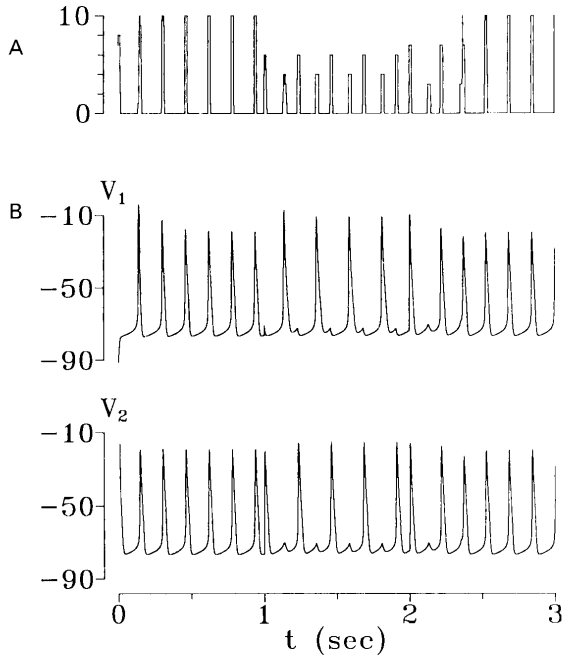

Fig. 2. Ten-cell simulation with all-to-all inhibitory coupling, expressed in Eqn (1) by $J_{ij} = 1/(n-1)$, for all $j \neq i$. (A) The total number of active cells (with membrane potential above the synaptic threshold θ_{syn}) plotted against time. At times $t = 1$ s and $t = 2$ s, brief random current pulses are delivered to all cells, which induce switching of network behavior between two coexistent rhythmic states. One is a state of total synchrony. In the second state ($1 \text{ s} < t < 2$ s), the cells are divided into two groups of four and six members, respectively. Cells are in-phase within each group while the two groups are out-of-phase, as shown in B. ($g_{syn} = 0.233$ mS/cm^2, $g_L = 0.033$ mS/cm^2, $\phi = 1$ and $k_r = 0.005$ m/s.)

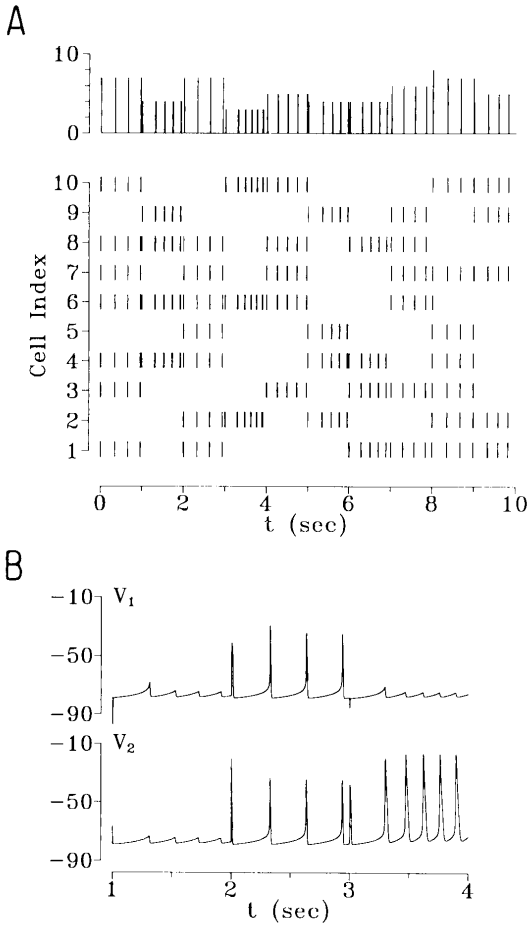

Fig. 3. Ten-cell simulation with strong coupling strength. (A) The number of active cells is plotted for 10 s, together with the rastergram of all ten cells (for each of them, a bar at a given time means that its membrane potential is above the threshold θ_{syn}). At each 1-s interval, random brief current pulses are applied, revealing a multitude of rhythmic patterns. In each pattern, a fraction of cells are oscillating while the rest of the population is silent. (B) Time-courses for cell no. 1 and cell no. 2, corresponding to three different patterns with four, seven and three active cells, respectively (cf. A). Note, from A, that more active cells in a pattern lead to greater inhibition, and therefore longer rhythmic period and smaller rebound spikes. Such silent/active segregation can occur if all cells do not receive identical input (like in the present case, due to the finite number of cells and lack of self-inhibition); or if there are certain heterogeneities in cell properties (unpublished results of simulations). ($g_{syn} = 0.833$ mS/cm^2, $g_L = 0.033$ mS/cm^2, $\phi = 1$ and $k_r = 0.005$ m/s.)

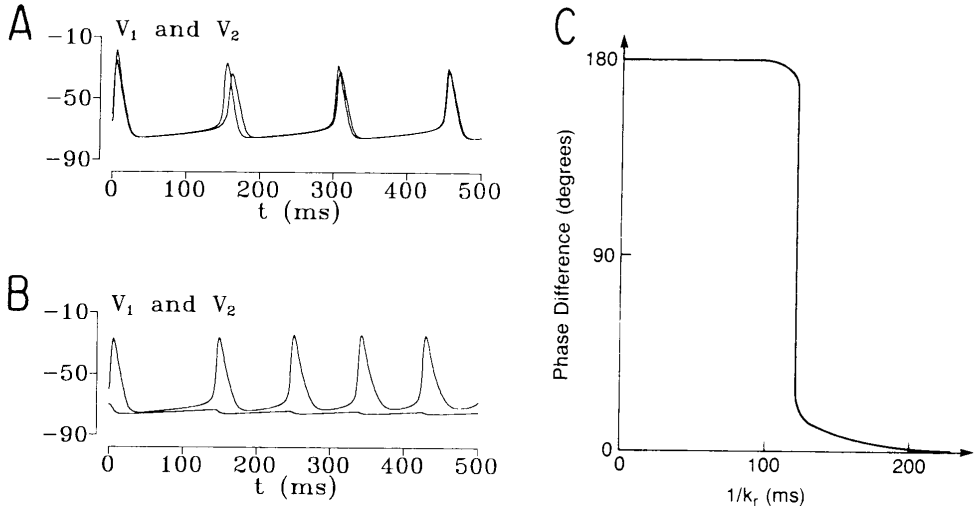

Fig. 4. Behavior of a pair of model neurons, each rendered autorhythmic by inclusion of a Ca^{2+}-dependent K^+ current, $I_{K\text{-}Ca}$. We employ an idealized representation for $I_{K\text{-}Ca}$, of the form $I_{K\text{-}Ca} = g_{K\text{-}Ca}(V - V_K)Ca/(Ca + K_d)$, where Ca is the intracellular Ca^{2+} concentration (μM) in a shell beneath the membrane, and K_d is the dissociation constant for calcium binding to the channel; g_{K-Ca} is voltage-independent and constant. Ca satisfies the following balance equation: (4) $dCa/dt = -\alpha I_T - k_{Ca}Ca$. I_T is in $\mu A/cm^2$, k_{Ca} is a decay rate-constant, and $\alpha = 1/2Fd$ with F the Faraday constant $F = 96.49$ C/mmol and d the shell thickness. We use $d = 2.6\,\mu$m, $g_{K\text{-}Ca} = 0.15$ mS/cm^2, $V_K = -80$ mV, $K_d = 0.5\,\mu$M, $k_{Ca} = 0.02$/ms. Voltage time-courses show in A approach to the in-phase oscillation with $g_{syn} = 0.05$ mS/cm^2, and $k_r = 0.005$ m/s, and in B with g_{syn} increased to 0.1 mS/cm^2, that one cell oscillates while the other cell is inhibited to a quasi-steady hyperpolarized state. In C absolute phase difference between two cells as function of $1/k_r$, shows that the in-phase state requires a slow synaptic decay. The transition at $1/k_r \simeq 130$ ms, from an out-of-phase to an in-phase state, is not necessarily continuous (we did not attempt to resolve it numerically), and an overlap between the two may exist over a small range of $1/k_r$ values.

state could coexist with the partially synchronized state (Fig. 2). With larger coupling strength g_{syn}, the network displays a new phenomenon. Instead of an asymmetric steady-state as seen in the two-cell case, we found that the total inhibition generated by a frac. tion of synchronously oscillating "active" cells could silence the rest of the population at a hyperpolarized, nearly steady, membrane potential level (Fig. 3). Moreover, the size of this active subpopulation and the rhythmic frequency are not unique for fixed parameter values. For the parameters used in Fig. 3, active groups of at least five different sizes are possible.

It has been argued that RTN cells may oscillate endogenously based on their intrinsic membrane properties.[2,3] This hypothesis relies on observations of active afterhyperpolarization following a PIR spike. Such hyperpolarization, which could be mediated by a voltage-independent, Ca^{2+}-activated K^+ current in RTN cells,[2,3] provides the opportunity for de-inactivation of I_T and for a subsequent rebound excitation, thereby allowing the cycle to repeat. With the addition to our model of a Ca^{2+}-dependent K^+ current, $I_{K\,Ca}$, isolated cells are now auto-rhythmic. In this case also, we find that a pair of cells coupled by mutual inhibition can synchronize, provided that the synaptic coupling has a slow decay and a suitable amplitude (Fig. 4A). If the coupling strength g_{syn} is too large, we observe a phenomenon similar to that seen in our network of multiple non-oscillatory units: one cell may be rhythmically active, while inhibiting its partner at a virtually constant hyperpolarized level (Fig. 4B). Analogous to the case without $I_{K\,Ca}$, here the two cells oscillate out-of-phase if k_r is not small enough. The phase difference between the pair changes abruptly from 180° to 0° as $1/k_r$ increases through $\simeq 130$ ms (Fig. 4C).

In conclusion, we have demonstrated the significant effect of synaptic decay rate on rhythmogenic and synchronizing mechanisms of mutual inhibition. With a minimal ionic model, we reached the qualitative conclusion that mutual inhibition can synchronize coupled neurons endowed with a PIR property, provided that the synaptic conductance possesses a slow decay. We found synchronization between two model cells which, when uncoupled, are either excitable with a stable rest state, or auto-rhythmic due to the interplay of an afterhyperpolarizing current and a PIR current. This latter case shows that synaptic inhibition may specifically mediate the synchronization among cells, without being essential for rhythmogenesis itself.

We particularly addressed the hypothesis that the RTN, where only GABAergic cells have been found, could sustain synchronous population rhythmicity. In this case, PIR is mediated by a T-type calcium current. Essential properties for synaptic inhibition to synchronize cells, a sufficiently negative reversal potential and a slow decay, are found in the $GABA_B$-type postsynaptic receptors. Pharmacological means might be used to determine whether postsynaptic $GABA_B$ receptors are indeed present and act in the RTN network.

Considering its critical location and widespread reciprocal connections with most major thalamic nuclei, the role of the RTN should perhaps be chiefly emphasized as a synchronizer of oscillations in the thalamocortical system, including spindling as well as the pathological activity during absence epilepsy.[5,11] It has recently been found in experiments using a rat model for absence epilepsy that direct application to the RTN of baclofen, a $GABA_B$ agonist, enhances the occurrence frequency of the pathological rhythm while CGP – 35 348, a $GABA_B$ antagonist, suppresses the rhythm.[20] This observation is consistent with our theory and the conclusion that mutual inhibition between RTN cells may be a key mechanism for, rather than a nuisance to, synchronization of thalamic oscillations associated with sleep spindles or with absence epilepsy.

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