Spike-and-Wave Oscillations Based on the Properties of GABA_B Receptors

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Neocortical and thalamic neurons are involved in the genesis of generalized spike-and-wave (SW) epileptic seizures. The cellular mechanism of SW involves complex interactions between intrinsic neuronal firing properties and multiple types of synaptic receptors, but because of the complexity of these interactions the exact details of this mechanism are unclear. In this paper these types of interactions were investigated by using biophysical models of thalamic and cortical neurons. It is shown first that, because of the particular activation properties of GABA_B receptor-mediated responses, simulated field potentials can display SW waveforms if cortical pyramidal cells and interneurons generate prolonged discharges in synchrony, without any other assumptions. Here the "spike" component coincided with the synchronous firing, whereas the "wave" component was generated mostly by slow GABA_B-mediated K^+ currents. Second, the model suggests that intact thalamic circuits can be forced into a ~3 Hz oscillatory mode by corticothalamic feedback. Here again, this property was attributable to the characteristics of GABA_B-mediated inhibition. Third, in the thalamocortical system this property can lead to generalized ~3 Hz oscillations with SW field potentials. The oscillation consisted of a synchronous prolonged firing in all cell types, interleaved with a ~300 msec period of neuronal silence, similar to experimental observations during SW seizures. This model suggests that SW oscillations can arise from thalamocortical loops in which the corticothalamic feedback indirectly evokes GABA_B-mediated inhibition in the thalamus. This mechanism is shown to be consistent with a number of different experimental models, and experiments are suggested to test its consistency.

Key words: computational models; thalamus; cerebral cortex; epilepsy; absence; intrinsic properties; low-threshold spikes; spindle oscillations; thalamocortical
MATERIALS AND METHODS

All models that are shown here were based on biophysical representations of the ionic mechanisms underlying synaptic currents, field potential generation, intrinsic firing properties, and network behavior. The modeling methods that were used to simulate these various aspects are described successively.

Synaptic currents. Postsynaptic currents mediated by glutamate AMPA and NMDA receptors as well as GABAergic GABA<sub>A</sub> and GABA<sub>B</sub> receptors were simulated by kinetic models of postsynaptic receptors (Destexhe et al., 1994, 1998b). When a spike occurred in the presynaptic cell, a brief pulse of transmitter concentration (0.5 mM during 0.3 msec) was simulated in the synaptic cleft, and binding of the transmitter to postsynaptic receptors occurred according to simple open/closed kinetics, leading to a transient increase of the postsynaptic current described by the following equation (Destexhe et al., 1994):

\[ I_{\text{syn}} = g_{\text{syn}} m (V - E_{\text{syn}}), \]

where \( I_{\text{syn}} \) is the postsynaptic current, \( g_{\text{syn}} \) is the maximal conductance, \( m \) is the fraction of open receptors, \( E_{\text{syn}} \) is the reversal potential, [T] is the transmitter concentration in the cleft, and \( a \) and \( \beta \) are forward and backward binding rate constants of \( T \) to open the receptors. This scheme was used to simulate AMPA, NMDA, and GABA<sub>B</sub> types of receptors, with the following parameters: \( E_{\text{syn}} = 0 \text{ mV}, \ a = 0.94 \times 10^6 \text{ M}^{-1} \text{s}^{-1}, \ \beta = 180 \text{ s}^{-1} \) for AMPA receptors; \( E_{\text{syn}} = 0 \text{ mV}, \ a = 11 \times 10^4 \text{ M}^{-1} \text{s}^{-1}, \ \beta = 6.6 \text{ s}^{-1} \) for NMDA receptors and \( E_{\text{syn}} = -80 \text{ mV}, \ a = 20 \times 10^4 \text{ M}^{-1} \text{s}^{-1}, \ \beta = 160 \text{ s}^{-1} \) for GABA<sub>B</sub> receptors. These parameters were obtained by fitting the model to postsynaptic currents recorded experimentally (see Destexhe et al., 1998b). In addition, NMDA receptors had a voltage-dependent term corresponding to an extracellular Mg<sup>2+</sup> concentration of 2 mM [Jahr and Stevens (1990); see Destexhe et al. (1998b)].

Intrinsic currents. Intrinsic voltage-dependent or calcium-dependent currents were modeled by kinetic models of the Hodgkin and Huxley (1952) type. These intrinsic membrane currents were described by the following generic equation:

\[ \frac{d}{dt} n = a_n (1 - n) - \beta_n n, \]

where \( I_{\text{int}} \) is the intrinsic membrane current, \( g_{\text{int}} \) is the maximal conductance, and \( E_{\text{int}} \) is the reversal potential. The gating properties of the current were dependent on N activation gates and M inactivation gates, with \( m \) and \( h \) representing the fraction of gates in open form, and with respective rate constants \( a_m, \beta_m, \alpha_h, \) and \( \beta_h \). Rate constants were dependent on either membrane voltage \( V \) or intracellular calcium concentration.

Thalamocortical networks. Network models were based on single-compartment representations of thalamic and cortical neurons. The thalamocortical network was simulated with four cell types: cortical pyramidal cells (PY), cortical interneurons (IN), thalamic reticular cells (RE), and thalamocortical (TC) cells. Cortical cells represent layer VI of the cerebral cortex, in which PY cells constitute the major source of corticothalamic fibers. Because corticothalamic PY cells receive a significant proportion of their excitatory synapses from ascending thalamic axons (Hersch and White, 1981; White and Hersch, 1982), these cells mediate a monosynaptic excitatory feedback loop (thalamus–cortex–thalamus) that has been modeled here. Each layer of cells has been arranged in one dimension (connectivity is schematized in Fig. 4A). This one-dimensional network model with four cell types is a greatly simplified representation of the multilayered structure of the thalamocortical system, but no additional complexity was required.

The cellular models had intrinsic and synaptic currents described by the membrane equation:

\[ C_m \frac{d V_i}{dt} = -g_i (V_i - E_i) - \sum_j r_{j,i} - \sum_k F_{i,k} \]

where \( V_i \) is the membrane potential, \( C_m = 1 \mu \text{F/cm}^2 \) is the specific capacity of the membrane, \( g_i \) is the leakage conductance, and \( E_i \) is the leakage reversal potential. Intrinsic and synaptic currents are represented by \( I_{\text{int}} \) and \( I_{\text{syn}} \), respectively.

The synaptic currents \( F_{i,k} \) from presynaptic cell \( k \) to postsynaptic cell \( i \) were simulated by activating a short pulse of transmitter when cell \( k \) fired an action potential (see above). The receptor types present in synaptic connections between cells depended on the cell type. All excitatory connections (TC→RE, TC→IN, TC→PY, PY→PY, PY→IN, PY→RE, PY→TC) were mediated by AMPA receptors; some inhibitory connections (RE→TC, IN→PY) were mediated by a mixture of GABA<sub>A</sub> and GABA<sub>B</sub> receptors, whereas intra-RE connections were mediated by GABA<sub>B</sub> receptors. Simulations also were performed with NMDA receptors added to all excitatory connections (with maximal conductance set to 25% of that of AMPA), and no appreciable difference was observed. They therefore were not included in the present figures. The total synaptic conductance on each neuron was the same for cells of the same type and was expressed as the sum over all individual synaptic conductances of the same connection type. The total conductances corresponding to the reference state, displaying spindle oscillations, were 0.2 \( \mu \text{S} \) (AMPA, TC→RE), 0.2 \( \mu \text{S} \) (GABA<sub>A</sub>, RE→RE), 0.02 \( \mu \text{S} \) (GABA<sub>B</sub>, RE→TC), 0.04 \( \mu \text{S} \) (GABA<sub>A</sub>, RE→TC), 0.6 \( \mu \text{S} \) (AMP, PY→PY), 0.2 \( \mu \text{S} \) (AMPA, PY→IN), 0.15 \( \mu \text{S} \) (GABA<sub>B</sub>, IN→PY), 0.03 \( \mu \text{S} \) (GABA<sub>B</sub>, IN→PY), 12 \( \mu \text{S} \) (AMPA, PY→RE), 0.01 \( \mu \text{S} \) (AMPA, TC→PY), 1.2 \( \mu \text{S} \) (AMPA, TC→PY), and 0.4 \( \mu \text{S} \) (AMPA, TC→IN).

The connectivity between thalamic and cortical layers was topographic: within the thalamus and within cortex, each axon contacted the 11 nearest neighbors to the presynaptic cell. The axonal divergence was of 21 cells for projections between thalamus and cortex. The connection
In computational models, reproducing this cortical control required more powerful corticothalamic EPSPs on RE cells as compared with TC cells (Destexhe et al., 1998a). In these conditions the excitation of corticothalamic cells led to mixed EPSPs and IPSPs in TC cells in which the IPSP was dominant, consistent with experimental observations (Burke and Sefton, 1966; Deschênes and Hu, 1990). If cortical EPSPs and IPSPs from RE cells were of comparable conductance, cortical feedback could not evoke oscillations in the thalamic circuit because of shunting effects between EPSPs and IPSPs (Destexhe et al., 1998a). The most likely reason for these experimental and modeling evidences for “IPSP dominance” in TC cells is that RE cells are extremely sensitive to cortical EPSPs (Contreras et al., 1993), probably because of a powerful T-current in dendrites (Destexhe et al., 1996b). In addition, cortical synapses contact only the distal dendrites of TC cells (Liu et al., 1995) and probably are attenuated for this reason. Taken together, these data suggest that corticothalamic feedback operates mainly by eliciting bursts in RE cells, which in turn evoke powerful IPSPs on TC cells that in large part overwhelm the direct cortical EPSPs.

The effect of corticothalamic feedback on the thalamic circuit is depicted in Figure 3A: simulated cortical EPSPs evoked bursts in RE cells (Fig. 3B, arrow), which recruited TC cells via IPSPs, and triggered a ~10 Hz oscillation in the circuit. During the oscillation TC cells rebounded after GABA$_\text{A}$-mediated IPSPs once every two cycles, and RE cells discharged only a few spikes, evoking GABA$_\text{A}$-mediated IPSPs in TC cells with no significant GABA$_\text{B}$ currents (Fig. 3B). These features are typical of spindle oscillations (Steriade et al., 1993; von Krosigk et al., 1993).

Repetitive stimulation of the same thalamic circuit at 3 Hz with larger intensity (14 spikes every 333 msec) entrained the system into a different type of oscillatory behavior (Fig. 3C). All cell types were entrained to discharge in synchrony at ~3 Hz. On the other hand, repetitive stimulation at 3 Hz with low intensity produced spindle oscillations (Fig. 3D) similar to those in Figure 3A. Strong-intensity stimulation at 10 Hz led to quiescence in TC cells (Fig. 3E) because of sustained GABA$_\text{B}$ currents, similar to a previous analysis [Lytton et al. (1997), their Fig. 12].

These simulations indicate that strong corticothalamic feedback at 3 Hz can force thalamic circuits in a different type of oscillation. Cortical EPSPs force RE cells to fire large bursts (Fig. 3C, arrows), fulfilling the conditions needed to activate GABA$_\text{B}$ responses (see Fig. 1A). The consequence is that TC cells were “clamped” at hyperpolarized levels by GABA$_\text{B}$ IPSPs during ~300 msec before they could rebound. The nonlinear properties of GABA$_\text{B}$ responses are therefore responsible for the coexistence between two types of oscillations in the same circuit: mild corticothalamic feedback recruits the circuit in ~10 Hz spindle oscillations, whereas strong feedback at 3 Hz could force the intact circuit at the same frequency because of the nonlinear activation properties of intrathalamic GABA$_\text{B}$ responses.
Suppression of intrathalamic GABA_A-mediated inhibition does not generate spike and wave

The impact of this mechanism at the network level was explored using a thalamocortical network consisting in different layers of cortical and thalamic cells (see details in Materials and Methods). The network included thalamic TC and RE cells and a simplified representation of the deep layers of the cortex with pyramidal cells and interneurons (Fig. 4A). In control conditions (Fig. 4B) the network generated synchronized spindle oscillations with cellular discharges in phase between in all cell types, as observed experimentally (Contreras and Steriade, 1996). TC cells discharged on average once every two cycles after GABA_A-mediated IPSPs, whereas all other cell types discharged approximately at every cycle at ~10 Hz, consistent with the typical features of spindle oscillations observed intracellularly (Steriade et al., 1990; von Krosigk et al., 1993). The simulated field potentials displayed successive negative deflections at ~10 Hz (Fig. 4B; in agreement with the pattern of field potentials during spindle oscillations) (Steriade et al., 1990). Consistent with the analysis of Figure 1C, this pattern of field potentials was generated by the limited discharge in PY cells, which fired approximately one spike per oscillation cycle.

When GABA_A receptors were suppressed in thalamic cells in this model, with cortical inhibition intact, spindle oscillations were transformed into slower oscillation patterns at 3–5 Hz (Fig. 4C). In this case there was an increase in synchrony, as indicated by the TC cells that fired at every cycle of the oscillation. RE cells generated prolonged burst discharges, leading to GABA_B-mediated IPSPs in TC cells and, consequently, to a slow oscillation frequency. The field potentials consisted of successive negative deflections (Fig. 4C, bottom) similar to that of spindles. This pattern of field potentials was generated by PY cells that discharged approximately single spikes at each cycle of the oscillation (similar to Fig. 1C). This simulation therefore suggests that removing intrathalamic GABA_A-mediated inhibition affects the oscillation frequency but does not generate SW, because pyramidal cells are still under the strict control of cortical fast inhibition. This is in agreement with in vivo injections of bicuculline into the thalamus, which reported slow oscillations with increased thalamic synchrony, but no SW patterns in the field potentials (Ralston and Ajmone-Marsan, 1956; Steriade and Contreras, 1998).

Suppression of intracortical GABA_A-mediated inhibition leads to spike and wave

On the other hand, the alteration of GABA_A receptors in the cortex had a considerable impact in generating SW. When GABA_A-mediated inhibition was reduced in the cortex, with no change in thalamic inhibitory mechanisms, then spindle oscillations transformed into 2–3 Hz SW-like discharges (Fig. 5). With intracortical fast inhibition decreased by 50%, increased occurrences of prolonged high-frequency discharges were seen during spindle oscillations (Fig. 5A). In field potentials these events tended to generate large-amplitude negative deflections, followed by small-amplitude positive waves (Fig. 5A, bottom).

With totally suppressed GABA_A-mediated inhibition in the cortex, the network generated a slow oscillation at 2–3 Hz, with field potentials similar to SW (Fig. 5B). Field potentials displayed one or several negative/positive sharp deflections, followed by a slowly developing positive wave (Fig. 5B, bottom). During the spike all cells fired prolonged high-frequency discharges in synchrony, whereas the wave was coincident with neuronal silence in all cell types. This portrait is typical of experimental recordings of cortical and thalamic cells during SW patterns (Pollen, 1964; Steriade, 1974; Avoli et al., 1983; McLachlan et al., 1984; Buzsáki et al., 1990; Inoue et al., 1993). Some TC cells stayed hyperpolarized during the entire oscillation (second TC cell in Fig. 5B), as also was observed experimentally (Steriade and Contreras, 1995). A similar oscillation arose if GABA_A receptors were suppressed in the entire network (data not shown).

These simulations thus indicate that spindles can be transformed into an oscillation with field potentials displaying SW and that this transformation can occur by the alteration of cortical inhibition with no change in the thalamus, in agreement with SW discharges obtained experimentally by diffuse application of diluted penicillin onto the cortex (Gloor et al., 1977). The mechanism of the ~3 Hz oscillation of this model depends on a thalamocortical loop in which both cortex and thalamus are necessary, but none of them generates the 3 Hz rhythmicity alone (see next section below).
The progressive transformation between spindles and SW oscillations in the model is shown in Figure 6. With intact cortical inhibition the discharge of cells in the network was limited to a few spikes. Consequently, IPSPs in PY cells were almost exclusively GABA<sub>B</sub>-mediated, leading to field potentials consisting of negative deflections only (Fig. 6, 100%). With the intracortical inhibition partially reduced, there was an increased tendency of producing prolonged discharges and an increased contribution of GABA<sub>B</sub> IPSPs in PY cells, leading to small positive waves in field potentials (Fig. 6, 50%). With a further reduction of intracortical GABA<sub>A</sub>-mediated inhibition, the system showed fully developed SW complexes in field potentials, with oscillation frequencies within the 2–3 Hz range (Fig. 6, from 25 to 0%). The frequency of SW oscillations was approximately proportional to the amount of fast inhibition still present in the cortex. The occurrence of a positive spike also was correlated with intracortical fast inhibition (Fig. 6), in agreement with the effect of GABA<sub>A</sub> conductances in Figure 2B.

The waxing and waning appearance of spindles (Fig. 6, 100%) was attributable here to intrathalamic mechanisms. A calcium-dependent upregulation of I<sub>h</sub> in TC cells was included here, similar to previous models (Destexhe et al., 1993, 1996a). Such regulation was demonstrated recently in thalamic slices (Lüthi and McCormick, 1998). This mechanism was responsible for the waxing and waning of oscillations in model thalamic and thalamocortical networks (Destexhe et al., 1996a, 1998a). It is interesting to note that SW oscillations also may follow a similar waxing and waning envelope (Fig. 6, 25%), which was attributable here to the same intrathalamic mechanisms as spindles. The model therefore suggests that the calcium-dependent upregulation of I<sub>h</sub> in TC cells is responsible for the temporal modulation of SW oscillations and may lead to bursts of several cycles of SW oscillations, interleaved with long periods of silence (~20 sec), as are observed experimentally in sleep spindles and SW epilepsy, thus stressing further the resemblance between the two types of oscillation.

**A thalamocortical loop mechanism for spike-and-wave oscillations**

The thalamocortical mechanism leading to SW oscillations in this model is illustrated and compared with spindles in Figure 7. During spindles the oscillation is generated by intrathalamic interactions (TC–RE loop in Fig. 7A). Oscillations can also be generated by a thalamocortical loop (TC–Cx–RE loop in Fig. 7A), as suggested previously (Destexhe et al., 1998a). The combined action of intrathalamic and thalamocortical loops provides a moderate excitation of RE cells, which evokes GABA<sub>A</sub>-mediated IPSPs in TC cells and sets the frequency to ~10 Hz. During SW oscillations (Fig. 7B) an increased cortical excitability provides a corticothalamic feedback that is strong enough to force prolonged burst discharges in RE cells, which in turn evoke IPSPs in TC cells dominated by the GABA<sub>B</sub> component. In this case the prolonged inhibition sets the frequency to ~3 Hz. The oscillation is generated by a thalamocortical loop (TC–Cx–RE loop in Fig. 7B) in which the thalamus is intact. Therefore, if the cortex is inactivated during SW, this model predicts that the thalamus...
should resume generating spindle oscillations, as observed experimentally in cats treated with penicillin (Gloor et al., 1979).

The relation between cellular events and field potentials in this model of SW is shown in Figure 8. The pattern displayed by the network is similar to Figure 1C2: high-frequency discharges generated spike components in the field potentials, whereas wave components were generated by GABA_A IPSPs in PY cells because of the prolonged firing of cortical interneurons. The hyperpolarization of PY cells during the wave also contained a significant contribution from the voltage-dependent K^+ current I_{K+} (data not shown), maximally activated because of the prolonged discharge of PY cells during the spike. The wave component is therefore attributable in this model to two types of K^+ currents, intrinsic and GABA_A-mediated. The relative contribution of each current to the wave depends on its respective conductance values.

During the spike component the discharges were not perfectly in phase. As indicated in Figure 8B, there was a significant phase advance of TC cells, as observed experimentally (Inoue et al., 1993). This phase advance was responsible for the initial negative spike in the field potentials, which coincided with the first spike in the TC cells (Fig. 8B, dashed line). This feature implements the precedence of EPSPs over IPSPs in the PY cell to generate SW complexes, as evidenced above (see Fig. 2A). The simulations therefore suggest that the initial spike of SW complexes is attributable to thalamic EPSPs that precede other synaptic events in PY cells.

**Determinants of spike-and-wave oscillations**

The critical factors involved in the genesis of SW oscillations in the thalamocortical model were characterized by investigating the range of synaptic conductances giving rise to SW complexes, as evidenced above (see Fig. 2A). The simulations therefore suggest that the initial spike of SW complexes is attributable to thalamic EPSPs that precede other synaptic events in PY cells.
Table 1 shows the optimal values of the conductance that were used and, for each connection, the range of values leading to SW oscillations. The minimal frequency of SW bursts when each parameter was varied within 50–200% of the optimal value is indicated in the last two columns of Table 1. The synaptic conductances that were influential on SW were PY3PY, PY3IN, IN3PY, RE3RE, RE3TC (GABA B), PY3RE, and a weak effect for RE3TC (GABAA). TC3RE, TC3PY, TC3IN, and PY3TC had minimal effect. As expected, the recurrent excitation between pyramidal cells (PY3PY) and the excitation of interneurons (PY3IN), as well as the inhibitory feedback on PY cells (IN3PY), are effective on SW because these conductance determine the excitability of the cortical network. Less expected was the role of cortical excitatory feedback on RE cells (PY3RE), intra-RE inhibition (RE3RE), and the GABA A inhibition from RE onto TC cells (RE3TC). These factors are examined in more detail below.

A first influential factor was the intra-RE GABAergic connections. Figure 9A shows the transition curve from SW oscillations to spindle waves as a function of intracortical GABA A inhibition, similar to Figure 6. Reinforcing intra-RE GABA A inhibition significantly reduced SW in favor of the spindles (Fig. 9A, compare open triangles with filled circles), whereas decreasing this inhibition had the opposite effect (Fig. 9A, open squares). Reducing T-current amplitude therefore diminishes the tendency of the cortical network. Less expected was the role of cortical excitatory feedback on RE cells (PY3RE), intra-RE inhibition (RE3RE), and the GABA A inhibition from RE onto TC cells (RE3TC). These factors are examined in more detail below.

An additional influential factor, not included in Table 1, was the T-current conductance in RE cells. Reducing the T-current of RE cells significantly reduced SW in favor of the spindles (Fig. 9C, compare open triangles with filled circles), whereas reinforcing this current had the opposite effect (Fig. 9C, open squares). Reducing T-current amplitude therefore diminishes the tendency of the
network to produce SW, similar to reinforcing GABAergic inhibition in the RE nucleus. This effect is consistent with the experimental finding that the T-current is increased selectively in RE cells in a rat model of absence epilepsy (Tsakiridou et al., 1995).

On the other hand, reducing the T-current conductance in TC cells had only a weak effect on SW threshold (data not shown), but T-current reduction 40% in TC cells led to the suppression of oscillatory behavior. This was consistent with the effect of the anti-absence drug ethosuximide in reducing the total T-current conductance in TC cells (Coulter et al., 1989).

As predicted from the mechanism of Figure 7B, the frequency of SW essentially was determined by GABA B-mediated IPSPs on TC cells (Fig. 9D, filled circles). Changing the decay of intrathalamic GABA B currents (parameter \( K_4 \)) affected only the frequency, with minimal changes in the bursting patterns of the different cell types (data not shown). This effect was attributable to the fact that, in this model, the duration of the wave is determined essentially by GABA B IPSPs in TC cells, longer IPSPs leading to slower SW by further delaying the rebound of TC cells. The frequency varied from 1 to 5 Hz for decay values of 50–250% of the control value, suggesting that the different frequency of SW bursts in different experimental models may be attributable to differences in the kinetics of GABA B-mediated inhibition in TC cells.

The T-current amplitude in TC cells also affected the SW frequency (Fig. 9D, open squares). Stronger T-current conductances led to earlier rebound and faster frequencies. By contrast, the T-current amplitude in RE cells had minimal effect on SW frequency (Fig. 9C, open triangles). Consistent with the mechanism depicted in Figure 7B, the frequency of SW was mostly attributable to intrathalamic mechanisms, whereas the threshold for SW was dependent on the different elements involved in the thalamus–cortex–thalamus loop.

DISCUSSION

This paper proposed a thalamocortical loop mechanism for the genesis of spike-and-wave oscillations. This mechanism, its simi-
EPSPs are strong enough. EPSPs may become strong enough to force the thalamus in the 3 strong discharges, then the ensuing corticothalamic feedback ability the thalamic-projecting cortical cells generate exceedingly thalamocortical loops. If because of an increase of cortical excitation can be forced in et al., 1993). The present model suggests that a similar oscillation rebound of types during a period of 300 –500 msec and generating a slow positive PY; TC; IN; RE; TC

Figure 8. Phase relations during simulated spike-and-wave discharges. A, Local field potentials (LFP) and representative cells of each type during SW oscillations. Spike. All cells displayed prolonged discharges in synchrony, leading to spiky field potentials. Wave. The prolonged discharge of RE and IN neurons evoked maximal GABA<sub>B</sub>-mediated IPSPs in TC and PY cells, respectively (dashed arrows), stopping the firing of all neuron types during a period of 300–500 msec and generating a slow positive wave in the field potentials. The next cycle restarted because of the rebound of TC cells after the GABA<sub>B</sub> IPSP (arrow). B, Phase relationships in the thalamocortical model. TC cells discharged first, followed by PY, RE, and IN cells. The initial negative peak in the field potentials coincided with the first spike in TC cells before the PY cells started firing and was generated by thalamic EPSPs in PY cells.

Similarities with experimental models of spike and wave

This thalamocortical loop model is consistent with a number of experimental results on SW epilepsy: (1) thalamic and cortical neurons discharge in synchrony during the spike, whereas the wave is characterized by neuronal silence (Pollon, 1964; Steriade, 1974; Avoli et al., 1983; McLachlan et al., 1984; Buzsáki et al., 1990; Inoue et al., 1993), similar to the data in Figures 4E and 8A; (2) TC cell firing precedes that of other cell types, followed by cortical model cells and RE cells (Inoue et al., 1993), similar to the phase relations of the present model (see Fig. 8B); (3) SW patterns disappear after the removal of either the cortex (Avoli and Gloor, 1982) or the thalamus (Pellegrini et al., 1979; Vergnes and Marescau, 1992), as also predicted by the present mechanism; (4) antagonizing thalamic GABA<sub>B</sub> receptors suppresses SW discharges (Liu et al., 1992), consistent with this model; (5) spindle oscillations can be transformed gradually into SW discharges (Kostopoulos et al., 1981a,b), as described in Figure 6.

The present mechanism also emphasizes a critical role for the RE nucleus. Reinforcing GABA<sub>A</sub>-mediated inhibition in the RE nucleus will antagonize the genesis of large burst discharges in RE cells by corticothalamic EPSPs, antagonizing the genesis of GABA<sub>B</sub>-mediated IPSPs in TC cells and therefore antagonizing SW. This property is consistent with the diminished frequency of seizures that is observed after the reinforcement of GABA<sub>A</sub> receptors in the RE nucleus (Liu et al., 1991). It is also consistent with the action of the anti-absence drug clonazepam, which seems to act preferentially by enhancing GABA<sub>A</sub> responses in the RE nucleus (Hosford et al., 1997), leading to diminished GABA<sub>B</sub>-mediated IPSPs in TC cells (Huguenard and Prince, 1994a; Gibbs et al., 1996).

The fact that injections of GABA<sub>A</sub> antagonists in the thalamus with intact cortex failed to generate SW (Ralston and Ajmone-Marsan, 1956; Gloor et al., 1977; Steriade and Contreras, 1998) also was considered. In the model, suppressing thalamic GABA<sub>A</sub> receptors led to “slow spindles” at ~4 Hz, very different from SW oscillations (see Fig. 4C). In this case the discharge of PY cells was extremely brief, because cortical GABA<sub>A</sub>-mediated inhibition was preserved and no GABA<sub>B</sub> IPSPs could be evoked. This result is consistent with the powerful control exerted on pyramidal cells by intracortical GABA<sub>A</sub>-mediated inhibition, as shown by intracellular recordings and modeling (Contreras et al., 1997).

Differences with experimental models of spike and wave

On the other hand, a number of experimental observations are not consistent with the mechanism presented here. First, an apparent intact cortical inhibition was reported in cats treated with penicillin (Kostopoulos et al., 1983). However, this study did not distinguish between GABA<sub>A</sub> and GABA<sub>B</sub>-mediated inhibition. In the present model, even when GABA<sub>A</sub> was antagonized, IPSPs remained approximately the same size because cortical interneurons fired stronger discharges (see Fig. 4D,E) and led to stronger GABA<sub>B</sub> currents. There was a compensation effect between GABA<sub>A</sub>- and...
misleading observation that inhibition is preserved. Interactions with GABAA receptors in TC cells (Hosford et al., 1997). A similar effect was seen in the model (Table 1, GABA A T-current conductance in TC (\(f \text{Hz} \)).

Conductance values represent the sum of all individual synaptic conductances of the same type converging to a given cell. The range of conductance values giving rise to SW is indicated in the last two columns when each respective conductance was set to 50 and 200% of the optimal value; a value equal to control (1.7 Hz) indicates that this parameter had no detectable influence on SW. All simulations were run by using the thalamocortical network model with suppressed GABA \(_A\) mediated inhibition in cortical cells (same conditions as in Fig. 5B).

Conductance values represent the sum of all individual synaptic conductances of the same type converging to a given cell. The range of conductance values giving rise to SW oscillations is indicated in the fourth column (*no value > 5 \(\mu S\) was tested, because sodium spike inactivation may occur for too high conductance values). The minimal oscillation frequency is indicated in the last two columns when each respective conductance was set to 50 and 200% of the optimal value; a value equal to control (1.7 Hz) indicates that this parameter had no detectable influence on SW. All simulations were run by using the thalamocortical network model with suppressed GABA \(_A\)-mediated inhibition in cortical cells (same conditions as in Fig. 5B).

Table 1. Range of values for synaptic conductances and their effect on spike-and-wave oscillations

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Location</th>
<th>Optimal value</th>
<th>SW range (50%) in Hz</th>
<th>SW frequency (200%) in Hz</th>
</tr>
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<tbody>
<tr>
<td>AMPA</td>
<td>PY→PY</td>
<td>0.6 (\mu S)</td>
<td>0.3–0.9 (\mu S)</td>
<td>3.0</td>
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<tr>
<td>AMPA</td>
<td>PY→IN</td>
<td>0.2 (\mu S)</td>
<td>0.06–2 (\mu S)</td>
<td>1.3</td>
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<tr>
<td>GABA (_B)</td>
<td>IN→PY</td>
<td>0.03 (\mu S)</td>
<td>0.02–5 (\mu S)</td>
<td>1.3</td>
</tr>
<tr>
<td>AMPA</td>
<td>TC→RE</td>
<td>0.2 (\mu S)</td>
<td>0–5 (\mu S)</td>
<td>1.7</td>
</tr>
<tr>
<td>GABA (_A)</td>
<td>RE→RE</td>
<td>0.2 (\mu S)</td>
<td>0–1.2 (\mu S)</td>
<td>1.4</td>
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<tr>
<td>GABA (_A)</td>
<td>RE→TC</td>
<td>0.02 (\mu S)</td>
<td>0–1 (\mu S)</td>
<td>1.7</td>
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<tr>
<td>GABA (_B)</td>
<td>RE→TC</td>
<td>0.04 (\mu S)</td>
<td>0.01–5 (\mu S)</td>
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<tr>
<td>AMPA</td>
<td>TC→PY</td>
<td>1.2 (\mu S)</td>
<td>0.15–5 (\mu S)</td>
<td>1.7</td>
</tr>
<tr>
<td>AMPA</td>
<td>TC→IN</td>
<td>0.4 (\mu S)</td>
<td>0–5 (\mu S)</td>
<td>1.7</td>
</tr>
<tr>
<td>AMPA</td>
<td>PY→RE</td>
<td>1.2 (\mu S)</td>
<td>0.4–5 (\mu S)</td>
<td>2.2</td>
</tr>
<tr>
<td>AMPA</td>
<td>PY→TC</td>
<td>0.01 (\mu S)</td>
<td>0–0.1 (\mu S)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Figure 9. Determinants of spike-and-wave oscillations. A. Effect of GABA \(_A\)-mediated inhibition between RE cells. The lowest frequency of SW complexes is represented as a function of the amount of GABA \(_A\) inhibition in cortex (simulations similar to Fig. 6). In control (filled circles) the frequency of SW increased steadily up to 60% of cortical GABA \(_A\); then a transition occurred to spindle oscillations (lowest frequency of ~8 Hz). With twice smaller intra-RE GABA \(_A\) conductances (open squares) this transition occurred at ~75% cortical GABA \(_A\). When intra-RE GABA \(_A\) conductances were doubled, the domain of SW was significantly smaller, with a transition occurring at ~20% of cortical GABA \(_A\) (open triangles). B. Effect of corticothalamic feedback on RE cells. With diminished AMPA conductance in PY→RE synapses (50% of control value), the domain of SW was reduced significantly (open triangles), whereas reinforced cortical EPSPs had the opposite effect (open squares). Filled circles, Same control as in A. C. Effect of the T-current conductance in RE cells. With reinforced T-current (200% of control value) the transition occurred at ~75% of cortical GABA \(_A\) (open squares), whereas with diminished T-current (50% of control value) the domain of SW was reduced significantly (open triangles). Filled circles, Same control as in A. D. Determinants of SW frequency. The frequency of SW bursts in the simulation of Figure 5B was represented when several parameters were varied. These parameters are represented as the percentage of their control value (100% = control). The parameters represented are the decay of intrathalamic GABA \(_B\) currents (filled circles), the T-current conductance in TC (open squares), and RE cells (open triangles).

GABA \(_A\)-mediated IPSPs (data not shown), which may lead to the misleading observation that inhibition is preserved.

Second, some GABA \(_A\) agonists, like barbiturates, may increase the frequency of seizures (Vergnes et al., 1984), possibly via interactions with GABA \(_A\) receptors in TC cells (Hosford et al., 1997). A similar effect was seen in the model (Table 1, GABA \(_A\) RE→TC), but this effect was weak. To be simulated more precisely, this type of data would require modeling the variants of GABA \(_A\) receptor types in different cells and addressing how the threshold for SW discharges is affected by various types of GABAergic conductances. These points should be considered in future models.

Third, the present model investigated only a thalamocortical loop scenario for the genesis of SW oscillations, but other mechanisms are possible. Although most experimental data are in favor of a mechanism involving both thalamus and cortex (see introductory remarks), numerous experimental evidence also points to a possible intracortical mechanism for SW. Experiments revealed SW in isolated cortex or athalamic preparations in cats (Marcus and Watson, 1966; Pellegrini et al., 1979; Steriade and Contreras, 1998). However, this type of paroxysmal oscillation had a different morphology and was slower in frequency compared with the typical “thalamocortical” SW (1–2.5 vs 3.5–5 Hz; Pellegrini et al., 1979). By contrast, intracortical SW was not
observed in athalamic rats (Vergnes and Marescaux, 1992). Because no intracellular recordings were made during the presumed SW in cat isolated cortex, it is not clear if this oscillation represents the same SW paroxysm as in the intact thalamocortical system. Nevertheless, the cortex is known to display intrinsic oscillations generated by bursting neurons (Silva et al., 1991) and also contains rebound-bursting pyramidal cells in some cortical areas (de la Pena and Geijo-Barrientos, 1996). It may be that these properties are sufficient to sustain a form of purely cortical SW, via a sequence of GABA_B IPSPs and rebound, similar to the mechanism analyzed here. When more precise experimental data become available, such as intracellular recordings, possible intracortical mechanisms for SW should be investigated by future models.

Predictions

Several predictions are generated by this model. First, the wave component of SW was generated by massive K^+ currents, mostly because of GABA_A receptor activation. This could be observable by performing intracellular recordings during SW while blocking GABA_A responses. At the network level the injection of GABA_A antagonists or K^+ currents blockers on the cortex should lead to significant alteration of the wave component in field potentials. One must, however, bear in mind that other mechanisms not taken into account here also may participate to the wave component, such as the activation of Ca^{2+}, spikes and Ca^{2+}-dependent K^+ currents, possibly in dendrites (Traub and Miles, 1991).

A second prediction is that intact thalamic circuits can be forced into a ~3 Hz oscillation by strong stimulation of corticothalamic feedback fibers. This experiment could be performed in slices or in decorticated animals by stimulating the internal capsule. The intensity should be high enough to force large bursts in RE cells, evoking GABA_A IPSPs in TC cells and delaying their rebound by ~300 msec. Two stimulation patterns are possible: either the stimulation period should match the delay to rebound, or the stimulation could be triggered by the multunit discharge of TC cells. In the latter case the model predicts a switch from ~10 Hz oscillations to ~3 Hz when the stimulation intensity is increased.

Finally, the model predicts a critical role for the dependence of GABA_A IPSPs on the number of presynaptic spikes. This dependence was simulated by assuming that the binding of four G-proteins is required to activate the K^+ channels underlying GABA_A responses (Destexhe and Sejnowski, 1995). In the thalamocortical model the dependence on the number of spikes is critical for generating the ~3 Hz oscillations as well as the spike-and-wave waveform in field potentials. Dual intracellular recordings between cortical inhibitory interneurons and their targets should shed light into this question in the near future (A.M. Thomson and A. Destexhe, unpublished data).

In conclusion, this paper suggests a thalamocortical loop mechanism for spike and wave, based on the intrinsic and synaptic properties of thalamic and cortical cells, the characteristics of which are consistent with several experimental models of SW as well as with thalamic slice experiments. The key biological components of this mechanism are the activation properties of GABA_A receptors, combined with the complex intrinsic firing properties of thalamic cells. The model also emphasizes a major role for corticothalamic feedback in triggering powerful bursts in RE cells, by which the cortex can force the thalamus to generate oscillations at ~3 Hz by activating intrathalamic GABA_A-mediated inhibition. Because thalamic RE cells may generate bursts through dendritic T-currents (Destexhe et al., 1996b), their sensitivity to corticothalamic feedback EPSPs therefore may be maximal (Contreras et al., 1993), leading to the prediction that this structure should be a major target for a possible suppression of seizures.

REFERENCES

Gloor P, Quesney LF, Zumstein H (1977) Pathophysiology of generalized penicillin epilepsy in the cat: the role of cortical and subcortical
structures II. Topical application of penicillin to the cerebral cortex and subcortical structures. Electroencephalogr Clin Neurophysiol 43:79–94.


Kontopoulos G, Avoli M, Gloor P (1983) Participation of cortical recur-