Realistic Modeling of Entorhinal Cortex Field Potentials and Interpretation of Epileptic Activity in the Guinea Pig Isolated Brain Preparation

E. Labyt, L. Uva, M. de Curtis, and F. Wendling

1Laboratoire Traitement du Signal et de L’Image, Institut National de la Santé et de la Recherche Médicale U642, Rennes University 1, Rennes, France; and 2Department of Experimental Neurophysiology, Istituto Nazionale Neurologico, Milan, Italy

Submitted 20 December 2005; accepted in final form 30 March 2006

Labyt, E., L. Uva, M. de Curtis, and F. Wendling. Realistic modeling of entorhinal cortex field potentials and interpretation of epileptic activity in the guinea pig isolated brain preparation. J Neurophysiol 96: 363–377, 2006. First published April 5, 2006; doi:10.1152/jn.01342.2005. Mechanisms underlying epileptic activities recorded from entorhinal cortex (EC) were studied through a computational model based on review of cytoarchitectonic and neurobiological data about this structure. The purpose of this study is to describe and use this model to interpret epileptiform discharge patterns recorded in an experimental model of ictogenesis (guinea pig isolated brain perfused with bicuculline). A macroscopic modeling approach representing synaptic interactions between cells subpopulations in the EC was chosen for its adequacy to mimic field potentials reflecting overall dynamics rising from interconnected cells populations. Therefore intrinsic properties of neurons were not included in the modeling design. Model parameters were adjusted from an identification procedure based on quantitative comparison between real and simulated signals. For both EC deep and superficial layers, results show that the model generates very realistic signals regarding temporal dynamics, spectral features, and cross-correlation values. These simulations allowed us to infer information about the evolution of synaptic transmission between principal cell and interneuronal populations and about connectivity between deep and superficial layers during the transition from background to ictal activity. In the model, this transition was obtained for increased excitation in deep versus superficial layers. Transitions between epileptiform activities [inter-ictal spikes, fast onset activity (25 Hz), ictal bursting activity] were explained by changes of parameters mainly related to GABAergic interactions. Notably, the model predicted an important role of GABA_{A,fast} and GABA_{A}-receptor–mediated inhibition in the generation of ictal fast onset and burst activities, respectively. These findings are discussed with respect to experimental data.

INTRODUCTION

The hippocampus has been largely implicated in temporal lobe epilepsy (TLE), based on the well-described alteration defined as mesial temporal sclerosis (Babb 1991; Falconer et al. 1964; Sloviter 1994). For the past decade, the importance of entorhinal cortex (EC) in temporal lobe epileptogenesis has been increasingly recognized. Electrophysiological studies in animal models have shown that EC is able to generate spontaneous epileptiform activity independent of hippocampal inputs (Bear and Lothman 1993). More recently, in combined entorhinal and hippocampal slices, seizure-like activity was generated primarily in EC and perirhinal cortex and, from there, propagated to the hippocampus (Avoli et al. 2002; de Guzman et al. 2004). In patients with intractable TLE, investigations with stereotactically implanted depth electrodes showed that seizures may originate in EC (Spencer and Spencer 1994). More recently, analysis of coupling directionality applied to stereoelectroencephalographic signals indicated that EC could be the leader structure in the interictal/ictal transition in mesial TLE (Bartolomei et al. 2004). EC atrophy ipsilateral to the seizure focus was also shown to be specific to mesial temporal lobe structural damage (Bartolomei et al. 2005). Neuropathologic examination of surgically resected specimens revealed cell loss and astrogliosis in EC (Bradford 1995; Yilmazer-Hanke et al. 2000). Overall, these experimental findings suggest that EC plays a pivotal role in the neuronal circuitry necessary for temporal lobe seizure activity. However, circuit and synaptic transmission mechanisms underlying epileptic activities recorded from this structure remain to be understood. Indeed, these mechanisms involve complex, integrated mixes of excitability of principal and inhibitory neurons, efficacy of synaptic transmission, kinetics of postsynaptic responses, synapses location, timing of inputs, and circuit response induced by activation of specific pathways, among other variables.

Without neglecting difficulties inherent to any model-based approach, a way to address this complexity (at least partially) is to relate observed field potentials to neuronal and interneuronal activities through relevant computational models based on cytoarchitectonic and neurobiological knowledge about the anatomical structure under analysis. In a previous study, a physiologically relevant macroscopic model of hippocampus was proposed (Wendling et al. 2002) and used to interpret electrophysiological patterns recorded during the transition from interictal to ictal activity in humans. Among other findings, the model predicted that fast onset ictal activity was explained by the impairment of dendritic γ-aminobutyric acid type a (GABA_{A})–receptor–mediated inhibition with slow kinetics.

In the present study, we use a similar modeling approach to establish a relationship between epileptic activity recorded from the EC (field potentials) and cellular mechanisms at the origin of this activity. The purpose of this study is to fully describe a computational EC model and to use this model to interpret epileptiform activities recorded in an experimental model of ictogenesis developed in the guinea pig isolated brain by arterial perfusion of bicuculline (de Curtis et al. 1994; Librizzi and de Curtis 2003). From realistic simulation of field
METHODS

Experimental data

Experimental data were obtained from brains of Hartley guinea pigs (150–200 g, Charles River, Calco, Italy), isolated and maintained in vitro according to the standard procedure described elsewhere (de Curtis et al. 1991, 1998; Muhlethaler et al. 1993).

In brief, animals were anesthetized with sodium thiopental (125 mg/kg administered intraperitoneally; Farmotal, Pharmacia) and tran
cardially perfused with a cold (4–10°C) oxygenated (95% O2-5% CO2) complex saline solution composed of 126 mM NaCl, 3 mM KCl, 1.2 mM KH2PO4, 1.3 mM MgSO4, 2.4 mM CaCl2, 26 mM NaHCO3, 15 mM glucose, 2.1 mM HEPES, and 3% dextran MW 70,000 (pH 7.1). Brains were rapidly dissected out and transferred in the recording chamber where they were perfused through the basilar artery with the same solution (5.5 ml/min, pH 7.3, 15°C).

Experiments were performed at 32°C after gradually raising the temperature in increments of 0.2°C/min.

Extracellular recordings were performed simultaneously in deep and superficial layers of the EC with 16-channel silicon probes. Temperature was maintained at 35°C in increments of 0.2°C/min.

Responses evoked in the limbic cortices by stimulating the lateral olfactory tract (LOT; see Biella and de Curtis 2000; Gnatkovsky et al. 2004; Uva and de Curtis 2005) through a Grass isolation unit driven by a Grass S88 pulse generator (Warwick, RI). Stimulating and recording electrodes were positioned under direct visual control with a stereoscopic microscope. At the end of the electrophysiological experiments, electrolytic lesions were made by passing a 30-µA current for 30 s between the two deepest contacts of the silicon probe. Brains were then fixed in paraformaldehyde 4% for 1 wk and cut with a vibratome in 75- to 100-µm-thick coronal sections to verify the position of the electrodes. The experimental protocol was reviewed and approved by the Committee on Animal Care and Use and by Ethics Committee of the Istituto Nazionale Neurologico.

Typical seizure activity (Uva et al. 2005) was recorded in ten isolated brains. The transition pattern from interictal to ictal-like activity recorded simultaneously from superficial and deep layers of the EC in an isolated guinea pig brain is displayed in Fig. 1. It includes four successive phases defined by typical and reproducible electrophysiological features. The first phase corresponds to normal background activity. After injection of bicuculline, sporadic spikes appear and become more frequent before seizure begins. This second phase is defined as the preictal phase. At seizure onset, a fast rhythmic activity centered around 25 Hz and defined in the sequel as “fast onset activity” is consistently observed. Then, as seizure develops, the fast onset activity is gradually substituted by ictal burst activity (observed in six of ten experiments), sometimes referred to as “afterdischarges.” During this last phase, the recurrence of bursts progressively decreases before seizure termination.

This animal model was chosen as the experimental framework to validate our computational model because the interictal to ictal transition pattern observed in this model well replicates the pattern observed in patients with TLE. Furthermore, solid experimental findings on the interictal to ictal transition pattern were obtained with this model (Librizzi and de Curtis 2003; Uva et al. 2005), whereas preliminary observations suggest that patterns observed with other acute models (4-aminopyridine, pilocarpine, or high potassium) are different.

The model

The model design started from data about neuronal organization and connectivity of the EC. Intrinsic properties of EC neurons such as persistent Na+ conductance and h-current, for example (Agrawal et al. 2001; Dickson et al. 2000b; Magistretti and Alonso 1999, 2002), were not taken into consideration in our macroscopic modeling approach that essentially represents postsynaptic interactions between subpopulations of cells, which are the main contributors to measured field potentials, we infer information about the evolution of synaptic transmission between principal cell and interneuronal populations and about connectivity between EC deep and superficial layers during the transition from background to ictal activity. Although the macroscopic approach leaves out intrinsic properties of neurons, it was motivated in this work by two considerations. First, it is adapted to interpretation of extracellular patterns of activity (field potentials recorded in the isolated brain model) and it has been used on a number of occasions to analyze how a complex neuronal circuit might produce observed electrophysiological patterns. Second, after validation in an appropriate experimental framework, such an approach could provide a unique window to understand ictogenesis in an animal model and, ultimately, to open the possibility to interpret ictal changes from intracerebral EEG signals recorded in patients with intractable partial epilepsies.
potentials. Main features obtained from a review of the literature are illustrated in Fig. 2 and summarized in the sequel.

CELLULAR ORGANIZATION OF ENTORHINAL CORTEX. In this work, we referred to Lorente de Nó’s classification (1933), which considers the EC as a six-layered cortical structure corresponding to “area entorhinalis” proposed by Brodmann (1909). In accordance with anatomical descriptions (Insausti et al. 1997; Wouterlood et al. 2002), we subdivide EC in “superficial layers” that are superficial to lamina dissecans (layer IV) and “deep layers” between lamina dissecans and the white matter. All of the following descriptions of cytology and network connectivity of the EC when not explicitly mentioned are from rat entorhinal cortex studies.

Principal excitatory neurons. Two types of principal neurons have been distinguished in the EC: pyramidal cells localized in superficial layers (mainly in layer III) and deep layer (mainly layer V) and stellate cells in superficial layers (mainly layer II) (Dolorfo and Amaral 1998a,b; Hamam et al. 2000, 2002; Insausti et al. 1997; Klink and Alonso 1997; Mikkonen et al. 1997; Wouterlood et al. 2002).

As suggested by anatomical studies, pyramidal neurons in superficial layers receive afferent inputs from deep pyramidal neurons (Dolorfo and Amaral 1998b; Gloveli et al. 1997; Kloosterman et al. 2003) and in turn project back to these neurons (Wouterlood et al. 2002). Furthermore, pyramidal neurons in deep layers send collateral axons to stellate cells (Gloveli et al. 2001; van Haeften et al. 2003). In accordance with connectivity in neocortex (Thomson and Bannister 2003), interconnections between deep and superficial EC layers are entirely sustained by principal excitatory neurons. This particularity could arise from the nature of the EC, which is a subdivision of paleocortex.

Interneurons and nonprincipal cells. Inhibitory GABA interneurons have been identified in all layers of the EC (Miettinen et al. 1996). This finding has been confirmed in the human EC with identification of GABAergic interneurons named basket cells (Mikkonen et al. 1997). In further works (Wouterlood and Pothuizen 2000; Wouterlood et al. 2000), GABA negative interneurons have also been observed. Authors suggested that this second class corresponded to excitatory nonprincipal neurons.

A recent whole cell patch-clamp study showed that two kinetically distinct spontaneous inhibitory postsynaptic currents (IPSCs) (fast or slow rise and decay times) could be recorded from EC inhibitory interneurons (layers II and V) (Woodhall et al. 2005). They appeared to be entirely mediated by GABAa receptors because they were abolished by gabazine. Based on functional studies supporting the existence of subtypes of GABAa receptors with differing kinetics, spatially segregated on the same neuron (Banks and Pearce 2000; Banks et al. 2000; White et al. 2000), it has been suggested that these IPSCs with different kinetics could result from activation of different subtypes of GABAa receptors (fast and slow), possibly postsynaptic to subpopulations of EC GABA interneurons (Woodhall et al. 2005). In accordance with this assumption, spatially segregated synapses (axosomatic and axodendritic) from inhibitory interneurons to pyramidal and stellate cells have been identified (Wouterlood and Pothuizen 2000; Wouterlood et al. 1995, 2002). Taken together, these observations suggest that dendritic inhibition would involve mainly GABAa,slow receptors, whereas somatic inhibition would involve mainly GABAa,fast ones (Banks and Pearce 2000; Banks et al. 2000; White et al. 2000).

Furthermore, GABAergic inhibition involving GABAa receptors was also identified in EC (Fountain et al. 1998; Funahashi and Stewart 1998), a finding that was confirmed in human EC (Mizukami et al. 2002).

The origin of these slow GABAa and GABAa responses has been identified in neocortex (Tamas et al. 2003) and more recently in hippocampus (Price et al. 2005) within an inhibitory network of neuroglialform neurons. This novel interneuronal network appears well suited for modulating the flow of information between the entorhinal cortex and CA1 hippocampus.

As suggested by several anatomical and electrophysiological studies (Jones and Buhl 1993; Woodhall et al. 2005; Wouterlood 2002), each of these GABA interneuron classes receives afferent excitatory inputs, presumably from stellate and pyramidal neurons as well as excitatory nonprincipal cells in superficial layers and from pyramidal neurons as well as excitatory nonprincipal cells in deep layers.

Similarly, excitatory nonprincipal cells receive afferent excitatory inputs from stellate and pyramidal neurons in superficial layers and from pyramidal neurons in deep layers. Moreover, excitatory nonprincipal cells also receive inhibitory feedback from GABA interneurons by GABAa,slow (slow and fast) receptors (Wouterlood 2002; Wouterlood and Pothuizen 2000; Wouterlood et al. 2000).

Finally, pharmacological study (Kirchner et al. 2003) demonstrated the effect of different glycine agonist-antagonist drugs on epileptiform activities recorded from EC superficial layers neurons. In a further work (Breustedt et al. 2004), glycine receptors were identified on these neurons and a cross-inhibition of glycine responses by GABA by GABAa,slow receptors was shown.

Extra-entorhinal inputs. An important input of EC comes from hippocampus and more precisely, from pre- and parasubiculum (Caballer-Bleda and Witter 1994) as well as from CA1 (Craig and Commis 2005; Tamamaki and Nojyo 1995; van Haeften et al. 1997; Wouterlood et al. 2004). This input is mainly excitatory. Target neurons of subicular fibers are mainly pyramidal (deep and superficial) and stellate cells, and a projection from subiculum to GABA interneurons in superficial layers was also observed (Wouterlood 2002). More recently, a connection between presubiculum fibers and dendrites of pyramidal neurons of entorhinal layer V was also demonstrated (Wouterlood et al. 2004).

In addition to the hippocampal input, EC receives another input from neocortex and olfactory cortex (Wouterlood 2002) and from subcortical structures (Pikkarainen et al. 1999; Wouterlood 2002). These cortical afferences project to superficial layer cells.

Entorhinal outputs. Anatomical studies in various mammalian species, including the rat, demonstrated that stellate cells in superficial layer II give rise to the perforant pathway, projecting to dentate gyrus and CA3/CA2 hippocampal fields (Gloveli et al. 2001; van Haeften et al. 2003; Witter et al. 1989a; Wouterlood et al. 2002). A second contribution to the perforant pathway comes from pyramidal cells in deep layers (Gloveli et al. 2001; van Haeften et al. 2003). Additionally, pyramidal neurons in superficial layers (mainly layer III) send their axons predominantly to hippocampal field CA1 and the subicu-
COMPUTATIONAL MODEL OF ENTRORHINAL CORTEX EXTRACELLULAR ACTIVITY. To interpret signals recorded from the EC during the transition from interictal to ictal activity in the experimental model of isolated brain (next paragraph), we designed a computational model of synaptic interactions between subpopulations of cells present in the EC, based on the above description. A macroscopic modeling approach (neuronal population level) was chosen because this level of modeling allows simulation of signals that can be directly compared with real signals (field potentials reflect overall dynamics rising from interconnected populations of principal neurons and interneurons). This approach was described theoretically by Wilson and Cowan (1972) and first used by Freeman (1978) and Lopes da Silva et al. (1974, 1976) for electrophysiological data interpretation. More recently, this class of models was exploited in various neurophysiological or clinical studies. Jansen et al. (1993, 1995) proposed a lumped-parameter model of the visual cortex to study the generation of evoked potentials (1995). Wendling et al. (2000, 2002) elaborated a model for the hippocampus. From comparison between simulated and real intracerebral signals recorded in human TLE, hypotheses were generated about the evolution of excitation, slow dendritic inhibition, and fast somatic inhibition in hippocampal circuits during the transition from interictal to ictal activity. Suffczynski et al. (2004) investigated the mechanisms of transition between normal EEG activity and epileptiform paroxysmal activity using a computational macroscopic model of thalamocortical circuits. Bojak and Liley (2005) also proposed a model of the same type for cortical activity and simulated realistic EEG signals in response to specific and quantifiable physiological changes related to different anesthetic agents. Generally speaking, in this class of model, a population of cells is considered. This population is composed by different subpopulations of cells (typically principal cells and interneurons) that interact by synaptic connections. At each subpopulation, a pulse-to-wave function transforms the average presynaptic pulse density of afferent action potentials (input) into an average postsynaptic membrane potential (output), whereas a wave-to-pulse function relates the average postsynaptic potential to an average pulse density of potentials fired by the neurons. The pulse-to-wave function is generally represented by a second-order linear transfer function impulse response

\[ h(t) = \frac{W}{\tau} e^{-\frac{t}{\tau}} \]

where \( W \) is the amplitude of the average receptor-mediated postsynaptic potential (denoted as \( EPSP \) in the excitatory case and as \( IPSP \) in the inhibitory case) and where \( \tau \) represents the decay time constant of this postsynaptic potential (PSP). According to the description above, excitatory PSPs are mediated by glutamate, whereas inhibitory PSPs are mediated by GABA or glycine (see the two following sections). GABA is considered as being exclusively inhibitory in our model. Although a depolarizing effect of GABA by GABA_\text{A} receptors has been demonstrated (Cohen et al. 2002, 2003; Cossart et al. 2005), this effect was shown in subicular cells and in immature neurons (Avoli et al. 2005). Because our objective is to use the model to interpret epileptiform activities in an acute experimental model obtained in adult animals, we chose to consider solely the hyperpolarizing (inhibitory) effect of GABA.

The wave-to-pulse function is modeled by a static nonlinear function of sigmoid shape

\[ S(v) = \frac{2v_0}{1 + e^{v_0-v}} \]

where \( 2v_0 \) is the maximum firing rate, \( v_0 \) is the postsynaptic potential corresponding to a firing rate of \( e_0 \), and \( r \) is the steepness of the sigmoid.

Interactions between neuronal and interneuronal subsets are represented in the model by connectivity constants that account for the average number of synaptic contacts.

The nonspecific influence from neighboring or distant populations is represented by a Gaussian input noise corresponding to an excitatory input \( p(t) \) that globally describes the average density of afferent action potentials.

One model output corresponds to the postsynaptic activity of principal neurons (summed postsynaptic potentials) and can be interpreted as a field potential. Other possible model outputs correspond to the postsynaptic activity of subpopulations, allowing us to assess the participation of each cellular type in the observed field activity.

Finally, model equations are derived from functions \( h(t) \) (Eq. 1), which introduce a pair of first-order ordinary differential equations of the form

\[ \dot{z}(t) = \frac{W}{\tau} x(t) - \frac{2}{\tau} z(t) - \frac{1}{\tau} z(t) \]

and

\[ \dot{z}(t) = \frac{W}{\tau} x(t) - \frac{2}{\tau} z(t) - \frac{1}{\tau} z(t) \]

where \( x(t) \) and \( z(t) \) are the respective input (afferent pulse density) and output (average postsynaptic membrane potential) signals. For a given model, the set of first-order nonlinear ordinary differential equations (ODEs) obtained for all synaptic interactions present in the model is numerically solved to simulate signals.

Following these above general principles and according to the detailed description reported in the previous section, we established a model for the EC. The model consists of two interconnected parts corresponding respectively to the EC superficial and deep layers.

Superficial EC model. As shown in the Fig. 2, for superficial layers, the model constitutes seven subsets of neurons corresponding to two subpopulations of main cells (pyramidal (P1) and stellate (St) neurons), one population of excitatory nonprincipal cells targeting gluta- materic receptors, and four subpopulations of interneurons (inhibitory interneurons targeting GABA_\text{A}slow, GABA_\text{A}fast, GABA_\text{B}, and glycine receptors). Consequently, for each type of synaptic interaction, Eq. 1 turns into

- For excitatory \( \mathcal{P} \text{SPs} \)

\[ h_i(t) = \frac{\text{EPSP}}{\tau_i} e^{-\frac{t}{\tau_i}} \]

- For slow inhibitory GABA_\text{A} \( \mathcal{P} \text{SPs} \)

\[ h_i(t) = \frac{\text{IPSP}_{\text{GABA}_\text{A}}}{{\tau}_i} e^{-\frac{t}{\tau_i}} \]

- For fast inhibitory GABA_\text{A} \( \mathcal{P} \text{SPs} \)

\[ h_i(t) = \frac{\text{IPSP}_{\text{GABA}_\text{A}}}{\tau_i} e^{-\frac{t}{\tau_i}} \]

- For inhibitory GABA_\text{B} \( \mathcal{P} \text{SPs} \)

\[ h_i(t) = \frac{\text{IPSP}_{\text{GABA}_\text{B}}}{\tau_i} e^{-\frac{t}{\tau_i}} \]

- For inhibitory glycine \( \mathcal{P} \text{SPs} \)

\[ h_i(t) = \frac{\text{IPSP}_{\text{glycine}}}{\tau_i} e^{-\frac{t}{\tau_i}} \]

with \( t \geq 0 \) and where \( \text{EPSP} \) denotes the amplitude of the average excitatory glutamate-mediated postsynaptic potential, \( \text{IPSP} \) denotes the amplitude of the average inhibitory postsynaptic potential mediated by receptors of type \( i \), and \( \tau \) represents the corresponding decay
time constant. According to previous work (Wendling et al. 2002), the time constant value $\tau_1 = 10$ ms for the average excitatory postsynaptic potential corresponds to an average value of N-methyl-D-aspartate (NMDA)– and $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA)–receptor-mediated current decay times. For GABAergic IPSPs, the faster time constant $\tau_2$ was set to 5 ms, i.e., lower than the slower time constant $\tau_2$ set to 30 ms, consistent with Traub et al. (1999) and White et al. (2000). Based on GABAa current recordings with whole cell patch-clamp technique (Otis et al. 1993), the value of $\tau_2$ was set to 300 ms, corresponding to the average of the two inactivation time constants identified in this study. Finally, for glycine inhibitory postsynaptic potentials represented in the model, we used a value $\tau_3$ set to 27 ms, corresponding to a weighted mean time constant as described in Lewis et al. (2003). These values are summarized in Table 1.

Interactions between main cells, excitatory nonprincipal cells, and interneurons are represented in the model by 28 connectivity constants $C_{xy}$, where $x$ and $y$ respectively denote the source and the target subpopulation. Because no information about the number of synaptic contacts between different classes of main cells and interneurons was available for the EC, we used the same range of values (20–50) as that used in Traub’s hippocampus model (Traub et al. 1999). Because our objective was to simulate epileptiform activities and to be consistent with increased recurrent excitation observed in epileptic tissues (Morimoto et al. 2004), we increased the number of synaptic contacts between pyramidal neurons and between stellate neurons ($n = 160$). Furthermore, as described by Banks and Pearce (2000), the spatial location of GABAergic receptors depends on their type (GABAa,slow receptors are distributed along the dendrites, whereas GABAa,fast receptors are located in the perisomatic region of pyramidal cells). Thus we introduced an imbalance in the connectivity between GABAa,slow/GABAa,fast interneurons and main cells assuming a higher number of synaptic contacts between GABAa,slow interneurons and main cells. Connectivity constant values are given in Table 2.

Finally, an excitatory input representing nonspecific afferences from neighboring or distant populations was attributed to each one of the two main neuronal subpopulations [Gaussian input noises $p_{x}(t)$ and $p_{y}(t)$].

The model output corresponds to the summated postsynaptic activities of both pyramidal and stellate cells.

**Deep EC model.** As shown in Fig. 1, the model is composed of five subsets of neurons: the main cells (pyramidal neurons, P2), excitatory nonprincipal cells, and three interneuronal subpopulations. In a similar way as described above, excitatory, slow and fast inhibitory GABAa, and inhibitory GABAa postsynaptic membrane potentials are obtained from impulse responses $h_1(t)$, $h_2(t)$, $h_3(t)$, and $h_4(t)$, respectively. Nonspecific influence from other areas is represented by a Gaussian input noise $p_{exc}(t)$. Synaptic contacts between interconnected subpopulations (average number) are represented by 14 connectivity constants (see Table 3). For EC deep layers, model output corresponds to the sum of postsynaptic activities of pyramidal cells.

**Global EC model.** The global EC model was obtained by interconnecting the superficial and deep EC models described above. According to the description given earlier, pyramidal neurons P2 (deep EC model) project to both pyramidal neurons P1 and stellate neurons (superficial EC model). In turn, pyramidal neurons P1 project back to pyramidal neurons P2. Thus three interlayer connectivity constants ($C_{P1P2}$, $C_{P2P1}$, and $C_{P1P2}^{h}$) were introduced to account for the average number of synaptic contacts between these three subpopulations of cells. Regarding these three parameters, it is the difficulty that connectivity between deep and superficial layers in the EC is poorly described in the literature. Nevertheless, for deep to superficial connections, we assumed equal values for parameters $C_{P1P2}$ and $C_{P2P1}^{h}$ in accordance with the recent stereological study of van Haeften et al. (2003). Parameters $C_{P2P1}$, $C_{P2P1}^{h}$, and $C_{P1P2}^{h}$ (with $C_{P1P2}^{h} = C_{P2P1}^{h}$) were identified by comparison between simulated and real signals using cross-correlation analysis (see Identification procedure of model parameters).

According to a previous work (Wendling et al. 2002), the mean and variance of Gaussian noises in the model were adjusted to obtain a rate ranging from 30 to 150 pulses/s.

Finally, regarding numerical simulation details, the whole EC model is governed by a set of 42 first-order nonlinear differential equations. For numerical integration, we used a fixed-step Euler method that accounts for stochastic ODEs [each subpopulation of main cells has an input noise $p(t)$]. To give an idea of the computation time, the generation of a 10-s period of EC activity requires a few seconds on a standard PC-type computer.

**Identification procedure of model parameters**

To gain insight into synaptic interactions involved in the generation of observed signals during the transition to bicuculline-induced seizures, a qualitative and quantitative identification procedure was designed to study the sensitivity of model parameters and used to determine the necessary conditions to reproduce, in the model, real field potentials recorded during the four phases described above. This procedure, summarized in Fig. 3, consisted of iteratively tuning model parameters to obtain realistic simulated activities that mimicked the experimental data. Only eight parameters were modified during this

### Table 1. Amplitude of average postsynaptic potentials (initial values for which normal background activity is simulated) and decay time constants used in the model

<table>
<thead>
<tr>
<th>Amplitude</th>
<th>Deep</th>
<th>Superficial</th>
<th>Decay Time, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitatory PSP (Glutamate)</td>
<td>$EPSP = 6$</td>
<td>$EPSP = 3$</td>
<td>$\tau_1 = 10$</td>
</tr>
<tr>
<td>Inhibitory PSP (GABAa,slow)</td>
<td>$IPSP_{GABA,s} = 35$</td>
<td>$IPSP_{GABA,s} = 35$</td>
<td>$\tau_2 = 30$</td>
</tr>
<tr>
<td>Inhibitory PSP (GABAa,fast)</td>
<td>$IPSP_{GABA,f} = 70$</td>
<td>$IPSP_{GABA,f} = 70$</td>
<td>$\tau_3 = 4$</td>
</tr>
<tr>
<td>Inhibitory PSP (GABAa)</td>
<td>$IPSP_{GABA} = 10$</td>
<td>$IPSP_{GABA} = 10$</td>
<td>$\tau_4 = 300$</td>
</tr>
<tr>
<td>Inhibitory PSP (Glycine)</td>
<td>Not present</td>
<td>$IPSP_{gly} = 40$</td>
<td>$\tau_5 = 27$</td>
</tr>
</tbody>
</table>

### Table 2. Local connectivity constants in superficial EC model

<table>
<thead>
<tr>
<th>$x$</th>
<th>P1</th>
<th>St</th>
<th>$In_{exc}$</th>
<th>$In_{GABA,s}$</th>
<th>$In_{GABA,f}$</th>
<th>$In_{GABA}$</th>
<th>$In_{gly}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>160</td>
<td>—</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>St</td>
<td>—</td>
<td>160</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>$In_{exc}$</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>$In_{GABA,s}$</td>
<td>35</td>
<td>35</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>$In_{GABA,f}$</td>
<td>25</td>
<td>25</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$In_{GABA}$</td>
<td>15</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$In_{gly}$</td>
<td>35</td>
<td>35</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

### Table 3. Local connectivity constants in deep EC model

<table>
<thead>
<tr>
<th>$x$</th>
<th>P2</th>
<th>$In_{exc}$</th>
<th>$In_{GABA,s}$</th>
<th>$In_{GABA,f}$</th>
<th>$In_{GABA}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>160</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>$In_{exc}$</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>$In_{GABA,s}$</td>
<td>35</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$In_{GABA,f}$</td>
<td>25</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$In_{GABA}$</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

J Neurophysiol • VOL 96 • JULY 2006 • www.jn.org
procedure: amplitudes of average excitatory and inhibitory postsynaptic potentials (EPSP and IPSP parameters) in deep and superficial EC models and connectivity $C_{P1}$, $C_{P2}$, and $C_{P2}$ between deep and superficial layers. To reduce the combinatorics of the identification procedure, we introduced two constraints in determining these parameters: 1) we assumed values for IPSP parameters in deep and superficial models to be the same (the effect of systemic perfusion of bicuculline can reasonably be assumed to be equivalent in deep and superficial layers) and 2) we kept identical values for parameters $C_{P2}$ and $C_{P2}$ as justified above. All other parameters (local connectivity and decay time constants) were kept unchanged for all simulations (see values in Tables 1, 2, and 3).

Realism of simulated activities was assessed by comparison of simulated signals to real field potentials. This comparison included temporal dynamics (visual inspection) and spectral features obtained by computing the power spectral density (periodogram method) and a time–frequency representation (spectrum method) of real and simulated activity. We also analyzed the cross-correlation between deep and superficial EC activity using nonlinear regression analysis. Readers may refer to Pijn (1993) for a detailed description of this technique. This analysis provided a way to determine values for interlayer connectivity constants by comparing cross-correlation values measured on real and simulated signals. In brief, this technique was introduced in the field of EEG analysis by Lopes da Silva and colleagues (1989). Evaluated in a model of coupled neuronal populations (Wendling et al. 2001), it was recently used on human intracerebral recordings to identify epileptogenic networks in TLE (Bartolomei et al. 2004). Nonlinear regression analysis is aimed at quantifying the degree of correlation between activities generated in two different sites. A fixed-duration sliding window is used, over which a parameter (nonlinear correlation coefficient $h^2$, ranging from 0 to 1) is computed. Low values of $h^2$ denote that analyzed signals are independent, whereas high values of $h^2$ mean that one signal may be explained by a transformation (possibly nonlinear) of the other (i.e., both signals are dependent).

RESULTS

As described in the following, for each of the four periods chosen during the transition from background to ictal activity, the model produced strikingly realistic signal dynamics and transitions compared with those reflected in real field potential recordings for appropriate modifications of average postsynaptic potential parameters detailed below. Results also show that the model offers the possibility of decomposing the global mean field potential into its main excitatory and inhibitory postsynaptic components originating from neuronal and interneuronal populations.

From background to preictal activity

We first verified whether the model generates realistic background activity compared with real field potentials for initial conditions (see values in Table 1). As shown in Fig. 4A, this activity mainly includes theta (3–7 Hz) and alpha (8–12 Hz) frequency components as observed in the real signals from deep and superficial layers of the EC. Before the beginning of seizure (preictal activity), sporadic spikes mixed with background activity could be observed in real recordings (Fig. 4B, left). In the model, this electrophysiological pattern could be obtained exclusively when the value of parameter EPSP in the deep EC model was at least twofold higher than that in the superficial EC model (Fig. 4B, right). In the opposite condition, preictal activity (and other epileptiform activities) was never simulated. Additional necessary conditions to reproduce preictal activity was to decrease parameter IPSPGABAa,s and values of IPSPGABAa,f ($-37\%$) and IPSPGABAb ($-30\%$). At this point, for fixed parameter values, the occurrence times of spikes were random. Then, for further gradual decrease of IPSPGABAa,s and IPSPGABAa,f parameters, spike frequency increased and spikes became biphasic just before fast onset activity, as also observed in real experimental recordings (asterisks in Fig. 4B).

From preictal to fast onset activity

In the model, fast onset activity with features similar to those observed in the real field potential was obtained for a very low value of parameter IPSPGABAa,s (initial value divided by 10) and a reincrease of parameter IPSPGABAa,f value (+43%). An additional condition was a new decrease of parameter IPSPGABAb ($-21\%$). As shown in Fig. 5A, spectral and time–frequency analysis revealed that both real and simulated signals reflect a narrow band activity (about 25 Hz) disrupted by short periods where a “flattening” followed by a
A spike/fast activity sequence is observed. These results were obtained with interlayer connectivity constants $C_{P1P2}/H1005 = 30$, $C_{P2P1}/H1005 = 60$, and $C_{P2St}/H1005 = 60$ identified from comparison of the cross-correlation values measured by the nonlinear correlation coefficient $h^2$ between deep and superficial layer activity in real and simulated signals. Moreover, in real experiments, the most striking feature is a dramatic increase of $h^2$ values from background ($0.09 \pm 0.02$) and to fast onset activity ($0.59 \pm 0.11$). In the model, this augmentation was also observed and similar average $h^2$ values were obtained on simulated background ($0.07 \pm 0.04$) and fast onset ($0.57 \pm 0.07$) activities, for unchanged interlayer connectivity constants $C_{P1P2}$, $C_{P2P1}$, and $C_{P2St}$ (Fig. 6, A and B).

From fast onset to ictal burst activity

In most experiments, the duration of fast onset activity ranged from 6 to 10 s. Then, the ictal electrophysiological pattern typically evolved into bursts of fast activity that occur rhythmically and simultaneously in deep and superficial layers, also described as afterdischarges. The evolution toward this burst activity was primarily obtained in the model by increasing $IPSP_{GABA_{a,s}} \leq 23\%$ of the initial value (set for background activity). This parameter change can be interpreted in the model as an augmentation of GABAergic inhibition efficacy (reduction of the number of blocked GABA$_{a,slow}$ receptors). For this new set of parameters, we observed realistic values of burst frequency (about 23 Hz), burst duration (from 200 to 400 ms), and interburst interval (about 1 s). As depicted in time–series and time–frequency representations shown in Fig. 5B, the model produced very realistic ictal burst activity. In both real and simulated signals, bursts occur simultaneously in superficial and deep layers. Another important point is that the model generated spontaneous bursting activity with a recurrence rate comparable to that observed in experimental data for constant values of parameters over this period. Moreover, as displayed in Fig. 6C, during bursting activity, we obtained comparable $h^2$ values (real: $0.63 \pm 0.05$; simulations: $0.64 \pm 0.04$). Here again, changes of interlayer connectivity constants $C_{P1P2}$, $C_{P2P1}$, and $C_{P2St}$ were not required to obtain realistic $h^2$ values.

Late decrease of ictal bursts and seizure termination

As observed in real recordings during ictal activity, the interval between bursts progressively extends, whereas the frequency of burst activity remains constant (about 23 Hz).
This effect was reproduced in the model by progressively increasing the parameter $IPSP_{GABA}$ with respect to previous values (up to +45%). Figure 7 provides the evolution of the interburst interval duration during the ictal period for simulated and real signals. The interval duration between two successive bursts was measured as the time separating their respective
onsets obtained from an automatic detection procedure. It can be observed that the model is able to accurately reproduce the progressive lengthening of the interburst interval for the aforementioned progressive increase of GABA\textsubscript{b} inhibition efficiency.

From visual inspection, it is usually observed that the occurrence rate of bursts decreases until seizure termination. In the model, this seizure termination is obtained for a further increase of parameters \( IPSP_{GABA_b} \) (\(+25\%) and \( IPSP_{GABA_a,s} \) (\(+33\%)\).

To summarize the evolution of average postsynaptic potentials detailed above we plotted the values of corresponding parameters as a function of the analyzed phases (from background activity to seizure termination; Fig. 8).

**Activities from each neuronal and interneuronal subpopulation**

In the model, simulated mean field potentials are obtained from the summation at the main cells of average postsynaptic activity generated by local subpopulations of cells. Thus the model offers the possibility of investigating the temporal dynamics of simulated activities as a function of the temporal dynamics of postsynaptic components. An illustrative example

---

**FIG. 6.** Nonlinear correlation coefficient \( (h^2) \) measured on real field potentials and simulated signals from deep and superficial layers for background (A), fast onset activity (B), and ictal burst activity (C).

**FIG. 7.** Comparison of the interburst interval measured during real and simulated ictal activity. In the simulation, lengthening of interval duration is obtained when inhibition mediated by GABA\textsubscript{b} receptors (parameter \( IPSP_{GABA_b} \)) increases with time according to the curve given in Fig. 8.
is given in Fig. 9 for ictal burst activity. Postsynaptic activities rising from excitatory and inhibitory subpopulations of cells start simultaneously but their time course depends on receptor kinetics. Fast oscillations are explained by \( \text{GABA}_{a,\text{fast}} \) inhibition, suggesting an important role of inhibitory interneurons projecting to the soma of principal neurons. Burst recurrence is controlled by inhibition mediated by \( \text{GABA}_n \) receptors: beyond a threshold value, inhibition overcomes excitation and burst activity stops. The long time constant of this inhibitory activity explains the fact that no new burst can occur before a certain time (about 1 s). One may also notice that the different time course of postsynaptic potentials in deep and surface layers is explained by glycine-mediated inhibition, which is present only in the superficial EC model. Even if this parameter remains unchanged in the model, the decrease of \( \text{IPSP}_{\text{GABA}_{a,s}} \) unmasks the influence of the parameter \( \text{IPSP}_{\text{Gly}} \) in the model, arising from the cross-inhibition of glycine-mediated inhibition by \( \text{GABA}_n \) receptors. Consequently, as observed in superficial but not in deep layers (Fig. 9), there is a magnitude modulation of glutamate-, \( \text{GABA}_n,\text{slow} \), and \( \text{GABA}_n,\text{fast} \)-receptor–mediated postsynaptic potentials. When \( \text{IPSP}_{\text{Gly}} \) reaches a threshold value, there is a transient decrease of these postsynaptic potentials.

**DISCUSSION**

Field potentials reflect either activities that diffuse across the cortical depth or locally generated events. We demonstrated that cortical layers represented by two groups in our EC model generate signals that are quantitatively comparable to real field potentials recorded from EC deep and superficial layers in terms of temporal dynamics, spectral features, and cross-correlation values. The findings derived by the analysis of the parameters of the model for which those realistic simulations were obtained are summarized below. In the model, the transition toward epileptic activity is obtained for increased excitation in deep versus superficial layers of the EC. This model prediction corroborates results reported in several studies. A patch-clamp experiment (Beretta and Jones 1996) showed that neurons exhibit larger-amplitude spontaneous excitatory postsynaptic currents in deep than in superficial layers. A more recent study (Woodhall et al. 2005) also revealed that the
overall level of background inhibition is higher in superficial than in deep EC layers. Furthermore, these differences in excitability between deep and superficial layers are strongly supported by several evidences that inhibitory neurons and terminals are more heavily concentrated in superficial layers than in deep layers (Jones and Buhl 1993; Miettinen et al. 1996; Wouterlood et al. 1995, 2000).

Transitions between different phases of the interictal-to-ictal activity (background to preictal, preictal to fast onset activity, fast onset to ictal burst activity, and from ictal burst activity to seizure termination) were obtained in the model by modifying only a small number of parameters. In this study, qualitative and quantitative procedures, respectively based on visual inspection and signal analysis techniques, were used to compare simulated signals to real field potentials. Results from this semi-quantitative model parameter exploration showed that 1) small variations around identified parameter values led to slight modifications of the temporal dynamics of simulated signals and 2) only larger and specific variations of parameters could lead the model to reproduce realistic transitions in these dynamics, as reported. Even if we did not prove it formally, these results tend to show that observed transitions of activity can be explained only by a reduced number of solutions in the model (parameter changes with respect to time). In the model, parameters modified to simulate realistic epileptiform activities are mainly related to GABAergic synaptic interactions between subpopulations of cells (except the twofold higher value of parameter $\text{EPSP}$ in the deep compared with the superficial EC model). Indeed, the only increase of parameter $\text{EPSP}$ did not allow the model to simulate realistic epileptiform activities, the decrease of GABAergic synaptic interactions being a necessary condition to obtain satisfactory matching between real and simulated signals.

In the model, the drop of GABA$_a$ (slow and fast)- and GABA$_b$-receptor–mediated inhibition led to the transition from background to preictal activity. For intermediate values, these parameters also controlled the frequency of transient epileptic spikes mixed to background activity, explaining the variability of electrophysiological patterns during this phase. For GABA$_a$ receptors, this finding is consistent with the bicuculline effect (antagonist) in the isolated guinea pig brain preparation. For GABA$_b$ inhibition, a transitory decrease in the involved potassium conductance is expected at seizure onset. The GABA$_b$ transmission is mediated by a potassium conductance and therefore can be modulated by changes in extracellular potassium concentration (Gahwiler and Brown 1985). Several reports demonstrated that during both ictal discharges and interictal spiking, extracellular potassium concentration increases rapidly (de Curtis et al. 1998; Jefferys 1995). The enhancement of potassium in the extracellular space decreases the driving
force of transmembrane potassium conductances and thus also affects GABA<sub>a</sub>-mediated potentials. The extracellular potassium rise during the preictal state and just at or ahead of seizure onset may induce a transitory decrease in GABA<sub>a</sub>-mediated potassium conductance that promotes the further development of seizure-like discharges.

Then, in the model, fast onset activity (about 25 Hz) was obtained for a reincrease of the GABA<sub>a,fast</sub>-receptor-mediated inhibition. This fast activity is obtained only when the level of GABA<sub>a,slow</sub>-receptor-mediated inhibition and GABA<sub>a</sub>-receptor-mediated inhibition (to a lesser extent) are still low. This result might be interpreted in two ways. First, it might be consistent with the findings of Kapur et al. (1997), who reported that bicuculline primarily acts on GABA<sub>a,slow</sub> receptors and, to a lesser extent, on GABA<sub>a,fast</sub> receptors. The possible interpretation is that membrane depolarization and extracellular potassium increases during the fast onset activity could increase the driving force for Cl<sup>-</sup>, thus increasing the synaptic response to activation of GABA<sub>a,fast</sub> receptors. Second, it can be hypothesized that the time course of bicuculline washout effect differs on both receptor types, with an earlier reincrease of GABA<sub>a,fast</sub>-receptor-mediated inhibition compared with GABA<sub>a,slow</sub>-receptor-mediated inhibition. Both cases lead to a transient period of time during which the level of GABA<sub>a,fast</sub> inhibition is higher than that of GABA<sub>a,slow</sub> inhibition. The global effect would be an augmentation of the IPSPs mediated by GABA<sub>a,fast</sub> receptors, which explains the higher-frequency oscillations observed at seizure onset.

This essential role of GABAergic network in the generation of fast oscillatory activity has already been suggested in several studies related to the mechanisms of generation of gamma activity (Chrobak and Buzsaki 1998b; Cunningham et al. 2003; Dickson et al. 2000a), ripples, and fast ripples (Bragin et al. 2004; Staba et al. 2002). More precisely, it has been shown in hippocampus that both gamma and higher-frequency oscillations reflect synchronized input into the perisomatic region of principal neurons from an interconnected network of GABAergic interneurons (Chrobak and Buzsaki 1998a). In accordance with these results, our modeling observations suggest that a strong GABA<sub>a,fast</sub>-receptor-mediated inhibition (targeting perisomatic region) might also be essential in generation of fast onset activity in the EC. This interpretation is in agreement with identification of two kinetically distinct spontaneous IPSCs (fast or slow rise and decay times) recorded from EC inhibitory interneurons (layers II and V), entirely mediated by GABA<sub>a</sub> receptors (Woodhall et al. 2005). In accordance with previous works (Wouterlood and Pothenius 2000; Wouterlood et al. 1995, 2002) reporting spatially segregated synapses (axosomatic and axodendritic) from inhibitory interneurons to pyramidal and stellate cells in EC, the authors suggested these IPSCs with different kinetics could result from activation of different subtypes of GABA<sub>a</sub> receptors (fast and slow), possibly postsynaptic to subpopulations of EC GABA interneurons (Woodhall et al. 2005). Presynaptic mechanisms affecting a given type of interneurons could be another mechanism to explain these changes in ratios of GABA<sub>a,slow</sub>/GABA<sub>a,fast</sub> receptor-mediated inhibitions. At present, the model represents only postsynaptic interactions and therefore cannot be used to investigate this hypothesis.

Fast onset activity evolves toward a spontaneous ictal burst activity in real recordings. Bursting activity with a recurrence rate could be generated in the model by appropriate setting of parameters. This model property (known as an intermittence phenomenon in nonlinear systems dynamics) results from the coupling of processes that express on slow and fast timescales, respectively related to GABA<sub>a</sub>- and GABA<sub>a,fast</sub>-receptor kinetics. In the model, spontaneous burst activity is ascribed to an “interplay” between GABA<sub>a,fast</sub>- and GABA<sub>a</sub>-receptor-mediated inhibition, whereas interburst interval is controlled by the latter. Indeed, the lengthening of interburst interval was reproduced by increasing GABA<sub>a</sub>-receptor-mediated inhibition and should be explained by an increased availability of GABA that does not bind to GABA<sub>a</sub> receptors blocked by bicuculline. A recent in situ hybridization study (Nishimura et al. 2005) revealed an impaired GABA<sub>a</sub>-receptor-mediated inhibition in hippocampus and a persistent upregulation of several subunits of GABA<sub>a</sub> and GABA<sub>a</sub> receptors in granule cells as compensatory anticonvulsant mechanisms. Besides, it has been shown that GABA<sub>a</sub> agonist drugs allowed shortening of ongoing ictal activity in hippocampus (Stringer and Lothman 1990), whereas GABA<sub>a</sub> antagonist drugs induced convulsions in cortical and limbic structures (Vergnes et al. 1997). Another possibility might be that changes in extracellular potassium concentration during the ictal onset decrease the driving force of GABA<sub>a</sub>, which then progressively recovers and consequently slows down burst frequency, as extracellular potassium concentration decreases. All these hypotheses need further investigation to be confirmed.

However, we noticed that the model was not able to reproduce (and consequently explain) one type of ictal activity encountered in one of the ten experiments performed in the isolated guinea pig brain, characterized by bursts mixed with slower waves. We interpreted this limit to be attributed to the influence of extrinsic activities that are not taken into account in the model, at present. Indeed, a recent study (Uva et al. 2005) showed that some features of real EC recordings could be the result of interactions between the EC and the hippocampus, the perihinal, and/or the piriform cortex. At present, the model represents only activity within the EC, independently from that of other structures.

Very few studies quantify synaptic contacts between neurons in EC deep and superficial layers. In the model presented in this work, information about interlayer connectivity and synaptic interactions between neurons and interneurons sub-populations within deep or superficial layers is based on the only available report by van Haften and colleagues (2003). Local connectivity constants in the model are based on previous work (Traub et al. 1999). These two points related to connectivity parameters may be seen as a limit of the model, directly related to available stereological data. Besides, as previously noticed, our modeling approach leaves out different intrinsic neuronal properties as h-current or persistent Na<sup>+</sup> conductance, or presynaptic GABA<sub>a</sub> receptors that are also able to modulate GABAergic neurotransmission. Nevertheless, the model proved its ability to simulate realistic epileptiform signals and to produce pathophysiological hypotheses (predictions) about mechanisms underlying the generation of these epileptiform activities. Furthermore, some of these model predictions seem to be in agreement with previous experimental findings. Other model predictions will need to be experimentally tested as the role of GABA<sub>a</sub>-mediated inhibition in the lengthening of the interburst interval and in the process of...
seizure termination or the hypothesis that a moderate decrease of GABA<sub>B</sub>-receptor–mediated inhibition results in spikes mixed to background activity (preictal phase). The relationship between GABA<sub>B</sub>-mediated potentials, pH, and extracellular potassium changes with respect to the seizure time course and the role of glycine-mediated inhibition in the burst shape in superficial layers constitute other examples of experimentally testable hypotheses. The model will also be improved by integration of presynaptic inhibition mechanisms. Indeed, amplitude of GABAergic average IPSPs could be modulated as a function of inhibitory effects related to GABA<sub>B</sub> receptors present on the presynaptic membrane (Bailey et al. 2004; Deisz et al. 1997).

Another perspective will be to connect the hippocampus model previously developed (Wendling et al. 2000, 2002) with the present EC model to obtain a more complete model of the hippocampus–EC loop. In this model extension, we will probably also need to represent the dentate gyrus and the subiculum because they constitute the input and output pathways of the hippocampus (Wouterlood 2002). Additionally, superficial EC neurons have also been shown to be inhibited by the hippocampal output by a feedforward inhibitory pathway (V Gnatkovsky and M de Curtis, unpublished observations). Without neglecting the difficulties inherent to any modeling approach, we think that advances in the interpretation of field potentials recorded from the hippocampus–EC system can be expected from such a model if based on strong intervalization with experimental data.

ACKNOWLEDGMENTS

We are grateful to J.-J. Bellanger for helpful discussion about the theoretical aspect of this work.

GRANTS

This work was supported by the French Foundation for Epilepsy Research.

REFERENCES


