Nervous system

Cellular and network mechanisms of electrographic seizures

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Epileptic seizures constitute a complex multiscale phenomenon that is characterized by synchronized hyperexcitation of neurons in neuronal networks. Recent progress in understanding pathological seizure dynamics provides crucial insights into underlying mechanisms and possible new avenues for the development of novel treatment modalities. Here we review some recent work that combines *in vivo* experiments and computational modeling to unravel the pathophysiology of seizures of cortical origin. We focus particularly on how activity-dependent changes in extracellular potassium concentration affect the intrinsic dynamics of neurons involved in cortical seizures characterized by spike/wave complexes and fast runs.

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Introduction

It is widely accepted that the development of epileptiform activity can result from a shift in the balance between synaptic excitation and inhibition toward excitation [1–4]. In fact, an easy way to elicit acute seizures experimentally is to block synaptic inhibition [5–11]. Accordingly, the traditional point of view is that the key intracellular correlate of epileptiform activity, the paroxysmal depolarizing shift (PDS), consists of a giant EPSP [12] enhanced by the activation of voltage-regulated intrinsic currents [1,13–17]. It was therefore a surprise when more recent evidence showed that synaptic inhibition remains functional in many forms of paroxysmal activities [18–26]. Also, disruption of inhibitory function does not affect neocortical kindling [27], which is associated with an increase in synaptic strength that mediates recruitment of larger cortical areas [28]. Furthermore, the firing of fast-spiking inhibitory interneurons (INs) during cortically generated seizures is much stronger than the activity of other types of cortical neurons [24]. Therefore, a decrease or even the absence of synaptic inhibition in the presence of synaptic excitation cannot serve as a general mechanism of cortical epileptic seizures.

Extracellular potassium concentration $[K^+]_o$ increases during neuronal activity. In the presence of neuronal hyperexcitability, the $[K^+]_o$ apparatus fails to maintain $[K^+]_o$ homeostasis (Grafstain, [100]; Somjen, [101]; Frohlich, [102]). The resulting increase in $[K^+]_o$ depolarizes the reversal potential of K^+ currents and can also affect the maximal conductances of some depolarizing currents such as the

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hyperpolarization-activated depolarizing current (I_h) [29] and the persistent sodium current ($I_{Na(p)}$) [30]. Thus, the overall effect of an increase in $[K^+]_o$ is an upregulation of neuronal excitability. Indeed, periodic bursting was found *in vitro* after increasing $[K^+]_o$ [31–33]. Thus, changes in $[K^+]_o$ may play a crucial role in seizure dynamics.

The complexity of the interaction dynamics between neuronal networks and ion concentrations during epileptiform activity requires a combined approach of experimental work and computational models. Here, we discuss recent modeling results regarding mechanisms of epileptic seizures in cortex. First, we present an analysis of the network and cellular mechanisms of electrographic seizures *in vivo*. Then, we discuss the results from computational models that incorporate extracellular K^+ concentration dynamics based on experimental data. Our findings suggest that (1) changes in $[K^+]_o$ activate latent intrinsic burst dynamics that result in paroxysmal bursting and (2) the dynamic interaction between network activity and $[K^+]_o$ causes the emergence of a stable paroxysmal network state in the form of selfsustained oscillations. We conclude with specific predictions derived from our model and propose that molecular mechanisms responsible for $[K^+]_o$ regulation should be examined as novel targets for pharmacological intervention in patients suffering from epilepsy.

Cortical origin of paroxysmal oscillations generated within the thalamocortical system

The origin of electrical seizures that accompany various types of epilepsy is largely unknown, especially for cortically generated seizures. Recent experimental studies strongly implicate a neocortical origin of spike–wave (SW) electroencephalographic (EEG) complexes at ~3 Hz, as in petit-mal epilepsy and seizures with the EEG pattern of the Lennox-Gastaut syndrome [11,34–38]. The etiologies of cortically generated seizures include cortical dysplasia, traumatic injury and other idiopathic/genetic forms [39]. The cortical origin of these seizure types is supported by (a) the presence of paroxysms in neuronal pools within the cortical depth, even without reflection at the cortical surface [40], and in isolated cortical slabs *in vivo* [37]; (b) their induction by the infusion of the GABA$_A$-receptor antagonist bicuculline in neocortex of ipsilaterally thalamectomized cats [36]; (c) the absence of paroxysmal patterns after intrathalamic injections of bicuculline, which rather induce low frequency, regularly recurring spindle sequences as previously described in ferret slices *in vitro* [41] and cat [36,42] or rat [43] thalamus *in vivo*; (d) the vast majority of thalamocortical (TC) neurons is hyperpolarized and does not fire spikes during paroxysmal discharges recorded in corresponding cortical areas [34,37,38,44,45].

As in the slow oscillation, cortical neurons are depolarized and fire spikes during the depth-negative (EEG spike) and are hyperpolarized during the depth-positive (EEG wave) com-

ponents of SW. A typical example of a seizure that consists of both SW–poly-SW (PSW) complexes recurring with frequencies of 1–3 Hz and fast runs with oscillation frequencies of 8–14 Hz is shown in Fig. 1. The seizure starts with SW–PSW discharges. The duration of PSW discharges increases progressively and the seizure displays a prolonged period of fast run. After the fast run the seizure transforms again to PSW complexes, the number of EEG spikes during these complexes decreases and the seizure terminates with SW discharges. Usually, SW–PSW complexes of electrographic seizures correspond to the clonic component of seizures, while fast runs correspond to the tonic component of seizures [46,47]. Similar to SW discharges, fast runs originate in neocortex. Because the frequency and the duration of fast runs are similar to spindles, it could be supposed that the runs of fast paroxysmal spikes share mechanisms with spindles and thus originate in the thalamus. However, the experimental evidence demonstrated that (a) during fast runs TC neurons display EPSPs that only rarely lead to the generation of action potentials [37] and not IPSP-mediated rebound Ca^{2+} spikes as during spindles, (b) the thalamic Ca^{2+} spike bursts precede the cortical depolarizing potentials during spindles, but, in the same cortex to TC neuronal pairs, the TC EPSPs occurring during fast runs follow the cortical neurons (see Fig. 11 in [37]). Also, runs of fast paroxysmal EEG spikes were found in isolated neocortical slabs [37]. These observations confirm the cortical origin of fast runs.

Cellular mechanisms mediating spike and wave discharges

The EEG 'spike' of SW complexes corresponds to the PDS of the membrane voltage in intracellular recordings (reviewed in [26,48,49]). Initially, PDSs have been regarded as giant EPSPs [12,50], enhanced by the activation of voltage-gated intrinsic (high-threshold Ca^{2+} and persistent Na^+) currents [1,13,15,17]. Specifically, the EPSPs initiate the PDS by depolarizing the postsynaptic neurons to the level of activation of the persistent Na^+ current that maintains and enhances the achieved depolarization. This proposed contribution of the persistent Na^+ current to the generation of PDSs has been recently demonstrated by intracellular recordings from pairs of neurons, in which one of the neurons was recorded with a pipette containing QX-314, an intracellular blocker of voltage-gated Na^+ currents. In all cells tested, the inclusion of QX-314 in the recording pipette caused a reduction of the maximal depolarization during the PDS (Fig. 2b). Also, the PDSs increased their duration upon intracellular injection of steady depolarizing current (see Fig. 5 in [24]). Intracellular recordings with the Ca^{2+} buffer BAPTA in the pipette indicate the role of Ca^{2+}-dependent potassium current to the generation of hyperpolarizing potentials during seizures and indirectly support a role of Ca^{2+} influx via Ca^{2+} channels (Fig. 2a). Together, these findings suggest that high-threshold Ca^{2+}
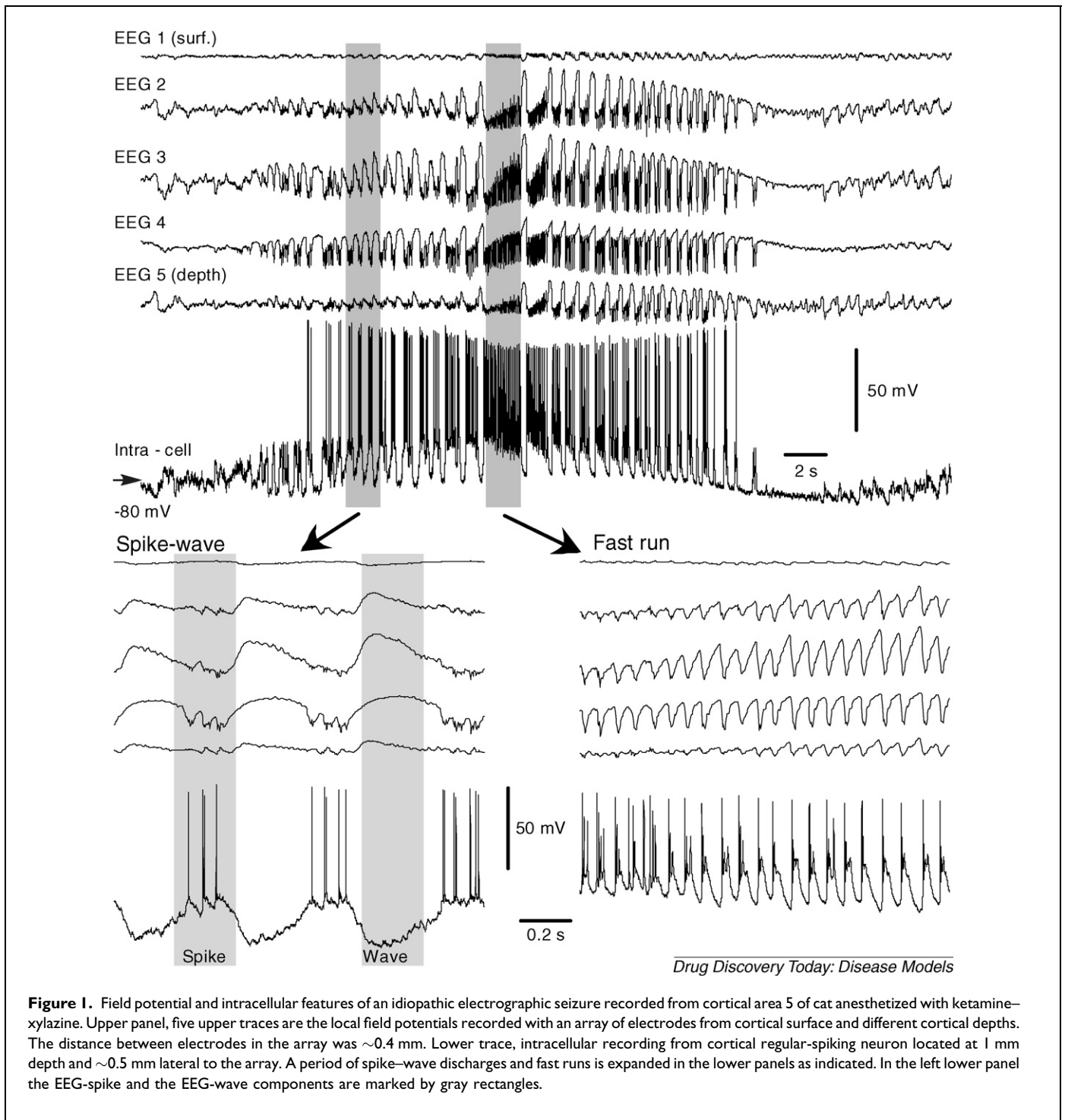
Figure 1. Field potential and intracellular features of an idiopathic electrographic seizure recorded from cortical area 5 of cat anesthetized with ketamine–xylazine. Upper panel, five upper traces are the local field potentials recorded with an array of electrodes from cortical surface and different cortical depths. The distance between electrodes in the array was ∼0.4 mm. Lower trace, intracellular recording from cortical regular-spiking neuron located at 1 mm depth and ∼0.5 mm lateral to the array. A period of spike–wave discharges and fast runs is expanded in the lower panels as indicated. In the left lower panel the EEG-spike and the EEG-wave components are marked by gray rectangles.

currents and the persistent Na$^+$ current could contribute to those depolarizations because these currents are activated at depolarized voltages.

In recent studies, inhibitory processes have been observed during different types of seizure activity [21,23,24,26,51]. Recordings from human and rat slices [18,52] as well *in vivo* experiments in cats [24] have demonstrated that PDSs contain an important inhibitory component. During the depolarizing components of seizures, the

fast-spiking inhibitory INs fire at high frequencies [24]. The activation of postsynaptic GABA$_A$ receptors was substantial and caused the intracellular chloride concentration to increase [24]. This change in ion concentration gradient depolarized the reversal potential for GABA$_A$ inhibitory currents and thus decreased IPSP amplitudes or even reversed the polarity of IPSPs [53]. Also, prolonged high-frequency stimulation [54,55] or spontaneous high-frequency firing of inhibitory INs [24] may induce a rapid
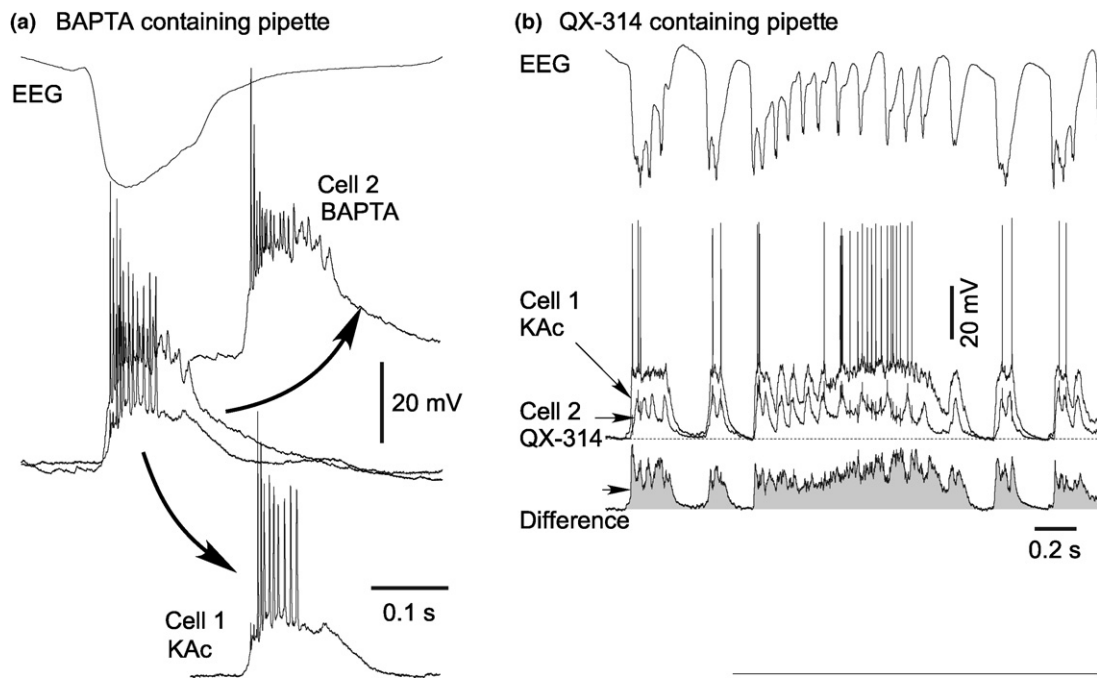
Figure 2. Role of Ca^{2+}-activated and persistent Na^+ currents in the generation of paroxysmal depolarizing shifts. **(a)** EEG and dual intracellular recordings during a paroxysmal depolarizing shift. Intracellular recording with BAPTA field pipette reveals much larger depolarization during the paroxysmal depolarizing shift as compared to control recording with K^+ acetate filled pipette. **(b)** EEG and dual intracellular recordings during a fragment of a seizure. One of the pipettes contained QX-314. The neuron recorded with this pipette revealed much smaller depolarization during paroxysmal activities as shown in the trace 'difference' (modified from [15]).

$GABA_A$-mediated bicarbonate-dependent increase in the $[K^+]_o$. An increase in $[K^+]_o$ in mature neocortical pyramidal (PY) neurons would result in further increase in $[Cl^-]_i$ [56]. The seizure-related depolarizing GABA responses are probably mediated via cation-chloride cotransporters [57].

Earlier hypotheses proposed that the EEG 'wave' component reflects summated IPSPs that were ascribed to GABAergic processes triggered in cortical PY neurons by local-circuit inhibitory cells [58,59]. In computational models, the 'wave' was similarly regarded as produced by $GABA_B$-mediated IPSPs [60]. However, during the EEG 'waves' associated with neuronal hyperpolarization, the input resistance increases relative to the 'spike' component [24,61,62]. These and similar results reported in a genetic rat model of absence epilepsy [63–65] and in cat *in vivo* [24], contradict the idea of a role played by inhibitory receptors in the generation of hyperpolarizations associated with the EEG 'wave' component of SW complexes. Furthermore, intracellular recordings with Cl^- filled pipettes did not reveal chloride-mediated effects during 'wave' components of seizures [24]. As to the possibility that $GABA_B$-mediated IPSPs underlie the 'wave' component of SW seizures, including QX-314 in the recording pipette to block the G-protein-coupled $GABA_B$-evoked K^+ current [66,67] did not significantly affect the hyperpolarization in our experiments (Fig. 2b) [15,38]. Together, these data suggested that

GABA-mediated currents are not important for the hyperpolarizations that occur during these cortically generated seizures.

Another group of mechanisms that can mediate hyperpolarization during SW complexes depends on K^+ currents [68,69]. In recordings with Cs^+-filled pipettes to nonselectively block K^+ currents, PY neurons displayed depolarizing potentials during the 'wave' component of SW seizures [24]. This indicates a leading role played by K^+ currents in the generation of seizure-related hyperpolarizing potentials. A particularly important role is played by $I_{K(Ca)}$ because in recordings with pipettes filled with BAPTA the 'wave'-related hyperpolarizations were reduced and the apparent input resistance increased [15,38]. The second factor that may contribute to the 'wave'-related hyperpolarization during cortically generated SW seizures is disfacilitation [62,63]. Indeed, during the EEG 'wave' component of SW seizures, cortical and TC neurons do not fire, thus creating conditions for disfacilitation. All these results indicate that the hyperpolarizations during SW seizure may be because of the combined effect of K^+ currents and disfacilitation.

What factors are implicated in the transition from neuronal hyperpolarization to depolarization during paroxysmal SW discharges? Intracellular recordings from glial cells and direct measurement of $[K^+]_o$ indicated an increase in $[K^+]_o$

during paroxysmal activities [70–73], leading to a positive shift in the reversal potential of K$^+$-mediated currents, including I_h [29]. More than half of neocortical neurons display resonance within the frequency range of 1–3 Hz or higher, which is mediated by I_h and enhanced by the persistent Na$^+$ current, $I_{Na(p)}$ [74–77]. In our experiments, 20% of neocortical neurons displayed depolarizing sags after the application of hyperpolarizing current pulses, probably caused by the activation of I_h. Also, models of isolated PY neurons with I_h included in their dendritic compartment showed that rebound depolarization was sufficient to generate single action potentials or spike-bursts [73]. The increased excitability of PY neurons after the prolonged hyperpolarizations during the EEG 'wave' component of SW complexes may contribute to the generation of the subsequent paroxysmal depolarization [38,73]. It is also possible that the Ca^{2+}-mediated low-threshold current (I_T), alone or in combination with I_h, contributes to the generation of the rebound over-excitation, as shown in cortical slices [78] and in computational studies [79]. However, the generation of I_T in cortical neurons requires voltages much more hyperpolarized than those normally seen during spontaneously occurring network operations [80]. Thus, the next paroxysmal cycle probably originates from the excitation driven by I_h in conjunction with synaptic inputs.

The summary diagram in Fig. 3 tentatively indicates the different synaptic and intrinsic currents activated by neocortical neurons during paroxysmal activity. The PDS consists of (a) summated EPSPs and IPSPs; and (b) an intrinsic current, $I_{Na(p)}$, as revealed by diminished depolarization in recordings with QX-314 in the recording micropipette. The hyperpolarization related to the EEG depth-positive 'wave' is a combina-tion of K$^+$ currents (mainly $I_{K(Ca)}$ and I_{leak}) and synaptic disfacilitation. Finally, the hyperpolarization-activated depolarizing sag, due to I_h, leads to a new paroxysmal cycle.

Changes in the extracellular milieu and epileptogenesis

Modulation of extracellular ionic concentrations has a profound impact on the excitability of neurons and neuronal networks. According to Grafstein's hypothesis [81], K$^+$ released during intense neuronal firing may accumulate in the interstitial space, depolarize neurons and lead to spike inactivation. During seizures, the increase in [K$^+$]$_o$ reaches 16 mM in the case of 4-AP-induced epileptiform discharges in hippocampus [82] and 7–12 mM in case of spontaneous electrographic seizures in neocortex [70,72,83]. A recent computational study showed that K$^+$-mediated increase in I_h might lead to periodic bursting in a cortical network model [73]. It was shown that a combination of I_h, $I_{K(Ca)}$ and $I_{Na(p)}$ in PY cells is sufficient to generate paroxysmal oscillations at a frequency of 2–3 Hz. These oscillations started when the $I_{K(leak)}$ and I_h reversal potentials were depolarized and the maximal conductance for I_h was increased to model the increased [K$^+$]$_o$ in paroxysmal foci [73]. A single PY cell with these properties was sufficient to mediate activity in an entire cortical network.

Cellular and network periodic bursting occurs *in vitro* after increasing [K$^+$]$_o$ [31–33]. Traumatic brain injury leading to the loss of K$^+$ conductance in hippocampal glia can result in the failure of glial K$^+$ homeostasis and abnormal neuronal function including seizures [84]. The role of elevated [K$^+$]$_o$ in producing synchronized neuronal bursts through the shift of the K$^+$ reversal potential was previously studied in hippocampal slice models [85]. An initial computational model [86]
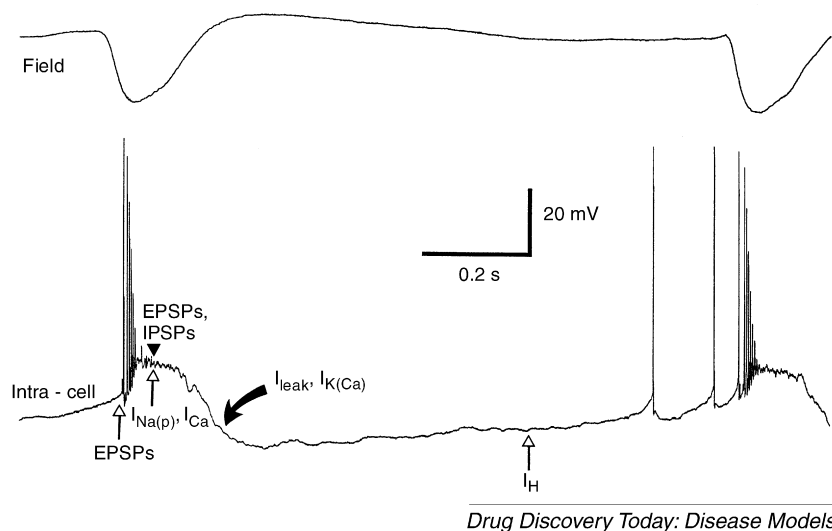
Figure 3. Tentative representation of different synaptic and intrinsic currents activated in neocortical neurons during paroxysmal activity. See text for the description of how these currents interact during paroxysmal activity. Modified from [38].

exhibited periodic bursting after $[K^+]_o$ increase in a single model cell; however, the bursts occurred at a very low frequency (every 10–15 s) which might be attributed to the lack of $I_{K(Ca)}$ in that model. Incorporation of $[K^+]_o$ regulation mechanisms in standard models of cortical pyramidal cells and fast-spiking inhibitory interneurons [96–98] not only explained potential contribution of elevated $[K^+]o$ to the seizure onset but also supported its role in mediating transitions between tonic spiking and bursting as observed during seizures in vivo. More recently neuronal models incorporating sodium and potassium dynamics were proposed to explain very slow and large amplitude oscillations in ion concentrations similar to what is seen physiologically in seizure dynamics [99]. An important role for the low-threshold Ca^{2+} (T-type) current for generating spike-and-wave oscillations has also been recently suggested [79]. In recordings from granule cells of the dentate gyrus in hippocampus at different levels of ionic concentrations in vitro, a simultaneous increase in $[K^+]_o$ and decrease in $[Ca^{2+}]_o$ caused cellular bursts to appear at K^+/Ca^{2+} concentrations that were previously recorded in vivo before the onset of synchronized reverberatory seizure activity [33]. Spontaneous nonsynaptic epileptiform activity was found in hippocampal slices after increasing neuronal excitability (by removing extracellular Mg^{2+} and increasing extracellular K^+) in the presence of Cd^{2+}, a nonselective Ca^{2+} channel antagonist, or veratridine, a persistent sodium conductance enhancer [87]. In recordings from rat hippocampal slices with high $[K^+]_o$, population bursts in CA1 were generated locally by intrinsically bursting PY cells, which recruited and synchronized other neurons [31].

Increases in $[K^+]_o$ unmasked a latent intrinsic burst mechanism that mediated 2–3 Hz oscillations in cortical neuron models that incorporate extracellular K^+ dynamics [88]. Such increases of $[K^+]_o$ can also lead to oscillations at the frequency of fast runs. An external stimulus (DC pulse of 10 s duration) applied to a single cortical PY neuron induced high-frequency spiking in this model cell (Fig. 4). The flow of K^+ ions to the extracellular milieu overpowered the effects of the K^+ pump and glial buffering, and led to $[K^+]_o$ increase (see insert in Fig. 4b). After stimulus termination, the neuron exhibited sustained periodic bursting in the 2–4 Hz frequency range. For each oscillation cycle, the slow membrane potential depolarization (owing to combined effects of I_h and high $[K^+]_o$ that depolarized the reversal potentials of all K^+ currents) activated the persistent sodium current and led to the onset of a new burst (see details in [88]). Each burst started with a few spikes followed by spike inactivation and a depolarizing plateau that lasted 50–100 ms (see insert in Fig. 4a). Progressive increase of the intracellular Ca^{2+} concentration during the depolarized state increased activation of the Ca^{2+}-dependent K^+ current until the neuron switched back to the hyperpolarized state. Deactivation of $I_{K(Ca)}$ determined the length of the hyperpolarized state and ultimately the frequency of slow bursting. Because K^+ reversal potentials remained below -80 mV in these simulations even when $[K^+]_o$ was elevated, the neuron stayed hyperpolarized below resting potential between bursts. During slow bursting, $[K^+]_o$
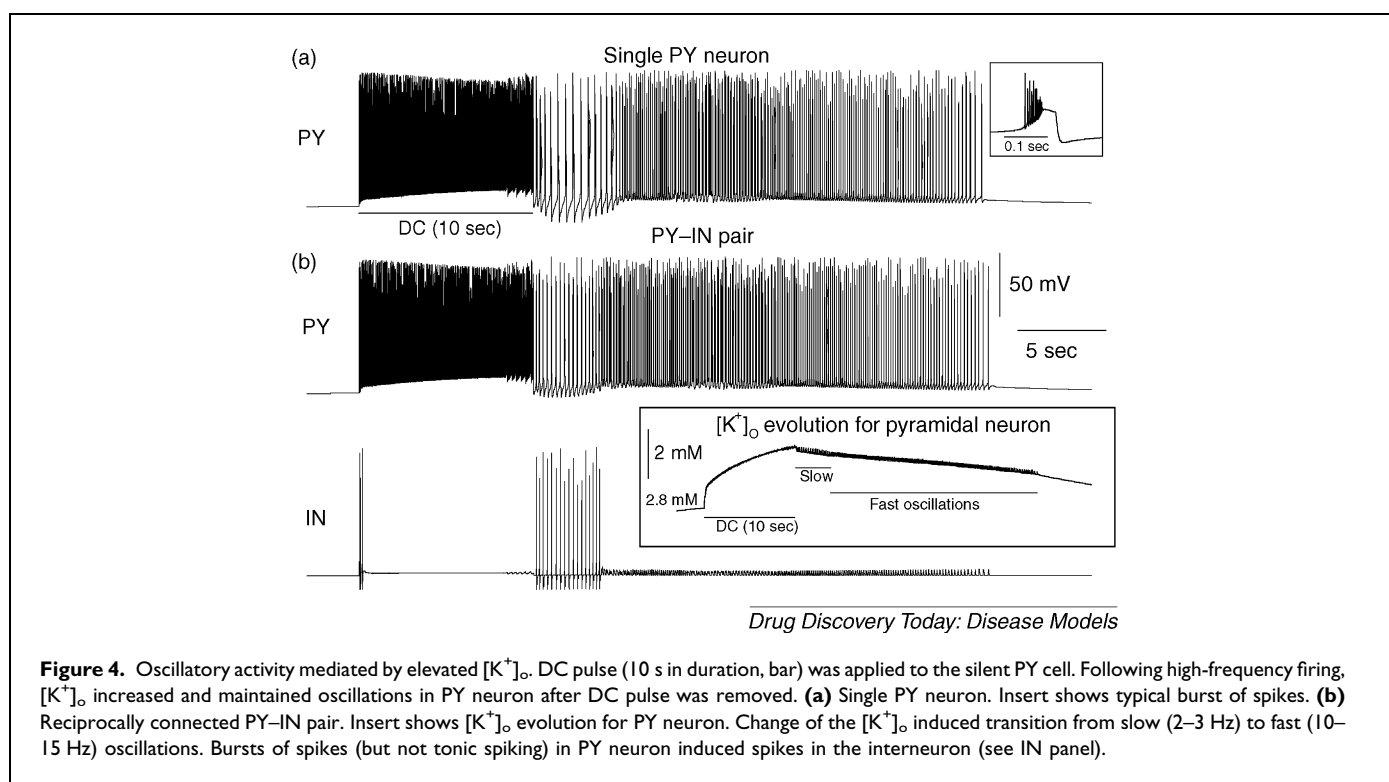

Figure 4. Oscillatory activity mediated by elevated $[K^+]_o$. DC pulse (10 s in duration, bar) was applied to the silent PY cell. Following high-frequency firing, $[K^+]_o$ increased and maintained oscillations in PY neuron after DC pulse was removed. **(a)** Single PY neuron. Insert shows typical burst of spikes. **(b)** Reciprocally connected PY–IN pair. Insert shows $[K^+]_o$ evolution for PY neuron. Change of the $[K^+]_o$ induced transition from slow (2–3 Hz) to fast (10–15 Hz) oscillations. Bursts of spikes (but not tonic spiking) in PY neuron induced spikes in the interneuron (see IN panel).

gradually decreased and 5–6 s later, bursting was replaced by faster oscillations in the 10–14 Hz range. Further decrease of $[K^+]_o$ restored 'normal' hyperpolarized K^+ reversal potentials. This increased the 'hyperpolarizing force' such that the neuron did not stay 'locked' in the depolarized state but repolarized back to the resting potential after one or few spikes. It also led to only minimal activation of the Ca^{2+}-dependent K^+ current, so the next spike (or short burst of spikes) occurred with smaller delay. Therefore, the frequency of bursting increased and the neuron stayed at more depolarized level of membrane potential. Fast oscillations lasted 20–25 s and eventually terminated when $[K^+]_o$ decreased below a level that was necessary to maintain spiking. Thus the change of the $[K^+]_o$ can account for transitions between slow and fast paroxysmal oscillations and silent state in the cortical neuron model.

To study the effect of inhibitory feedback on the circuit dynamics, we included an inhibitory IN that receives synaptic excitation (AMPA-type) from the PY cell and in turn inhibits the PY cell (GABA$_A$-type synapse). The strength of PY–IN synapse was adjusted so that IN remained silent during tonic firing of the PY neuron (Fig. 4b). When the PY neuron started to burst, the excitatory drive from PY to IN cell was sufficient to trigger periodic IN spiking. These inhibitory spikes reduced the duration of PY bursts and thus increased the oscillation frequency. In agreement with *in vivo* recordings [24], the IN spiking stopped when the PY neuron switched from slow bursting to the tonic firing. Two main factors contributed to the absence of IN spiking during fast runs. First, steady-state depression of excitatory coupling between PY and IN neurons was stronger during fast runs because average frequency of PY spiking was higher on account of the continuous firing. During slow bursting, short-term depression was significantly reduced by the end of hyperpolarized (interburst) state. Second, during slow bursting the first few spikes at the burst onset occurred at a higher frequency than the spikes during fast run, therefore promoting EPSP summation in the IN.

Effects of intrinsic conductances on K^+-induced oscillations

In agreement with *in vivo* results (see Fig. 3), high-threshold Ca^{2+} and persistent Na^+ currents were important in creating periodic bursting in our model of neocortical activity in moderately elevated $[K^+]_o$ (Fig. 5). After oscillations were induced by long DC stimulation, sufficiently high maximal conductances for $I_{Na(p)}$ and I_{Ca} were required to maintain periodic bursting. On the $g_{Ca}(g_{Na(p)})$ plane (see Fig. 5a, left) the region for bursting was bounded by two curves. Below the bottom curve, no oscillations were observed. Above the top curve, strong I_{Ca} and/or $I_{Na(p)}$ induced a transient 'lock' of the membrane potential in a depolarized state (spike inactivation). All these regimes are illustrated in panel Fig. 5c, where the maximal change in $[Ca^{2+}]_i$ during a burst is plotted for a

cell held at a constant elevated level of $[K^+]_o = 5.5$ mM. In particular, region C corresponds to long bursts with spike inactivation. In region D, the membrane potential was permanently 'locked' in a depolarized state, which occurred for high $g_{Na(p)}$ and relatively low g_{Ca}. The latter condition ensured weak $I_{K(Ca)}$ activation. Examples of different firing patterns are shown in Fig. 5b.

The value of the conductance that mediates $I_{K(Ca)}$ significantly affected both frequency and duration of the poststimulus oscillations (Fig. 5a, right). When $g_{K(Ca)}$ was below about 2 mS/cm^2, only fast long-lasting oscillations were observed. For higher conductances 2–3 Hz periodic bursting was found. The frequency increased slightly for $g_{K(Ca)}$ above 5 mS/cm^2, which was primary the result of reduced burst duration. Stronger $I_{K(Ca)}$ was more effective in terminating the depolarized plateau. As a result, less Ca^{2+} entered during the depolarized state and therefore the repolarization from the hyperpolarized state was also faster.

Among all the currents, I_h was most effective in controlling the oscillation frequency. Decrease of g_h reduced the frequency to about 1 Hz and very small values of g_h eliminated bursting (Fig. 5d, left). This is consistent with the importance of I_h in maintaining paroxysmal oscillations as proposed previously [73]. Increase of the maximal conductances for $I_{Na(p)}$ and I_{Km} had opposing effects on the oscillation frequency (Fig. 5d, middle and right). Changing maximal conductance for I_{Ca} had a relatively weak effect on the frequency, although the conductance value had to be above certain limit to maintain bursting. This limit depended on the maximal conductance for $I_{Na(p)}$, as shown in Fig. 5a, left.

Synchronization during fast runs and slow bursting

We recently reported very low levels of both short- and long-range synchronization during paroxysmal fast runs [89]. To study synchrony of population oscillations during different oscillatory regimes, we used computer simulations of network models composed of 100 PY neurons and 25 INs. Without synaptic coupling, the model neurons fired independently because of random variability of the model parameters across neurons and different initial conditions (Fig. 6a, top). Upon termination of a simulated DC stimulus, all neurons displayed slow bursting followed by fast spiking; in different neurons, these transitions between fast and slow oscillations occurred at different times. When excitatory/inhibitory coupling between neurons was included, slow paroxysmal bursting became synchronized across neurons (Fig. 6a, bottom). Fig. 6b shows the time-dependent crosscorrelation between neighbor PY cells in the network; during slow paroxysmal oscillations PY neurons fired with minimal phase delays. Similar to the single neuron model (Fig. 4), progressive decrease in $[K^+]_o$ triggered a transition from slow to fast oscillations. In most cases, neighboring neurons displayed this transition nearly simultaneously; however, we found a few large clusters with very different transition
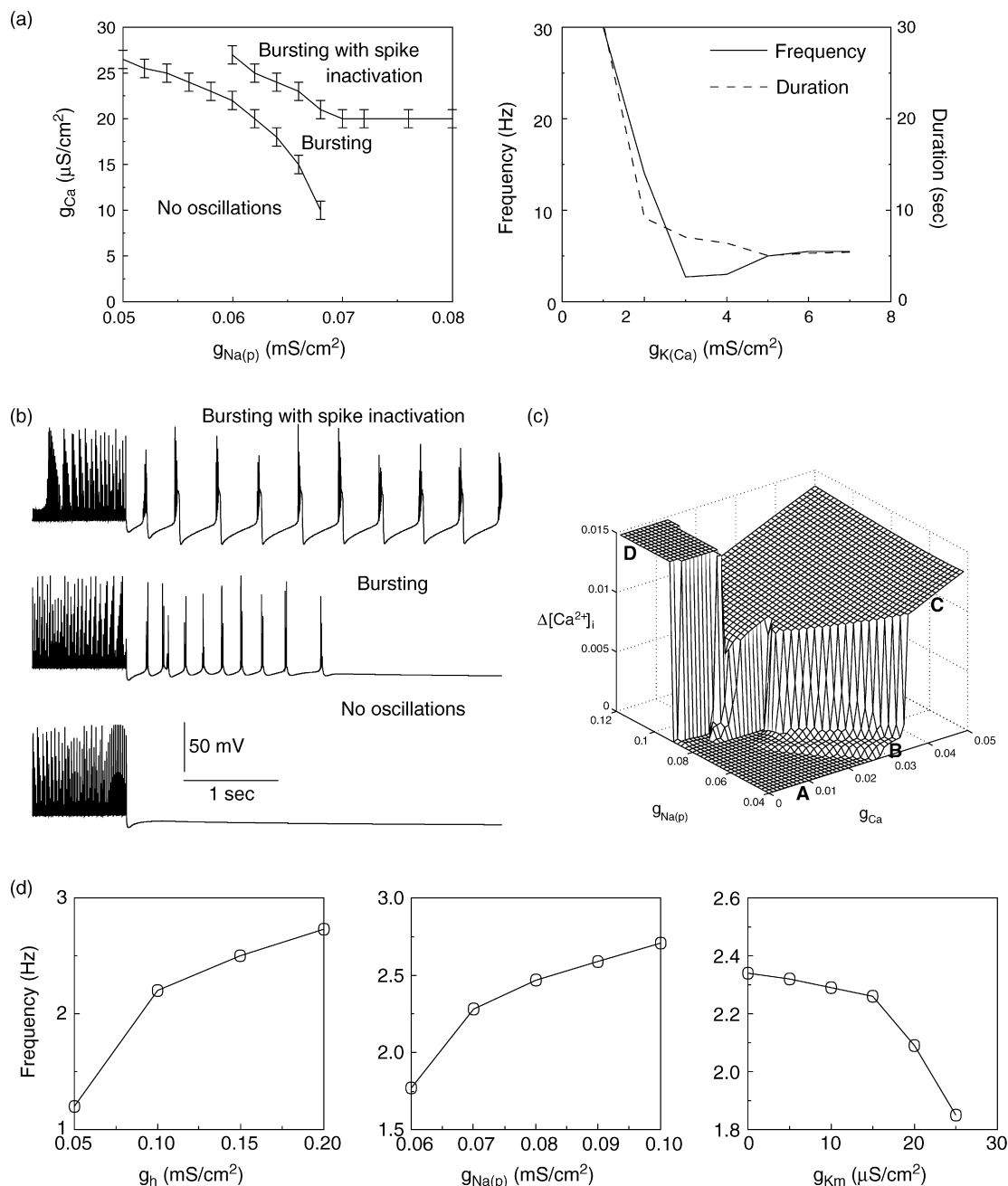
Figure 5. Effect of intrinsic conductances on neuronal oscillations. **(a)** Increase of $[K^+]_o$ during DC stimulation led to oscillations. Sufficiently high levels of persistent Na^+ and high-threshold Ca^{2+} conductances were required to maintain periodic bursting (top left). Increase of Ca^{2+}-dependent K^+ current reduced both duration and frequency of oscillations (top right). **(b)** Examples of PY oscillations corresponding to different regimes indicated in panel a, left. **(c)** $[Ca^{2+}]_i$ increase during a burst as a function of parameters $g_{Na(p)}$ and g_{Ca} for a cell held at a constant level of $[K^+]_o$ (5.5 mM). Longer bursts (more spikes or spike inactivation) produced higher $[Ca^{2+}]_i$ change. Four different regions can be discerned: A: no oscillations; B: bursting; C: bursting with spike inactivation; D: membrane potential 'locked' in depolarized state. **(d)** Effect of the intrinsic conductances on frequency of oscillations. The most significant frequency changes (1–3 Hz) occurred with variations of the I_h maximal conductance (modified from [88]).

times (compare neurons #1–50 and #51–100 in Fig. 6a, bottom). We hypothesized that including long-range connections between PY neurons would increase the global synchrony of transitions between epochs of slow and fast oscillations. To test this hypothesis, we included random long-range connections between PY neurons and varied the probability of this long-range coupling P. Indeed, when $P > 0.02–0.03$, the transition from slow bursting to fast run occurred almost simultaneously (within a 200 ms time window). Including random long-range connections with such low probability did not produce any
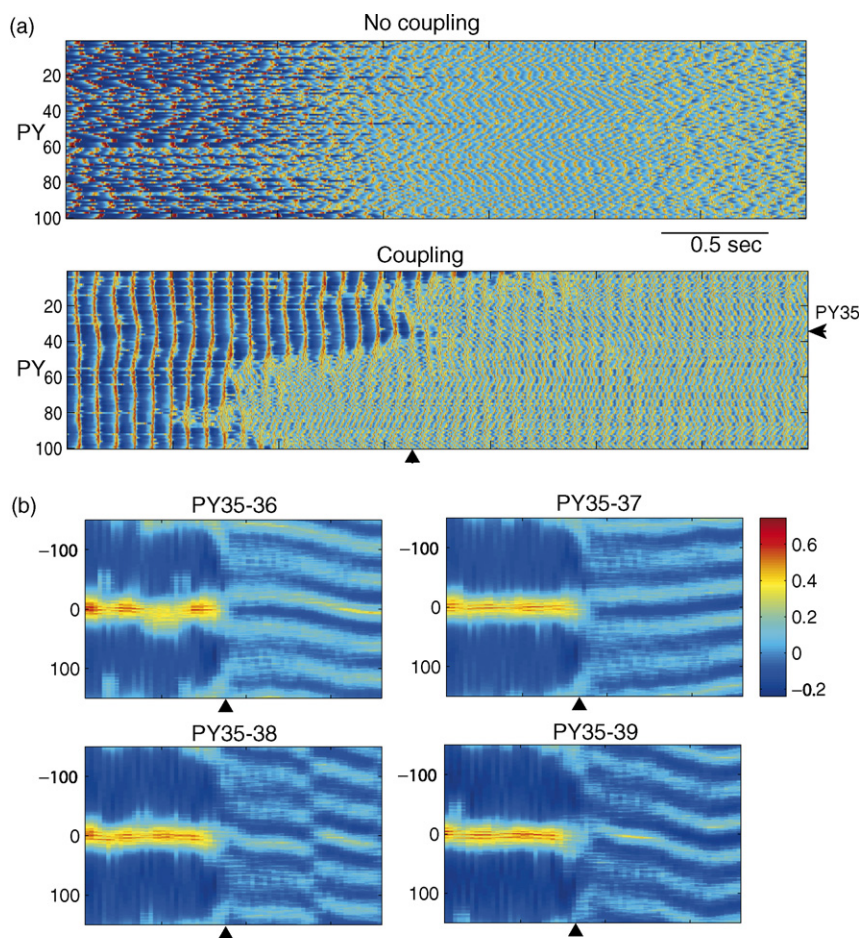
Figure 6. Oscillations following DC stimulation in network (100 PY–25 IN) model. **(a)** Top, no synaptic coupling. Bottom, coupled network. **(b)** Time-dependent crosscorrelations between one PY neuron (PY35) and its neighbors (PY36–PY39). Without synaptic coupling all PY neurons fired independently. Including excitatory/inhibitory connections synchronized the slow oscillations. During fast run, however, PY neurons remained desynchronized. Oscillations in the neighboring PY cells displayed phase shift (local activity propagation) with sudden phase changes (modified from [89]).

systematic effect on phase relations between closely positioned neurons.

In contrast to the slow bursting mode, the degree of synchrony between neurons (even in close proximity) was reduced during fast runs. Typically, neighboring neurons fired with a phase shift that was consistent for a few cycles of network oscillation thus suggesting local spike propagation. Different cell pairs displayed phase delays of different signs (propagation in different directions). Phase relations between neurons changed from in-phase to out-of-phase oscillations or *vice versa* either gradually (see, e.g., crosscorrelation plot for PY35 and PY36 in Fig. 6b) or suddenly (see, e.g., crosscorrelation plot for PY35 and PY38 in Fig. 6b). These modeling results suggest that during fast runs, local synaptic excitation controls phase relations between neighbor neurons but is not sufficient to arrange stable network synchronization. Furthermore, the synchronizing effect of feedback inhibition was absent during fast runs because of low spiking activity of inhibitory INs. Thus, random long-range connections may increase the synchrony of transitions between slow bursting and fast runs but do not affect the synchrony of oscillations on a cycle-to-cycle basis.

Selfsustained oscillations mediated by extracellular K⁺ dynamics

In our modeling studies, the occurrence of oscillatory patterns displayed by cortical neurons (slow bursting or fast run) depended on the absolute level of $[K^+]_o$ [88,90]. In the model of an isolated cortical neuron, fast runs were the only stable firing pattern in the presence of moderately elevated levels of $[K^+]_o$ ($[K^+]_o < [K^+]_o^{cr1} \cong 5.75$ mM). For higher $[K^+]_o$ levels ($[K^+]_o > [K^+]_o^{cr2} \cong 6.4$ mM), slow bursting was the only stable firing pattern. Importantly, for an intermediate range of $[K^+]_o$, these two different oscillatory states coexist ($[K^+]_o^{cr1} < [K^+]_o < [K^+]_o^{cr2}$) [90,91] – a phenomenon called bistability. In this range of $[K^+]_o$, the system could display
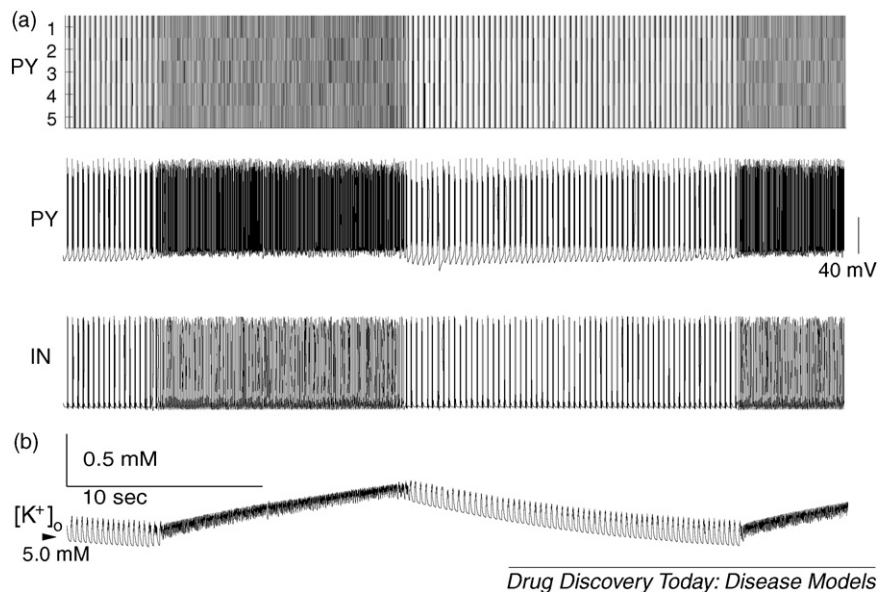
Figure 7. Selfsustained oscillations in globally connected network with five PY cells and one IN. **(a)** Top, network activity of PY cells (40 s duration) shows alternating epochs of fast run and slow bursting. Bottom, membrane voltage time course of PY cell and of IN. **(b)** $[K^+]_o$ increased during fast run and decreased during slow bursting. Upper switching point for transition from fast run to slow bursting and lower switching point for transition from slow bursting to fast run correspond to the end points of the hysteresis region. From [90], with permission. Copyright 2006 Society for Neuroscience.

either tonic spiking or slow bursting depending on the initial state of the cell. In the single cell model, however, this bistability does not play a significant role because of the progressive monotonic $[K^+]_o$ decay. In the network model, however, the same bistability leads to selfsustained oscillations shaped into an alternating sequence of slow bursting and fast run epochs, each lasting several seconds (Fig. 7a). Owing to the lateral excitatory connections, the frequency of fast runs was higher in the network model compared to the isolated neuron. Thus, during fast runs, the activity-dependent K^+ efflux overwhelmed the $[K^+]_o$ regulation mechanism

and therefore the level of $[K^+]_o$ progressively increased. This further increased the network excitability (positive feedback) until the network switched to the slow bursting mode at $[K^+]_o^{cr2}$ (Fig. 7b). During slow bursting, the average network activity was much lower because it was dominated by relatively long intervals of silence between bursts. Owing to the relatively weak K^+ efflux during slow bursting, the $[K^+]_o$ regulation apparatus was sufficiently strong to clear excess $[K^+]_o$. As a result, $[K^+]_o$ decreased until it reached the point ($[K^+]_o^{cr1}$) where the network could not sustain bursting anymore and the network switched back to fast run, thus starting
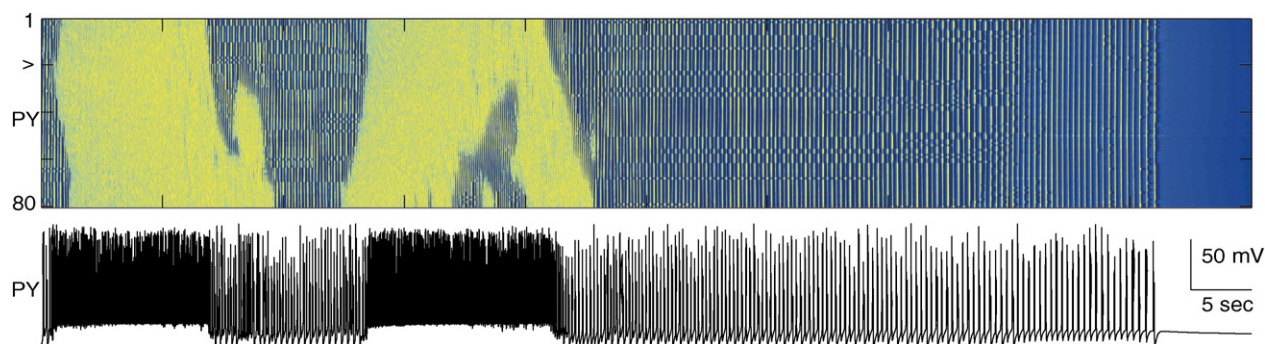

Figure 8. $[K^+]_o$ controls transitions between fast runs and slow bursting. Computational model showing hysteresis between regimes of fast and slow oscillations as a function of $[K^+]_o$, leading to spatial patterning of slow bursting and fast runs in a cortical network model of 80 PYs and 16 INs. Transient increase in initial $[K^+]_o$ triggered oscillations in network which was previously silent. Activity-dependent increase in intracellular chloride concentration caused shift in balance between synaptic excitation and inhibition resulting in the termination of oscillatory activity. Top, network activity; bottom, membrane voltage of representative PY neuron (PY#20).

a new cycle of slow-state transitions between fast run and slow bursting. We also found that the persistence of this transient dynamics depended on the balance between synaptic inhibition and excitation in the network [90,91]. An activity-dependent increase in intracellular chloride concentration mediated by inhibitory synaptic currents caused a depolarizing shift in the reversal potential of chloride leading to a decrease in inhibition. The resulting overall shift in the balance between synaptic excitation and inhibition favored the slow bursting state during which $[K^+]_o$ decreased to eventually return to baseline causing termination of the oscillatory activity (Fig. 8) [92]. Our model shows that the hysteresis between slow and fast oscillations in a single neuron could serve as the basis for both the maintenance and termination of slow bursting and fast runs seen in cat neocortex *in vivo*.

Conclusion

Epileptic seizures are commonly considered unstable runaway dynamics of neuronal networks. Specifically, it has been suggested that positive feedback interaction between extracellular potassium and neural activity mediates cortical seizures. In a series of studies, reviewed here, we showed that epileptic seizures might represent a stable (or quasi-stable) cortical state caused by extracellular potassium concentration dynamics. This pathological state consisted of alternating epochs of tonic firing and bursting and coexisted with another attractor representing normal (healthy) cortical dynamics. This novel and surprising finding is in contrast to the currently held belief that epileptic seizures represent runaway network instabilities.

The basin of attraction of the 'pathological' brain state depends on the variety of factors including intrinsic and synaptic conductances, synaptic connectivity patterns and may vary between healthy and epileptic brains. An increase in the size of this basin in patients suffering from epilepsy would reduce the threshold for transitions from the physiological to the pathological state. It may also affect an average time the brain spends in the pathological state (i.e. duration of seizures). The proposed model may explain the relatively random occurrence of most seizures. In the epileptic brain, internal fluctuations or external inputs would more easily drive the network into the basin of attraction of the seizure state because of its increased size. By contrast, such transitions may never occur in the nonepileptic brain.

Current antiepileptic drugs mainly either enhance $GABA_A$ inhibition or decrease sodium currents. Approximately one-third of patients with symptomatic localization-related epilepsy syndromes (e.g., trauma) are refractory to available antiepileptic medications [93]. In these patients, therapeutical agents that stabilize $[K^+]_o$ at physiological levels could block the epileptic activity. A promising target for such therapeutics may be the astroglial KIR channels, which play

a role in the K^+ reuptake and spatial buffering [94,95]. The successful development of such treatment modalities could eventually reduce the number of patients suffering from drug-resistant epilepsy.

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