Research Signpost
37/661 (2), Fort P.O., Trivandrum-695 023, Kerala, India

Recent Res. Devel. Physiol., 3(2005): ISBN: 81-308-0069-1

Mechanisms of cortical trauma induced epileptogenesis and seizures

Igor Timofeev[1] and Maxim Bazhenov[2]
[1]Dept. of Anatomy and Physiology, Laval University, Québec, PQ, G1K 7P4 Canada; [2]The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA

Abstract

Cerebral cortical trauma may lead to paroxysmal activity. Within 24 hours following head injury with penetrating wounds, up to 80 % of patients display clinical seizures. In this review article we present data pointing towards mechanisms of acute trauma-induced seizure generation and suggest how alterations of homeostatic plasticity could lead to epileptogenesis and chronic epilepsy. This chapter is organized as follows. We describe briefly (a) the organization and normal oscillation of the thalamocortical system, (b) the cellular basis of paroxysmal oscillations generated within the thalamocortical system, (c) major consequences and alterations of cortical intrinsic and synaptic excitability associated with penetrating wounds and (d) long-lasting homeostatic alterations of excitability triggered by neocortical trauma that are implicated in the process of epileptogenesis.

Correspondence/Reprint request: Dr. Igor Timofeev, Dept. of Anatomy and Physiology, Laval University Québec, PQ, G1K 7P4, Canada. E-mail: Igor.Timofeev@phs.ulaval.ca

Introduction

Epilepsy is one of the most common neurological disorders and has no age, racial, social, sexual or geographical boundaries. Up to 5 % of people in the world may have at least one seizure in their lifetime. At any one point in time, 50 million people have epilepsy, especially in childhood, adolescence and old age. Studies in developed countries suggest an annual incidence of epilepsy of approximately 50 per 100,000 of the general population. However, studies in developing countries suggest that this figure is nearly double at 100 per 100,000 people. Up to 30% of people with epilepsy may not respond to drug therapy. (http://www.who.int/mediacentre/factsheets/fs165/en/).

Epilepsy may be divided in two major types: (a) genetically predetermined and (b) acquired. Trauma and brain infection, the primary sources of acquired epilepsy, can cause epilepsy at any age, and may account for the higher incidence of epilepsy in developing countries. Acute cerebral cortical trauma leads to paroxysmal activities. Up to 80 % of patients with penetrating wounds display clinical seizures within 24 hours [1, 2]. Epidemiological studies of the Vietnamese and Croatian wars demonstrate that about 50 % of patients with penetrating cranial wounds developed epilepsy characterized by recurring seizures 10-15 years later [3, 4]. What causes the establishment of epilepsy in

patient with penetrating brain wounds? What are the mechanisms of trauma-related epileptogenesis? The answers to these questions remain largely unknown. Generally, the process of epileptogenesis is divided on three stages: (a) an initial insult; (b) a latent period; and (c) spontaneous seizures [5, 6]. Understanding the process of epileptogenesis will reveal the conditions leading to seizures, thus enabling the creation of efficient preventive antiepileptic therapy. Since penetrating wounds, more often than not, induce damage in neocortical areas, in this review we will focus on possible mechanisms of trauma-induced epileptogenesis within the thalamocortical (TC) system.

Morphological organization and normal oscillations generated by the thalamocortical system

The TC network is organized in a loop (Fig. 1). The main gateway of the TC system is dorsal thalamus, which receives specific inputs from ascending sensory pathways and from the brainstem modulatory systems reviewed in [7]. The TC neurons send their glutamatergic axons to the cerebral cortex and the

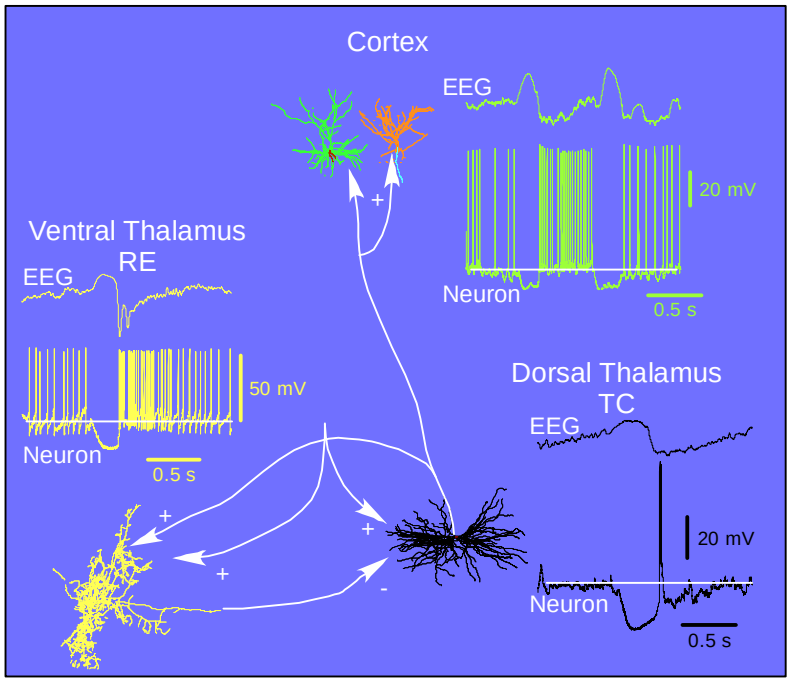

Figure 1. Thalamocortical architecture and main patterns of neuronal activities during slow oscillation. The neurons are stained intracellularly with neurobiotin in anesthetized cats. The direction of their axons is indicated by arrows. Cortical layer III pyramidal neuron and its intrcellular activity during natural slow-wave sleep are shown in green. During depth-positivity the neuron reveals a long-lasting hyperpolarizing potential. Cortical layer III interneuron is shown in orange. RE thalamic neuron from rostrolateral sector and its activity in ketamine-xylazine anesthetized cat are shown in yellow. Similarly to cortical neurons the neurons from RE nucleus are hyperpolarized during field-depth positivity. At the onset of depth-negative field potential they reveal high-frequency spike-bursts. TC neuron from VPL nucleus and its activity in ketamine-xylazine anesthetized cat are shown in black. During field-depth positivity TC neurons are hyperpolarized. At the transition to the field depth-negative potentials, TC neurons may generate rebound spike-burst and being a subject of strong inhibitory influences from RE neurons the TC neurons are hyperpolarized and often reveal spindle sequences during field depth-negative potential (I.Timofeev, M. Rosanova, unpublished).

reticular (RE) thalamic nucleus. The axons of TC neurons terminate in the middle layers of neocortex (primarily layer IV). In the visual system of cats the synapses of TC neurons form approximately 5-6 % of the total number of synapses on layer IV neurons [8, 9]. The major sources of afferents to the RE thalamic nucleus are the collaterals of TC and corticothalamic fibers (Fig. 1), all of which pass through the RE nucleus [10]. Both, the TC and corticothalamic fibers are glutamatergic and thus excitatory. The amplitudes of excitatory postsynaptic conductances evoked in RE neurons by minimal stimulation of corticothalamic fibers are 2.4 times larger than in relay neurons, and quantal size of RE excitatory postsynaptic conductances is 2.6 times greater. GluR4-receptor subunits labeled at corticothalamic synapses on RE neurons outnumbered those on relay cells by 3.7 times [11]. Thus, the excitatory influence of corticothalmic fibers on RE neurons is much larger than their influence on TC neurons. All the neurons within the RE thalamic nucleus are GABAergic [12, 13]. The axons arising from RE neurons, after giving off one or two collaterals in the nucleus enter the underlying dorsal thalamus and terminate [14-16]. The main axons of RE thalamic cells ramified in the thalamus, and in the ventrobasal nucleus of thalamus they form three branching patterns: cluster, intermediate, and diffuse [17]. A distinct feature of RE intranuclear connections is the presence of gap junctions, which couple electrotonically RE neurons [18, 19]. An ensemble of these factors suggests that synchronous cortical volleys generated during sleep or paroxysmal activity through a primary synaptic relay in GABAergic thalamic reticular (RE) neurons, may overcome the direct excitation of TC neurons [20]. The TC neurons would remain in prolonged hyperpolarizing states and would not actively function during cortical synchronous discharges.

Normal oscillations generated within the thalamocortical system

Various oscillatory rhythms generated in the TC system may be divided in two main classes: intrinsic that are generated by a single neuron as a result of interplay between specific intrinsic currents and extrinsic or network that requires interaction in a population of neurons. Typically later means excitatory and/or inhibitory interactions between neurons of the same or different classes. Intrinsic neuronal currents contribute to the generation of network oscillations. Oscillations may be also generated by a population of non-pacemaker neurons coupled though gap junctions.

a. Infra-slow oscillation

This is type of oscillatory activities with a period from tens of seconds to a minute range [21]. The mechanisms of these oscillations are unknown. At least some of the factors responsible for the generation of these oscillations could depend on nonneuronal dynamics, such as changes in CO_2 concentration [22]. The presence of infra-slow activities in isolated neocortical slabs suggests their cortical origin [23].

b. Slow oscillation

The slow oscillation is rhythmic activity that is generated with frequency (0.3 - 1 Hz). The slow rhythms dominate cortical activity during natural sleep and under some types of anesthesia [24-27]. Figure 2 shows electrophysiological recordings during transition from waking state through a brief period of drowsiness to slow-wave sleep (SWS). During waking state the EEG shows activated pattern characterized by high-frequency, low amplitude oscillations. The membrane potential of cortical neurons is relatively depolarized (around -62 mV), stable and most of neurons fire spontaneous action potentials [26, 27]. The electromiogram (EMG) recordings show occasional muscle contractions and the electrooculogram (EOG) recordings demonstrate the presence of eye movements. The drowsiness is characterized by appearance of EEG slow-waves and the depth-positive components of these slow-waves are associated with neuronal hyperpolarization. During drowsiness the aperiodic slow-waves are interrupted by short (several seconds) periods of activated EEG patterns. During SWS the EEG recordings reveal periodic slow-waves and the intracellular recordings demonstrate bimodal membrane potential distribution. During dept-positive EEG waves the cortical neurons are hyperpolarized (see arrowheads in the right low panel of Fig. 2) and during depth-negative EEG waves they are depolarized and fire spikes (Fig. 2). The periodic (less than 1 Hz) changes of EEG depth-positive and EEG depth-

negative waves accompanied with neuronal hyperpolarization, followed by neuronal depolarization constitute the distinctive features of slow oscillation.

The slow oscillation has cortical origin. The facts supporting this conclusion are following: (a) Slow oscillation survives extensive thalamic lesions [28], (b) Slow oscillation was not found in the thalamus of decorticated cats [29], (c) Slow oscillation could be recorded from isolated neocortical slabs [30] and even from neocortical slices maintained in modified ACSF [31]. Single study shows that following activation of the metabotropic glutamate receptor (mGluR), mGluR1a, cortical inputs can recruit cellular mechanisms that enable the generation of an intrinsic slow oscillation in TC neurons in vitro with frequencies similar to those observed in vivo [32]. Intracellular studies on anesthetized and non-anesthetized cats have shown that the hyperpolarizing phase of the slow oscillation is associated with disfacilitation, a temporal absence of synaptic activity in all cortical, TC and RE neurons [27, 33, 34]. During disfacilitation the membrane potential of cortical neurons is mediated by K^+ currents, primarly leak current [27]. The long-lasting hyperpolarizations of cortical neurons are absent when the brain cholinergic structures are set into action [28, 35] or during rapid eye movement (REM) sleep and waking (Fig. 2) [26, 27].

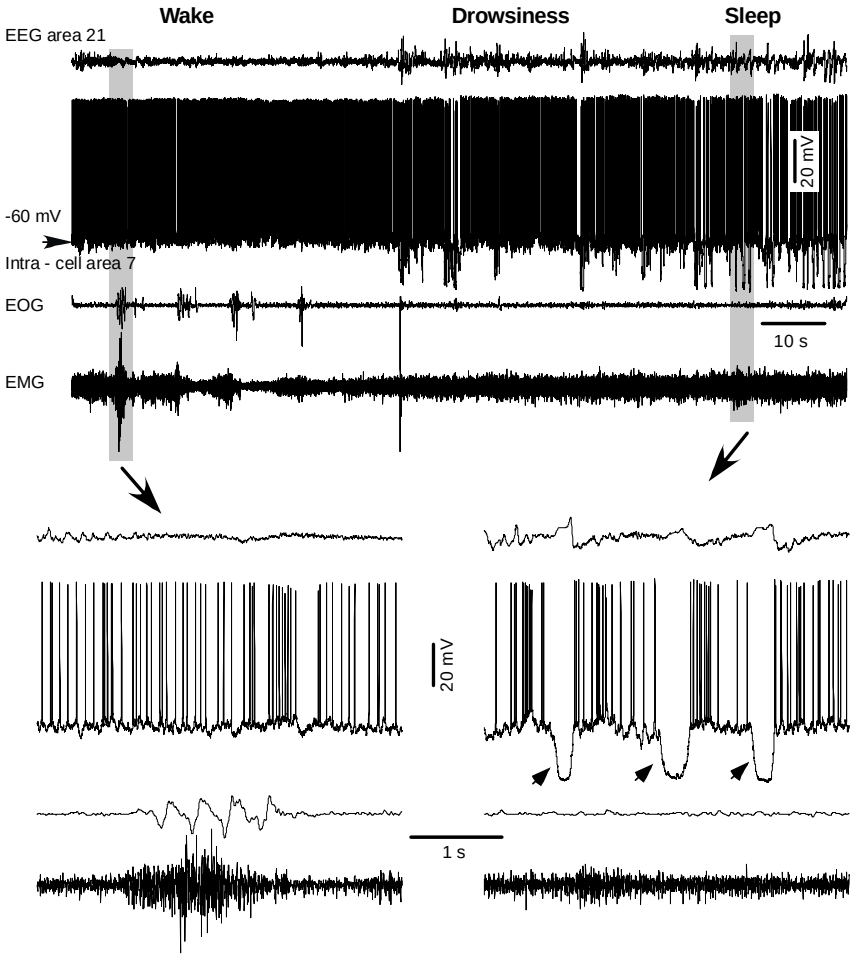

Figure 2. Cortical intracellular correlates of waking, drowsiness and slow-wave sleep. The four traces depict (from top to bottom): EEG from area 21, intracellular activity of area 7 neuron (membrane potential is indicated, -60 mV), EOG and EMG. Low-amplitude and high-frequency field potential oscillations, tonic firing with little fluctuations in the membrane potential, and muscle tone with periodic contractions are characteristics of the waking state. Aperiodic slow waves accompanied with neuronal hyperpolarization appear during drowsiness. High-amplitude and low-frequency field potentials, intracellular cyclic hyperpolarizing potentials and stable muscle tone are distinctive features of SWS. Parts indicated by arrows are expanded below (arrows). Note cyclic hyperpolarizations in SWS (indicated by arrowheads) (I. Timofeev, S. Chauvette, unpublished data).

Human studies have shown that each wave of slow oscillation originates at a definite site, more frequently in prefrontal-orbitofrontal regions and propagate in an anteroposterior direction [36]. Different hypotheses suggest different basic mechanisms of the active states: (a) spontaneous mediator release in a large population of neurons leading to occasional summation and firing [30], (b) spontaneous intrinsic activity in layer 5 intrinsically bursting neurons [31] and (c) the selective synchronization of spatially structured neuronal ensembles involving a small number of cells [37].

c. Delta oscillation

The field potential recordings from neocortex in human and animals during sleep reveal the presence of delta oscillation with frequencies 1-4 Hz. The fact that delta and slow oscillation represent two distinct phenomena was demonstrated by Achermann and Borbély [38] who showed differences in the dynamics between the slow and the delta oscillations, as the latter declines in activity from the first to the second non-REM sleep episode, whereas the former does not. The delta oscillation has likely two different components, one of which originates in neocortex and another one in the thalamus. Surgical removing of the thalamus or recordings from neocortical slabs in chronic conditions demonstrated significant enhancement of delta activity in neocortex [39-41]. Little is known about cellular mechanisms mediating cortical delta oscillation. One of the hypothesis suggests that cortical delta activity is driven by intrinsic discharge of IB neurons [42]. The legitimacy of this hypothesis is not clear, because the firing pattern of IB neurons could be revealed only by intracellular application of depolarizing current pulses, however intracellular recordings from cortical neurons during sleep demonstrated the presence of long-lasting hyperpolarizing, but not depolarizing potentials [26, 27, 43]. Therefore, IB neurons can contribute to the spread of activity, but the initial group of neurons driving delta activity remains unidentified.

Thalamic delta (1-4 Hz) oscillation is well known example of rhythmic activity generated intrinsically in thalamic relay neurons. These oscillations arise as an interplay of low-threshold Ca^{2+} current (I_T) and hyperpolarization activated cation current (I_h) and may be observed during deep sleep when TC neurons are hyperpolarized sufficiently to deinactivate I_T [44-47]. Sufficiently long and deep hyperpolarization of TC neuron removes I_T inactivation and makes possible rebound burst generation triggered by a depolarized input [48, 49]. Additional factor required for sustained bursting in the isolated TC cell is the presence of I_h [44, 50]. The interplay of I_T and I_h during delta oscillation was first described in vitro [44] and later was studied with computational models [51]. The mechanisms of single cell delta activity is following: a long-lasting hyperpolarization of TC neuron leads to slow I_h activation that depolarizes the membrane potential and triggers rebound burst, mediated by I_T, which was

deinactivated by the hyperpolarization. Both I_h (because of voltage dependency [50]) and I_T (because it is transient current [52]) inactivate during burst, so the membrane potential becomes hyperpolarized after the burst termination. This after hyperpolarization starts the next cycle of oscillations. Synchrony between different TC neurons during delta activity has not been found in decorticated cats [29]. Thus, it is unlikely that thalamic delta activity could play a leading role in the initiation and maintenance of cortical delta rhythm. However, the presence of a corticothalamic feedback in intact-cortex animals could synchronize thalamic burst-firing at delta frequency and generate field potentials [47, 53]. At certain level of leak current *(I_{leak})*, the 'window' component of I_T may create oscillations similar in frequency to the intrinsic thalamic delta oscillation [54].

d. Sleep spindle oscillations

Sleep spindle oscillations consist of waxing-and-waning field potentials of 7-14 Hz which last 1-3 sec and recur every 5-15 sec. In vivo, spindle oscillations are typically observed during early stages of sleep or during active phases of slow-wave sleep oscillations. In cats, the maximal occurrence of sleep spindle was found in motor, somatosensory and to a lesser extent in associative cortical areas [55]. A presence of spindle oscillations after decortication [29, 56, 57] provides strong evidence to the thalamic origin of this activity. Spindle-like activity was found in thalamic LGN slice preparations of ferrets with preserved interconnections with perigeniculate nucleus [58-60]. However, the spindle activity was not reported in the visual cortex of cats and ferrets, where the LGN nucleus project, thus, the mechanisms of spindle-like activity found in the LGN slices from ferrets maintained in vitro may not be directly applied to the interpretation of spindle activity generated in the brain.

In vivo, in vitro and modeling studies suggest that the minimal substrate contributing to the generation of spindle oscillations is the interaction between thalamic RE and TC cells. According to this hypothesis, the RE inhibitory neurons fire a spike-burst that elicits IPSP in TC neurons, at the end of IPSP the TC neurons generate rebound spike-burst that excites RE neurons, which then generate spike-burst starting the next cycle of spindle oscillation [60, 61-64]. There are at least two sets of data, which demonstrate that this hypothesis does not represent all spindle generating mechanisms. (a) The spindles are generated in isolated RE nucleus [65] and the spindles are absent in the dorsal thalamus that is disconnected from RE nucleus [61]. (b). During the initial 3-4 IPSPs composing the spindle, the TC neurons do not display rebound spike-bursts [66], suggesting that the feedback TC-RE connections are not contributing to the early phase of a spindle sequence. Generally, the early part of spindles is not seen or less marked at the neocortical level. More complex model suggests the presence of at least three phases with different underlying

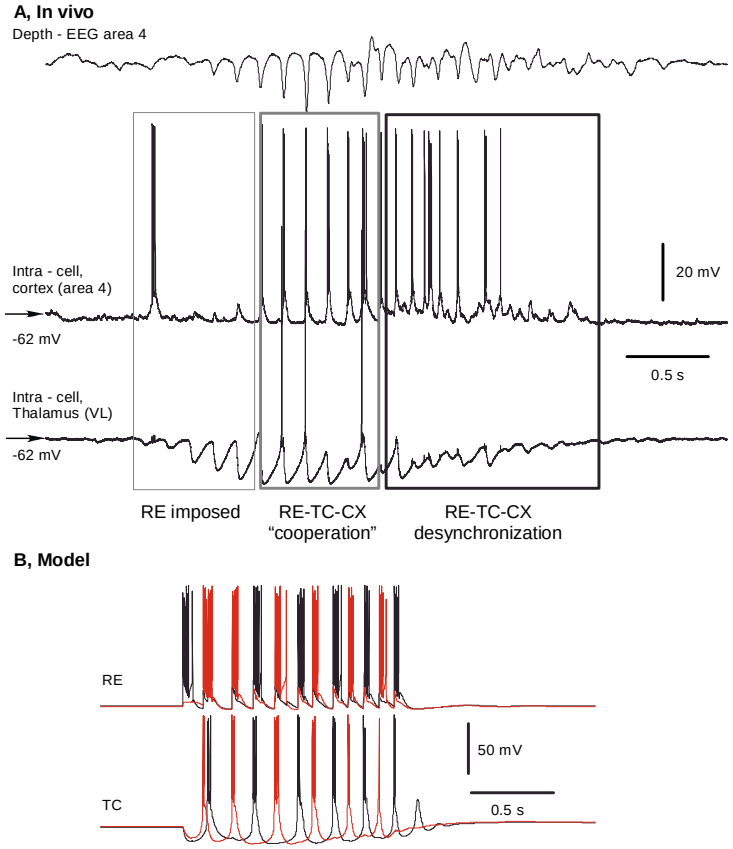

Figure 3. Cellular basis of spindle activity. A, In vivo recordings. Three phases of a spindle sequence. Dual intracellular recording of cortical (area 4) and TC (VL) neurons. 1) Initial phase consists of series of IPSPs in TC neurons that are not followed by rebound spike-burst, suggesting that they are imposed from RE network. Spontaneous firing of some cortical neurons may trigger activities of RE network. 2) During the middle phase of the spindle, the rebound spike-bursts of TC neurons excite both RE and cortical neurons. The activity of cortical, RE and TC neurons is phase-locked. 3) At the end of spindles cortical neurons no longer fire in phase-locked manner. This firing induces depolarization of both RE and TC neurons that create conditions for the spindle termination. B, computational model. Spindle oscillations in the circuit of 2 RE and 2 TC cells. RE cells fire every cycle of oscillations while TC cells skip every other cycle. Progressive increase of intracellular Ca^{2+} concentration during spindle increases a fraction of I_h channels in the open state. It leads to depolarization that eventually terminates spindle. (A – modified from [49], B – M. Bazhenov and I. Timofeev, unpublished data).

mechanisms that contribute to the spindle generation [49] (Fig. 3). The waxing phase of spindle oscillations is associated with recruitment of neurons from dorsal thalamic and RE nuclei [24]. During an early phase of spindles, the RE nucleus is driving the spindles by its own mechanisms [67-69]. The second part of spindles primarily develops as result of interactions between the RE and TC neurons as described above, but cortical firing contributes to the spindle synchronization via firing of cortico-thalamic neurons imposing simultaneous excitation of RE and TC neurons. Given robust cortical influence on RE neurons [11], the inhibitory influences of RE neurons onto TC neurons reinforce the spindle. The waning phase occurs as a result of Ca^{2+} induced cAMP up-regulation of hyperpolarization activated cation current, I_h, in TC cells [70-72] and network desychronization [49].

e. Beta-gamma oscillation

The waking state of the brain is characterized by low correlation of spike discharges across neighbouring neurons [73] and the predominance of EEG frequencies in the beta (15-30 Hz) and gamma (30-60 Hz) ranges [74, 75]. Cortical gamma activity is associated with attentiveness [76, 77], focused arousal [78], sensory perception [79] and movement [80, 81]. It has been proposed that synchronization in the gamma frequency range is related to cognitive processing and to the temporal binding of sensory stimuli [82-84]. The fast rhythms are also synchronized between neighboring sites during deep anesthesia, natural SWS and REM sleep [85, 86], when consciousness is either suspended or bizarre. During SWS the fast rhythms follow the onset of depth-negative EEG wave. Large-scale network simulations revealed that coherent gamma range oscillations may appear through occasional increases in spiking synchrony within local groups of cortical neurons [87].

At least two non-exclusive basic mechanisms have been proposed to explain the origin of beta-gamma oscillations. One of them emphasizes extracortical and another one point to the intracortical origin of these activities. A transient feed-forward synchronization to high-frequency peripheral (retinal, lemniscal or cerebelar) oscillations [88, 89] could impose the peripheral fast activities onto the TC system. Intracortical mechanisms itself include several possibilities. The first one is based on the intrinsic property of fast-rhythmic-bursting (FRB) neurons to fire fast spike-bursts at frequencies 20-60 Hz. These neurons were first described as fast pyramidal tract neurons from somatosensory cortex [90], later were found in layer II-III visual cortex (small pyramids called “chattering cells” [91]). Later studies demonstrated that FRB neurons could be found in most of cortical layers (they are seemingly absent in layer I) and they could be both aspiny non-pyramidal and pyramidal cells [92, 93]. Experimental and modeling studies provide two possible mechanisms of fast rhythmic burst generation. The first depends on the interplay of Na^+ and

K^+ currents [94, 95] and the second requires a reduction of intracellular Ca^{2+} concentration [96, 97].

The second intracortical mechanism of gamma activity generation depends on the activity of inhibitory interneurons and was described both *in vitro* and in computational models [98-102]. Transition between gamma and beta oscillations was simulated by alternating excitatory coupling between pyramidal neurons and by change in K^+-conductances [98, 102]. Lastly, the role of gap junctions between axons of pyramidal cells in generating gamma oscillation was proposed [102, 103]. The FRB neurons may function by providing a large-scale input to an axon plexus consisting of gap-junctionally connected axons from both FRB neurons and their anatomically similar counterparts, regular spiking neurons [104]. The resulting network gamma oscillation demonstrated in computational model shares all of the properties of gamma oscillations and shows critical dependence on multiple spiking in FRB cells.

f. Ripples (very fast oscillations, >100 Hz)

The fast oscillations (>100 Hz), termed ripples, were described in CA1 hippocampal area and perirhinal cortex, where they were associated with bursts of sharp potentials during anesthesia, behavioral immobility, and natural sleep [105-109]. In the neocortex, the fast oscillations (>200 Hz, up to 600 Hz) have been found in sensory-evoked potentials in rat barrel cortex [110, 111], during high-voltage spike-and-wave patterns in rat [112]. During natural states of vigilance in cats, the ripples were generally more prominent during the depolarizing component of slow oscillation in SWS than during the states of waking or rapid-eye movement (REM) sleep [113]. Around epileptic foci in humans and cats the amplitude of ripples is dramatically enhanced [114-118]. Studies in epileptic patients have revealed the presence of high-frequency oscillations also in the hippocampus and entorhinal cortex [119-121].

The high-frequency field potential oscillations during ripples are phase-locked with neuronal firing [111, 113, 116, 122]. The dependence of ripples on neuronal depolarization was shown by their increased amplitude in field potentials in parallel with progressively more depolarized values of the membrane potential of neurons [113]. Of all types of electrophysiologically identified neocortical neurons, FRB and fast-spiking cells displayed the highest firing rates during ripples and the inhibitory processes controlled the phase precision of ripple-dependent neuronal firing [109, 113]. As ripples can be generated within small isolated slabs of cortex, neocortical networks seems to be sufficient to produce them [113]. In addition to active inhibition, the electrical coupling mediated by gap junctions contributes to the ripple synchronization [116, 122, 123]. The electrical coupling may occur between axons of principal cells [124] or via a network of inhibitory interneurons [125-129]. The field potentials increase the neuronal excitability, and by a positive feedback loop they could be also involved in the generation of neocortical ripples

[118]. Since ripples are recorded also in glial cells, the electrical coupling between gial cells could also play a role in the synchronization of ripples [116].

Cortical origin of paroxysmal oscillations generated within the thalamocortical system

The origin of electrical seizures that accompany various types of epileptic fits is hotly debated. This is particularly the case of cortically generated seizures. Recent experimental studies strongly suggest that seizures characterized by 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 originate in neocortex [117, 130-134]. The etiologies of cortically generated seizures include cortical dysplasia, traumatic injury and other ideopatic/genetic forms [135]. This conclusion is based on following facts: (*a*) the presence of such paroxysms in neuronal pools within the cortical depth, even without reflection at the cortical surface [136], and in isolated cortical slabs *in vivo* [131]; (*b*) their induction by infusion of the $GABA_A$-receptor antagonist bicuculline in neocortex of ipsilaterally thalamectomized cats [130]; and (*c*) absence of paroxysmal patterns after intrathalamic injections of bicuculline, which rather induce low-frequency, regularly recurring spindle sequences in ferret slices *in vitro* [137] and cat [130, 138] or rat [139] thalamus *in vivo*, but not SW seizures, (*d*) the vast majority of TC neurons is hyperpolarized and do not fire spikes during paroxysmal discharges recorded in corresponding cortical areas [20, 131, 132, 134, 140].

Similar to slow oscillation (see above) during SW discharges the cortical neurons are depolarized and fire spikes during depth-negative (EEG spike) components and hyperpolarized during depth-positive (EEG wave) components. The typical seizure consisting of SW – poly-SW (PSW) complexes recurring with frequencies 1-3 Hz and fast runs with frequencies of oscillations at 8-14 Hz is shown in the Fig. 4. The seizure starts with SW-PSW discharges. Progressively the duration of PSW discharges increases 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, the SW-PSW complexes of electrographic seizures correspond to clonic components of seizure, while the runs of fast spikes correspond to tonic components of seizures [141, 142]. Similar to spike-wave discharges the runs of fast spikes originate in neocortex. The frequency and the duration of fast runs are similar to the frequency of spindles. Thus, it could be supposed that the runs of fast paroxysmal spikes could share some similar mechanisms with the spindles and originate in the thalamus. However, the experimental

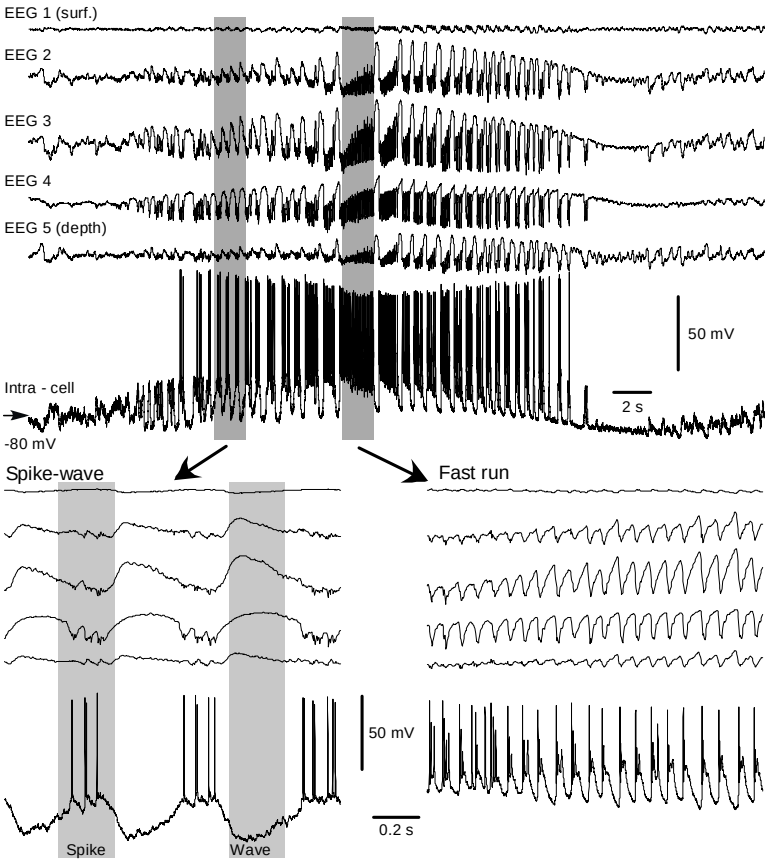

Figure 4. Field potential and intracellular features of ideopatic electographic seizure recorded from cortical area 5 of cat anesthetized with ketamine-xylazine. Upper panel, five upper traces are the local field potentials recorded with an array of electrodes from cortical surface and different depth. The distance between electrodes in the array was ~0.4 mm. Lower trace, an 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 grey rectangulars.

evidences demonstrated that (a) TC neurons display EPSPs during fast runs rarely leading to the generation of action potentials [131] and not IPSP-mediated rebound Ca^{2+} spikes as during spindles (see above), (b) the 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 [131]). The runs of fast paroxysmal EEG spikes could be obtained in isolated neocortical slabs [131]. These observations confirm the cortical origin of the fast runs.

Shift of balance between excitation and inhibition as seizure triggering factor

It is widely accepted that the development of epileptiform activity results from a shift in the balance between excitation and inhibition towards excitation [143-145]. The easiest way to elicit acute seizures is blockage of inhibition [117, 146-151], which is a well-known approach to elicit experimental seizures (reviewed in [132, 152, 153]). Increased inhibition and decreased excitation also may lead to functional unbalance in cortical circuits; however their role in the seizure initiation is poorly explored. By increased “inhibition” we mean either increased number of IPSPs or disfacilitation, i.e. temporal absence of network activity. By decreased excitation we mean significantly decreased activity in afferent structures or decreased effectiveness of EPSPs. If one of the above factors occurs, it would create conditions that are favorable to seizure generation.

One of the conditions for seizure generation is the functional heterogeneity of cortical networks, such as the presence of two or more different cortical regions with relatively high and low levels of synaptic activity. Transitory or persistent reduction in synaptic activity within some cortical foci would increase the sensitivity of cortical neurons in those foci and in surrounding areas [154-156]. Therefore, the synaptic inputs from cortical regions exhibiting moderate or high levels of activity would lead to an increased responsiveness in those cortical areas where the sensitivity is increased. Evidence from *in vitro* work suggests that chronic blockade of activity may modify the synaptic strength and intrinsic neuronal excitability; after a few days of pharmacological blockade of activity in cortical cell cultures, excitatory postsynaptic currents (EPSCs) and mEPSCs in pyramidal cells increase in amplitude [157, 158] and the release probability increases [159].

The reasoning for disfacilitation through deafferentation to be an important factor eliciting seizures is in line with two groups of facts. One of them is that seizures occur most often during SWS or during transition from waking to SWS (see [132, 133]). As we mentioned above the state of SWS is characterized by the presence of long-lasting periods of disfacilitation associated with neuronal hyperpolarization ([27]). During periods of disfacilitation synapses are likely released from a steady depression [144] and the synaptic transmission is strengthen that could contribute to the onset of seizures. The other line of evidence is that penetrating wounds or acute experimental deafferentation have

been described as strong epileptogenic factors [1, 2, 160-164]. In such conditions, a part of axons impinging onto postsynaptic neurons is not functioning as they are damaged, which creates a partial deafferentation that in turn enhances the effectiveness of remaining incoming synaptic inputs. Thus, both factors, the sleep-related disfacilitation and the traumatic deafferentation, increase the probability of seizures via the same mechanism of an increased effectiveness of synaptic transmission [165, 166]. The increased effectiveness of synaptic transmission depends on higher levels of extracellular Ca^{2+} concentration, as reported during silent periods of network activities [166, 167], and on synaptic facilitation that follows periods of neuronal silence [144]. Increased levels of extracellular Ca^{2+} increase the intrinsic excitability of cortical neurons and convert some of them to burst firing [97]. The synaptic excitability is also enhanced by trauma-related increase in glutamate levels [168]. In trauma-related acute seizures, however, other than synaptic factors could be considered as promoting seizures. These factors primarily depend on increase in extracellular levels of K^+ [169] that lead to enhanced intrinsic excitability of neurons [152, 161, 170].

Thus, the appearance of inhomogeneous levels of excitability via overexcitation or blockage of inhibition (as following repetitive sensory or electrical stimulation, or focal injection of inhibition blockers) as well as disfacilitation or deafferentation (sleep or trauma) can play the role of epileptogenic factors.

Cellular mechanisms mediating spike and wave discharges

In this section we will address the following questions: (a) what is the cellular basis of paroxysmal deperpolarizing components that correspond to EEG wave, (b) what is the cellular basis of hyperpolarizing paroxysmal components that correspond to EEG spike and (c) what are the mechanisms mediating the transition from hyperpolarizing to depolarizing components during the seizure?

The EEG “spike” of SW complexes corresponds intracellularly to the paroxysmal depolarizing shift (PDS) (reviewed in [152, 153, 171]). Initially, PDSs have been regarded as giant EPSPs [172, 173], enhanced by activation of voltage-gated intrinsic (high-threshold Ca^{2+} and persistent Na^+) currents [143, 174-176]. The EPSPs that onset the PDS depolarize postsynaptic neurons to the levels of activation of persistent Na^+ current that maintain and enhance achieved depolarization. The contribution of persistent Na^+ current in the generation of PDSs was recently demonstrated by intracellular recordings from pairs of neurons, in which one of the neurons was recorded with pipettes containing QX-314, an intracellular blocker of voltage gated Na^+ currents. On

all occasions the inclusion of QX-314 in the recording pipette causes the reduction of maximal depolarization achieved by neurons during the PDS (Fig. 5 B). The PDSs increase their duration on intracellular injection of steady depolarizing current (see Fig. 5 in [177]). This suggests that high-threshold Ca^{2+} currents and the persistent Na^{+} current could contribute to those depolarizations because these currents are activated at depolarized voltages. The intracellular recordings with BAPTA containing pipettes confirmed the contribution of Ca^{2+} currents in the generation of PDS. BAPTA is an intracellular chelator of Ca^{2+} currents. An intracellular chelating of Ca^{2+} increases the Ca^{2+} gradient and thus the opening of Ca^{2+} channels creates stronger depolarizing response. This was indeed the case during paroxysmal discharges. The use of BAPTA in the pipette primarily reduced the hyperpolarizing components of seizures, via reduction in Ca^{2+}-activeted K^{+} current [175]. When the membrane potential was returned to the initial values by injection of negative current, the amplitude of PDSs was always bigger in the pipettes that contained BAPTA (Fig. 5, A).

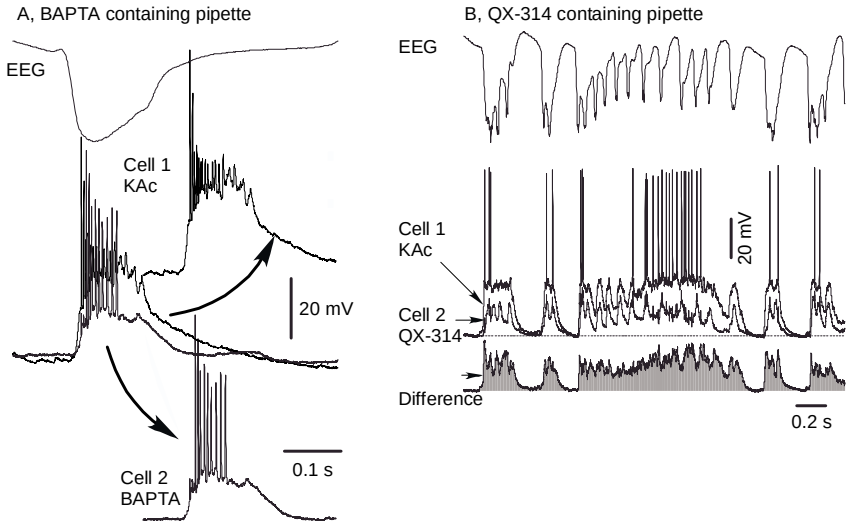

Figure 5. Role of Ca^{2+} and persistent Na^{+} currents in the generation of paroxysmal depolarizing shifts. A, EEG and dual intracellular recordings during paroxysmal depolarizing shift. Intracellular recording with BAPTA field pipette uneven much larger depolarization during the paroxysmal depolarizing shift as compared to control recording with K^{+} acetate filled pipette. B, EEG and dual intracellular recordings during a fragment of 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 [175]).

Recently, the presence of inhibitory processes during different types of seizure activity was reported [153, 162, 177-179]. The work on human and rat slices [180, 181] as well as in *in vivo* experiments with cats [177] demonstrated that PDSs contain an important inhibitory component. During depolarizing components of seizures the fast-spiking inhibitory interneurons fire with high frequencies [177]. This cause the postsynaptic uptake of Cl^-, the $[Cl^-]_i$ increases and this causes a decreased amplitude or even a change in the polarity of IPSPs that become depolarizing [182]. Prolonged high-frequency stimulation [183, 184] or spontaneous high-frequency firing of inhibitory interneurons [177] may induce a rapid $GABA_A$-mediated bicarbonate-dependent increase in the $[K^+]_o$. An increase in $[K^+]_o$ in mature neocortical pyramidal neurons would result in further increase in $[Cl^-]_i$ [185]. The seizure-related depolarizing GABA responses are likely mediated via cation-chloride co-transporters [186].

Earlier hypotheses considered that the EEG "wave" component reflects summated IPSPs that were ascribed to GABAergic processes triggered in cortical pyramidal neurons by local-circuit inhibitory cells [187, 188]. In computational models, the "wave" was similarly regarded as produced by $GABA_B$-mediated IPSPs [189]. However, during the EEG "waves" associated with neuronal hyperpolarization the R_{in} increases relative to the "spike" component [177, 190, 191]. These and similar results, reported in a genetic rat model of absence epilepsy [192-194] and in *in vivo* experiments on cats [177], contradict the idea of a role played by inhibitory receptors in the generation of hyperpolarizations associated with the EEG "wave" component of SW complexes. Intracellular recordings with Cl^- filled pipettes did not reveal any effects during 'wave' components of seizures [177]. 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 [195, 196] did not significantly affect the hyperpolarization in our experiments (Fig. 5 B) [132, 175]. Together, these data suggest that GABA-mediated currents are not important for the hyperpolarizations occurred during these cortically generated seizures.

Another group of mechanisms that can mediate hyperpolarization during SW complexes depends on the different K^+ currents [197, 198]. Recordings with Cs^+-filled pipettes to non-selectively block K^+ currents showed that, during the "wave" component of SW seizures, pyramidal neurons displayed depolarizing potentials [177]. This indicates a leading role played by the K^+ currents in the generation of seizure-related hyperpolarizing potentials. 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 [132, 175]. The second factor that may contribute to the "wave"-related hyperpolarization during cortically generated SW seizures is disfacilitation [191, 193]. 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 are due to the combined effect of disfacilitation and K^+ currents.

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 [169, 199-201], leading to a positive shift in the reversal potential of K^+-mediated currents, including I_h. 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, $I_{Na(p)}$ [202-205]. In our experiments, 20% of neocortical neurons displayed depolarizing sags after application of hyperpolarizing current pulses, probably caused by activation of I_h, and models of isolated pyramidal neurons with I_h included in their dendritic compartment showed that rebound depolarization was sufficient to generate single action potentials or spike-bursts [201]. The increased excitability of pyramidal neurons after the prolonged hyperpolarizations during the EEG "wave" component of SW complexes may contribute to the generation of the subsequent paroxysmal depolarization [132, 201]. It is also possible that the Ca^{2+}-mediated low-threshold current (I_T), alone or in combination with I_h, also contributes to the generation of the rebound overexcitation, as shown in cortical slices [206] and in computational studies [207]. However, the generation of I_T in cortical neurons requires voltages much more hyperpolarized than those normally seen during spontaneously occurring network operations [208]. Thus, the next paroxysmal cycle likely originates from the excitation driven by I_h that follows the neuronal silence during the EEG "wave" in the SW complex.

The summary diagram in Figure 6 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 combination of K^+ currents (mainly $I_{K(Ca)}$ and I_{leak}) and disfacilitation. Finally, the hyperpolarization-activated depolarizing sag, due to I_h, leads to a new paroxysmal cycle.

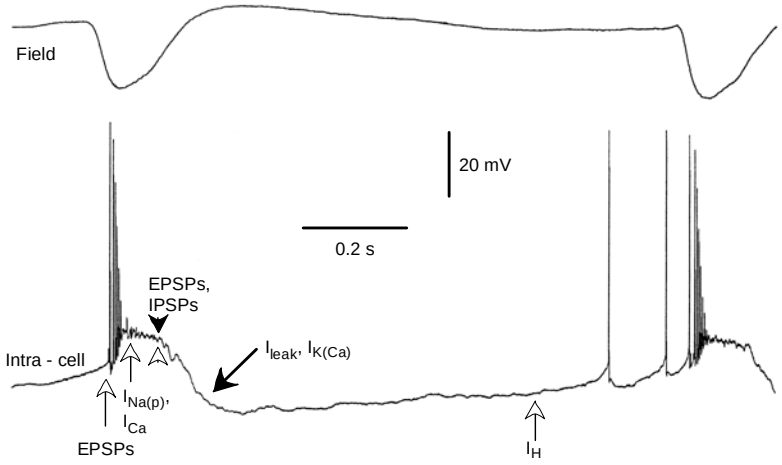

Figure 6. Tentative representation of different synaptic and intrinsic currents activated in neocortical neurons during paroxysmal activity. Explanations in the text. Modified from [132].

Acute trauma induced seizures

Cerebral cortical trauma may lead to paroxysmal activities. Within 24 hours following head injury with penetrating wounds, up to 80 % of patients display clinical seizures [1, 2]. Immediately after trauma, the level of extracellular K^+ increases and this may increase the propensity to seizures [152, 169, 170, 209]. Trauma also elicits a partial deafferentation and, consequently, a decrease in input signals that can result in enhanced intrinsic and synaptic excitability of individual neurons [155, 157, 210]. Chronic neuronal hyperexcitability and epileptogenesis in experimental animals have been demonstrated in isolated neocortical islands with intact pial circulation *in vivo* [211-213] and in neocortical *in vitro* slices after chronic cortical injury [162, 165, 214-216]. Computational models of posttraumatic epileptogenesis in isolated cortical islands concluded that paroxysmal discharges are possible due to the changes in intrinsic properties of pyramidal cells and enhanced excitatory synaptic conductances without altering synaptic inhibition [41, 217].

However, there is little information about the spontaneous development of paroxysmal activity immediately after neocortical injury. In view of earlier data from human cortical slabs isolated at the time of surgery, showing that the deafferented cortical tissue can display paroxysmal, high-voltage activity shortly after isolation [218, 219], we hypothesized that early functional modifications in the deafferented cortex can develop neuronal hyperexcitability, due to the anatomical and functional changes in synaptic efficacy and cortico-cortical

connectivity; these modifications may lead to spontaneously occurring paroxysmal activity.

In the past several years we investigated electrographical activities induced by cortical partial deafferentation [160, 161, 220]. This partial deafferentation was achieved by means of cortical undercut. The undercut cortex (Fig. 7 A) was produced by large white matter transections below the suprasylvian gyrus (13-15 mm postero-anteriorly, 3-4 mm medio-laterally, and 3-4 mm deep). A knife was inserted into the posterior part of the suprasylvian gyrus, perpendicularly to its surface at a depth of 3-4 mm, then rotated 90^0 and advanced rostrally along the gyrus parallel to its surface for a total distance 13-15 mm, then moved back, rotated 90^0, and removed from the same place where it entered the cortex. Thus, the white matter below the posterior part of the gyrus was transected, creating conditions of partial cortical deafferentation. Under ketamine-xylazine anesthesia, the EEG from the cortical depth demonstrated a spontaneous slow oscillation (<1 Hz) (Fig. 7 B, left panel - CONTROL). Immediately after the undercut of suprasylvian gyrus (earliest measurements were obtained 5 min following the undercut), the amplitude of EEG waves was reduced, especially in the posterior and middle parts of the suprasylvian gyrus where the degree of deafferentation was maximal (Fig. 7 B-C, middle panel - UNDERCUT). The EEG activity in this partially deafferented cortex remained markedly decreased up to 1-2 hours. In a few experiments, surviving spindles (7-14 Hz) could be observed in the anterior part (electrodes 6-7) of the undercut cortex (see Fig. 7 - UNDERCUT), probably because some TC connections remained intact in those areas. Two to three hours after the undercut, the activity in the undercut cortex reorganized, and increased amplitude of EEG waves in the middle and anterior parts of the suprasylvian gyrus could be detected (Fig. 1 B-C, panels indicating 3 HOURS AFTER; **a**, **b** and **c**, three different animals). The 40% of animals demonstrated paroxysmal-like activity or clear-cut electrographic seizures. By paroxysmal-like activity we mean high-amplitude slow waves with the morphological features of interictal spikes. Their amplitude was at least twice as high as during the normal slow oscillation (Fig. 7 B-C, 3 HOURS AFTER). In approximately 50 % of cases electrographic seizures developed progressively from the slow oscillation, while in the other half of the cases seizures started suddenly. The paroxysmal activities were variable in their electrographic patterns. In different experiments we observed interictal spikes, sharp waves (Fig. 7 B-C - upper right panel), spike-wave (SW) and polyspike-wave (PSW) complexes at 2-3 Hz and fast runs at 10-15 Hz. Following cortical undercut the field potential activities with increased amplitude were also found in barbiturate anesthetized cats, but those didn't evolve in full-blown seizures. Recording of paroxysmal activity from the intact neighboring cortical areas revealed that electrographic seizures were always initiated in the intact cortical regions surrounding the undercut [160].

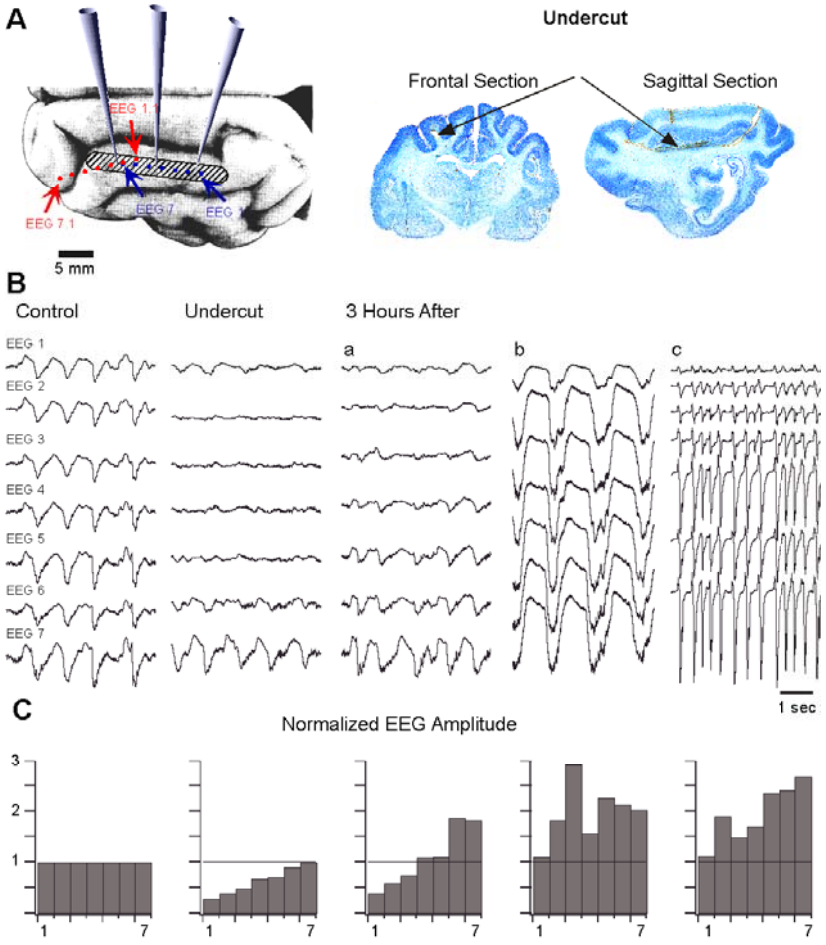

Figure 7. Slow oscillation in intact suprasylvian gyrus is modified by cortical undercut. A. Position of EEG arrays of electrodes and of intracellular pipettes and histology of the undercut suprasylvian gyrus. Upper panel, dorsal view of the left hemisphere. The zone of undercut is tentatively indicated by shaded area. Blue points show the generally used position of EEG electrodes (EEG1-EEG7) along the suprasylvian gyrus. Red points show the second position of EEG electrodes (EEG1.1-EEG7.1) in the postcruciate gyrus and anterior part of suprasylvian gyrus. Position of pipettes is schematically indicated. Bottom panel shows frontal and parasagittal section of the left hemisphere from two different cats showing the extent of the undercut (indicated by arrows). **B**. Field potential recordings (EEG) from the intact cortex (left panel - CONTROL), undercut suprasylvian gyrus, immediately after the undercut

Figure 7. Continued

(middle panel - UNDERCUT), and 3 hours later (three right panels; **a**, **b** and **c**, three different animals). Position of EEG electrodes was indicated in **A** by blue points. **C** depicts normalized EEG amplitude (vertical axis) of the corresponding EEG from different sites (horizontal axis). Mean EEG amplitude for each electrode in control was taken as 1. EEG1 - field potential recording from the posterior part of the suprasylvian gyrus, EEG7 - recording from the anterior part of this gyrus. Note the decreased EEG amplitude immediately after the undercut and partial recovery or increase in the amplitude 3 hours later, especially during the paroxysmal activity. (From [160]).

The patterns of synchronization and propagation of normal and paroxysmal activities were studied in 23 acute experiments. The horizontal propagation of the slow oscillation mainly depended on the direction the undercut was performed. In all cases the slow oscillation started near the electrode from the relatively intact part of the partially deafferented cortex and propagated toward more deafferented sites.

The experimental animals could be divided into two groups: ***(a)*** In those cases that did not reveal paroxysmal activities within 8-10 hrs following the undercut, the cross-correlation analysis of EEG waves as well as wave-triggered averages (WTAs) showed strong synchrony between different recording sites before the undercut (time lag between the EEG electrodes separated by 8-10 mm was 1.8±0.8 ms). The undercut led to a slightly increased time lag in the propagation from anterior to posterior sites, 4.3±1.7 ms. Recovery in EEG patterns was seen 2-3 hrs after the undercut, but the time lag increased to 7.8±6.0 ms. Thus, the slow oscillation occurred highly synchronously within a distance of ~9 mm. Partial cortical deafferentation decreased the velocity of propagation of slow oscillation from 5.0 m/s to 1.1 m/s. ***(b)*** In cases with paroxysmal development, the comparison between the EEG-waves' propagation before the undercut and seizures (triangles in bottom plots) revealed that the time lag between area 5 and area 21 was 20.8±11.8 ms before undercut, and significantly increased 2-3 hrs after the undercut, during paroxysmal activity. In all experiments, a significant slowing-down in the EEG propagation started from a site between EEG electrodes 4 and 5, likely representing the region with significantly decreased neuronal excitability. The velocity of propagation of paroxysmal events in the partially deafferented cortex was between 0.3 and 0.5 m/s [160].

The above data display the following tendencies: *(a)* if animals demonstrated a higher long-distance synchrony of EEG activity before the undercut, it would not display paroxysmal activity after the undercut; (b) if, however, EEG activity was less synchronous between the anterior and posterior suprasylvian areas before the undercut, cortical deafferentation led to a further synchrony decrease and those animals later displayed paroxysmal activity.

What could be the factors triggering the acute seizures after neocortical trauma? The essential factor in the cortical overexcitation may be the I_h [198] whose depolarizing sag may lead to activation of the low-threshold transient Ca^{2+} current, I_T [206]. This mechanism resembles the well known mechanism of intrinsic delta oscillation of TC neurons [44] (see above). It has previously been reported that, during seizures, there is an increase in the level of maximal hyperpolarization achieved by neurons between depolarizing events [117]. Such an increased hyperpolarization would support an increase of the efficiency of I_h. An increased $[K^+]_o$ during seizures would shift the reversal potential for all K^+-mediated currents and further involve I_h in the generation of seizures [201]. Then, the neurons located at the border between the undercut and the intact cortex could behave like the triggers of paroxysmal activity under the conditions of some epileptogenic factors.

Many other trauma-activated factors can be regarded as epileptogenic in the cortical undercut experimental model. Neuronal and glial damage elicited by the undercut can increase, to a certain degree, the level of $[K^+]_o$, which is known to promote the development of seizures [169, 221]. In acute conditions, brain lesions produce an immediate increase of $[K^+]_o$ from intracellular pools, leading to cellular depolarization, increased excitability and decreased inhibition [170]. It was shown that in conditions of increasing $[K^+]_o$ the regular-spiking firing pattern of some neurons can converse into intrinsically bursting patterns, which would further increase the excitability of network [222]. Also, the accumulation of $[K^+]_o$ can result in neuronal swelling and electrotonic coupling between neurons [152, 170]. The last factor in turn can lead to the hyperexcitation [223]. Some consequences of traumatic insult can also play an epileptogenic role by resulting in excessive accumulation of extracellular glutamate [224] and in the raise of intracellular Ca^{2+} via transmitter- and voltage-gated channels. Increased intracellular Ca^{2+} in turn enhances the response to glutamate [225]. Finally, a reduction in functional inhibition can underlie epileptiform activity; for example, the depolarizing effect of GABA may result in a positive shift in Cl^- reversal potential (from – 70 to – 44 mV) and in increasing the intracellular Ca^{2+} [177, 226, 227].

The changes in intrinsic and synaptic excitability that precede acute, trauma-induced electrographic seizures were recently investigated *in vivo* [161]. The study demonstrated that both intrinsic and synaptic excitability were enhanced in the undercut cortex. Following cortical undercut the number of intrinsically-bursting neurons in undercut and surrounding cortical areas doubled as compare to control conditions. Besides, ~20% of neurons recorded from both sites demonstrated spontaneously occurring bursting, a feature that could be indicative of increased $[K^+]_o$ [222, 228]. During slow oscillation neurons in the partially deafferented areas were relatively more hyperpolarized than the neurons in relatively intact areas, which, in most cases, prevented them from firing (Fig. 8). There were no

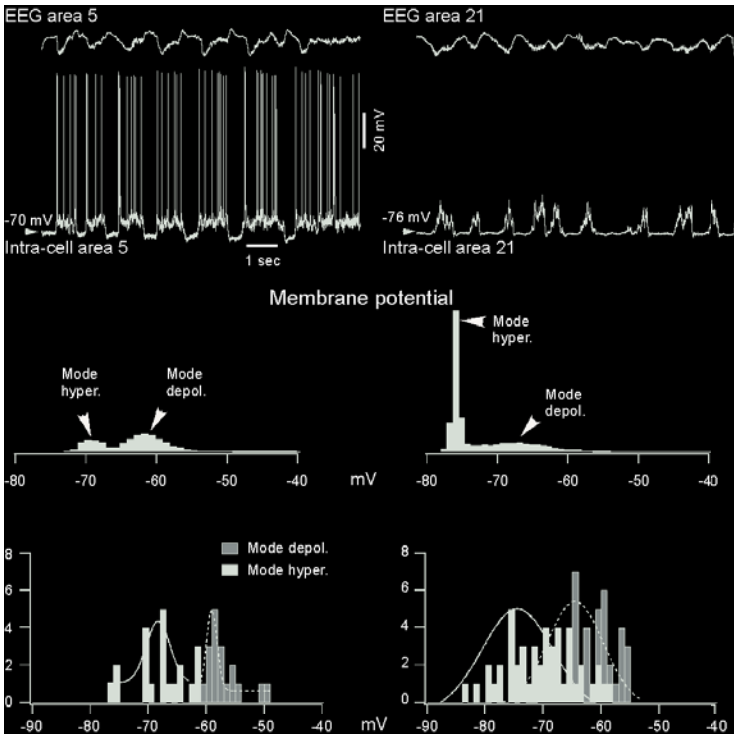

Figure 8. Comparison of spontaneous synaptic activity and level of membrane potential in neurons recorded from relatively intact (left panel) and partially deafferented (right panel) cortical areas. Upper panel illustrates EEG and intracellular recordings from relatively intact and partially deafferented sites within the suprasylvian gyrus. Below, histograms of membrane potential (V_m) of these neurons. Histograms were constructed by sampling of neuronal activity at 20 kHz and counting the number of samples with bin of 1 mV. Bottom panel, population histograms of the modes of V_m for all recorded cells within relatively intact and partially deafferented cortical areas (gray bars: V_m during neocortical depolarization; black bars: V_m during hyperpolarization). Note a shift in V_m to hyperpolarizing direction in partially deafferented neurons (From [161]) .

significant alterations in the apparent input resistance (R_{in}) or membrane time constant (τ_m) between both neuronal populations. Analysis of spike parameters also indicated that partial cortical deafferentation did not affect spike threshold, duration or amplitude. Further, we examined the relationship between the magnitude of intracellularly applied current steps and neuronal firing rate (n = 6) (Fig. 9). Pooling the number of spikes and instantaneous firing rate (inverse of the first interspike interval) for neurons from both

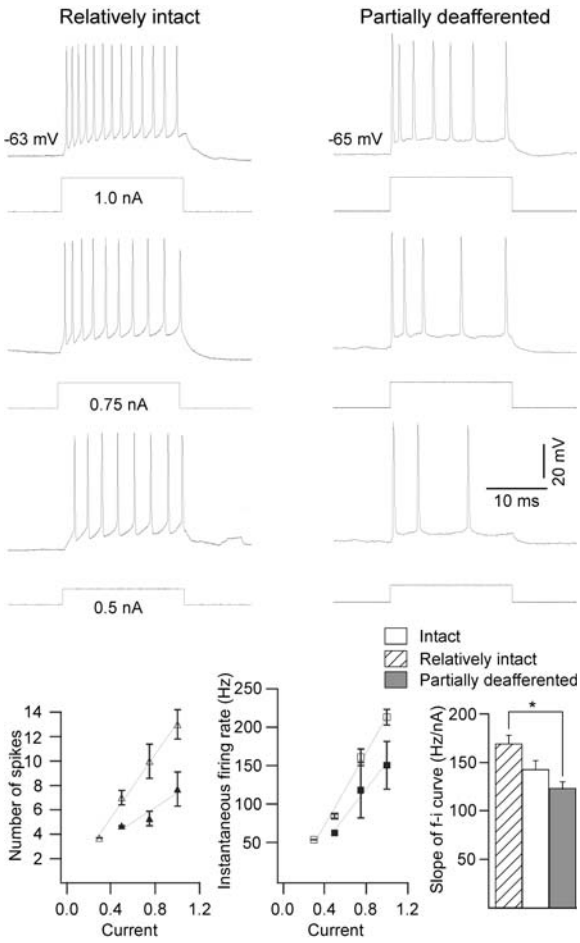

Figure 9. Comparison of intrinsic excitability of relatively intact and partially deafferented neocortical neurons. Upper panels are responses of neurons from relatively intact (left panels) and partially deafferented (right) cortical areas to intracellularly applied current pulses of different intensities. The neurons shown had similar V_m (intact, -63 mV; partially deafferented, -65 mV). Bottom left plot represents the spike numbers in response to depolarizing current pulses of increasing intensity. Bottom middle plot shows initial instantaneous firing frequency (reciprocal of first spike interval) versus amplitude of current injection. Bottom right bars demonstrate the initial slope of the f-I curve for a sample of neurons from intact, relatively intact and partially deafferented cortex. Note the significant differences in spike number and f-I curve slope between partially deafferented and relatively intact neurons (From[161]).

relatively intact and partially deafferented areas showed an enhancement between the amount of applied depolarization and the output firing rate in relatively intact neurons (Fig. 9, bottom right panel). By contrast, partially deafferented neurons demonstrated a weaker input-output relationship, with a greater level of frequency adaptation. We compared the above-mentioned responses to responses of neurons in intact cortex (no undercut, data from previous unpublished experiments). The slope of frequency current relations in the intact cortex was 143.2±9.8 Hz/nA, which lied between slopes of partially deafferented and relatively intact neurons (Fig. 9), but was not statistically different from both groups of neurons. Statistical difference was found only between partially deafferented and relatively intact neurons. These data suggest that the increased intrinsic excitability of neurons from the relatively intact area, adjacent to the undercut, is an important determinant for triggering electrographic seizures in the immediate hours after this type of cortical deafferentation. Keeping in agreement with a reduced intrinsic excitability of neurons in the areas surrounding the undercut, the spontaneous neuronal firing was reduced in these areas in particular at depths between 0.7 and 2.0 mm.

To further characterize differences in responses of neurons in relatively intact vs. partially deafferented cortex, we compared responses of neurons to intracellularly applied hyperpolarizing current pulses in order to reveal depolarizing sags mediated by I_h. We found that the proportion of neurons revealing depolarizing sag in relatively intact cortex (~20%) was similar to neurons in intact cortex [201]. By contrast, in partially deafferented cortex the proportion of neurons revealing depolarizing sag in response to hyperpolarizing current pulse applied during hyperpolarizing states of the network was much higher (50%). In these neurons, the depolarizing sag obviously contributed to the repolarization of neurons during hyperpolarizing phases of slow oscillation. Such depolarizing sag was not found when the hyperpolarizing current pulses were applied during depolarizing phases of the slow oscillation, suggesting contribution of I_h in its generation. The fact that I_h related depolarizing sag was found in larger proportion of neurons in places closer to the undercut could be attributed to the increased extracellular levels of K^+ due to direct cellular damage.

The role of synaptic activity in the generation of electrographic seizures in the undercut cortex was also studied using simultaneous recordings of evoked potentials within relatively intact and partially deafferented cortical areas. We compared the depth distribution of cortically evoked potentials in both sites before and after the undercut. Evoked potentials in the partially deafferented area 21 were comparable before and after the undercut. By contrast, in the relatively intact area 5, cortically evoked potentials were dramatically increased after the undercut. These findings suggest that synaptic inputs

produce much greater impact onto neurons in relatively intact, than in partially deafferented, areas.

We asked whether altered inhibitory processes could also contribute to the development of electrographic seizures in this model of cortical trauma. To test this possibility, we measured the reversal potential of early IPSPs in neurons recorded from both sites of the undercut cortex. All neurons recorded along the partially deafferented suprasylvian gyrus showed a reversal potential for early IPSPs shifted in a depolarizing direction (-58 ± 3 mV; n = 30), as compared with neurons from non-traumatized, control cortex (-70 ± 2 mV; n = 30). This observation is in agreement with previous studies showing that deafferentation can initiate a regressive switch in GABAergic response polarity from hyperpolarizing to depolarizing [229, 230].

Taken together, these results strongly implicate the increased intrinsic and synaptic excitability of neurons from the relatively intact area, adjacent to undercut, as key events in the generation of electrographic seizures. The existence of the form of electrographic seizure that does not require long-term neuronal hyperexcitability has implications for the network and cellular mechanisms of acutely developing trauma-induced epilepsy [2]. Obviously, only relatively intact neurons, spatially localized in the vicinity of a traumatic lesion, are expected to produce the first signs of electrographic paroxysmal activity. Although growing seizures invade much of the partially deafferented sites, their spread in the region with decreased excitability is more limited, implying that trauma-induced partial deafferentation will first induce seizure within confined cortical domains. Highly localized hyperexcitability may therefore arise from the non-uniform distribution of synaptic weight within the dendritic tree of single neurons and clusters of effective synapses in dendritic domains. Synaptic inputs to neurons with an increased intrinsic excitability would promote initial paroxysmal discharges that (via intracortical connections) would involve neighboring areas into paroxysmal activities.

Our data suggest, therefore, that, following penetrating wounds, early local therapy around the damaged cortex, which would decrease the incidence of bursting neurons, will prevent development of acute seizures and may also prevent subsequent epileptogenesis.

Long-lasting homeostatic alterations of excitability and chronic epileptogenesis

Evidence from *in vitro* studies suggests that chronic blockade of activity may modify synaptic strengths and intrinsic neuronal excitability. After a few days of pharmacological blockade of activity in cortical cell cultures, the amplitudes of mEPSCs and EPSCs in pyramidal cells increase [157, 158] as well as quantal release probabilities [159]. Conversely, prolonged enhanced

activity levels induced by blockade of synaptic inhibition or elevated $[K^+]_o$, reduce the size of mEPSCs [157, 231, 232]. Similar activity-dependent changes in mEPSC size have been observed in spinal cell cultures [233]. Synaptic scaling occurs in part postsynaptically by changes in the number of open channels [157, 158], although all synaptic components may increase [159] including numbers of postsynaptic glutamate receptors [231, 233-235]. There is a similar regulation of NMDA currents by activity [158]. The ratio of NMDA to AMPA is preserved following activity-dependent synaptic scaling [158]. Interestingly, mIPSCs are scaled down with activity blockade, in the opposite direction to excitatory currents. This effect is reversible [236] and is accompanied by a reduction in the number of open $GABA_A$ channels and $GABA_A$ receptors clustered at synaptic sites [237]. Recent studies suggest that synaptic scaling has a predominantly postsynaptic locus and functions as a gain control mechanism to regulate neuronal activity without affecting the dynamics of synaptic transmission [238]. Not only synaptic but also intrinsic excitability is regulated by activity. After chronic activity blockade, Na^+ currents increase and K^+ currents decrease in size, resulting in an enhanced responsiveness of pyramidal cells to current injections [155]. These observations suggest that homeostatic mechanism may regulate the average levels of neuronal activity. Recent evidence indicates that some of these processes, collectively termed `homeostatic plasticity' [210], may also occur *in vivo* [239].

Homeostatic plasticity is usually considered as a gain control mechanism serving a “positive” functions to regulate neuronal activity [238]. Indeed, the changes in synaptic and intrinsic excitability can compensate for certain range of the network activity changes and restore the “original” level of activity. What happens when the brain network underlies severe alternations of intrinsic properties or connectivity patterns followed by significant changes of the activity level? Such alternation may occur after trauma when a population of neurons is partially deafferented and thus underexcited, inducing homeostatic plasticity that upregulates depolarizing influences and downregulates hyperpolarizing ones. Recent modeling studies suggest that a severe deafferentation of the cortical network can trigger homeostatic plasticity leading to the pathological development of paroxysmal activities [41]. In the model consisted of 5,000 cortical pyramidal neurons and 1,250 interneurons deafferentation consisted of removing the extrinsic excitatory inputs from all the cells. Following deafferentation, the firing rates of pyramidal cells and interneurons were reduced to on average 0.7 and 0.2 Hz, respectively (Fig. 10). This reduction of the average network activity activated homeostatic synaptic plasticity (HSP) leading to upregulation of excitatory and downregulation of inhibitory synapses. In the model, homeostatic synaptic plasticity had initially little effect on network activity; up to 60% HSP firing rates were similar to

those in the acutely deafferented network (Fig. 10). After 63% HSP, the spontaneous activity of the network changed in a qualitative manner; occasionally, locally generated spike bursts propagated through the network. Further HSP increased the occurrence of network bursts. Eventually a steady state was reached where bursts repeated at frequencies of about 0.5 Hz and the average PY cell firing rate (5.0 Hz) equaled the homeostasis target firing rate (Fig. 10). These individual bursts resemble paroxysmal discharges found in slices of chronically isolated ("undercut") cortex [214]. It was proposed that

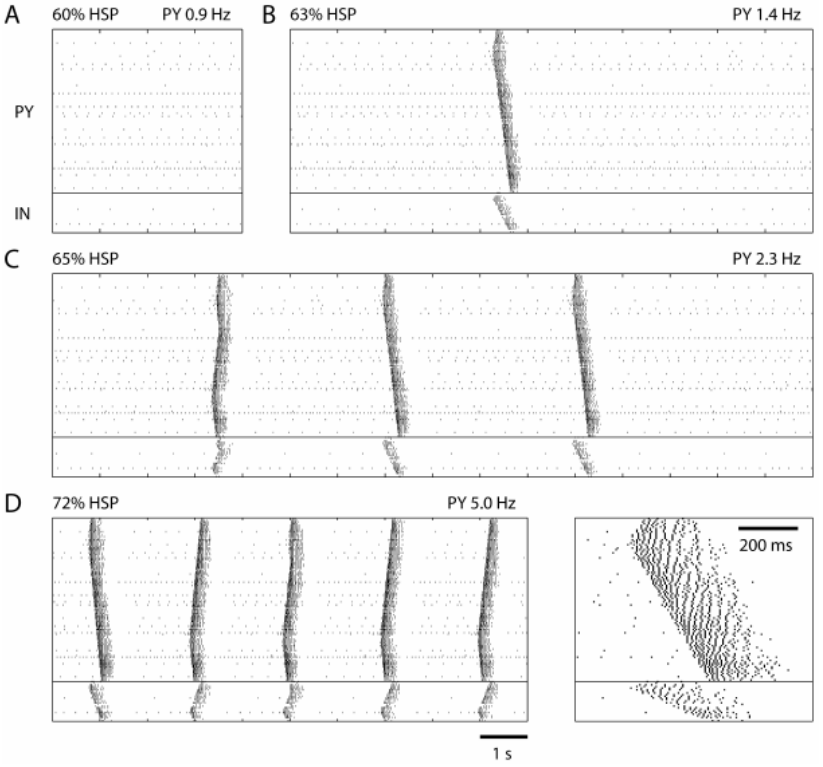

Figure 10. Computer model of propagating burst discharges in deafferented cortex after homeostatic synaptic plasticity. Each dot represents the spike from a single model neuron. Each line in the raster plot is from a single neuron. The pyramidal cells are in the top part of the diagram and the interneurons are shown in the bottom part. These spike rasterplots show network activity after (A) 60% HSP, (B) 63% HSP, (C) 65% HSP and (D) 72% HSP. After 72% HSP a steady state was reached for which PY cells fired on average 5.0 Hz. The inset shows an expanded spontaneous burst at 72% HSP. [Modified from [41]].

activity dependent scaling of synaptic connectivity may be a primary factor contributing to posttraumatic epileptogenesis [41]. This study suggests that restoring a normal state with random nonsynchronized firing of individual neurons may become impossible in the severely deafferented network, then the same plasticity mechanisms lead to paroxysmal oscillations.

Rearrangement of neuronal circuitry may be another factor contributing to the epileptogenesis in chronically injured neocortex. Recent study demonstrated in the young age group of mesial temporal lobe epileptic patients (3–10 years old) an enhanced glutamate receptor subunit profiles, suggesting that the dendritic change precedes axonal sprouting [240]. There is evidence for sprouting of layer 5 pyramidal cell axons and formation of new synapses in chronically isolated cortex [241]. It is not known, however, whether new synapses are formed predominantly on pyramidal cells, which would create an enhanced recurrent excitatory circuit such as after mossy fiber sprouting in a model of temporal lobe epilepsy [242]. In computer studies, new synapses between pyramidal cells support epileptogenesis, but not when an equal number of new synapses was added from pyramidal cells to interneurons [243]**.** It is possible that axonal sprouting and the formation of new synapses is a secondary effect induced by paroxysmal activity. Indeed, the axonal sprouting of corticostriatal neurons after ischemic cortical lesions was shown to depend on synchronous neuronal activity in perilesion neocortex [244].

Trauma induced 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 [245], K^+ released during intense neuronal firing may accumulate in the interstitial space, thus depolarizing neurons and leading to spike inactivation. As we discussed earlier in this chapter, increase of $[K^+]_o$ depolarizes the K^+ currents reversal potential and can affect the maximal conductances of some depolarizing currents such as the hyperpolarization-activated depolarizing current (I_h) [246] and the persistent sodium current ($I_{Na(p)}$) [247], increasing excitability. A recent study showed that K^+-mediated increase of I_h may lead to periodic bursting in a cortical network model [201]. It was shown that a combination of $I_{h,}$, $I_{K(Ca)}$ and $I_{Na(p)}$ in pyramidal cells are sufficient to organize paroxysmal oscillations with a frequency at 2-3 Hz. These oscillations started when $I_{K(leak)}$ 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 [201]. A single PY cell with these properties was sufficient to mediate activity in a whole cortical network of 40 neurons. Increase in $[K^+]_o$, sufficient to produce oscillations could result from

excessive firing (e.g., induced by external stimulation) or inability of K^+ regulatory system (e.g., when glial buffering was blocked) [209]. In a single PY neuron when $[K]_o$ increased sufficiently, slow 2-3 Hz bursting often accompanied by spike inactivated was found (Fig. 11). Typically, after 1-2 spikes the cell membrane potential became "locked" into the depolarized state maintained by the balance of intrinsic conductances. An increase in the intracellular Ca^{2+} mediated by a high-threshold Ca^{2+} current, eventually increased $I_{K(Ca)}$ to the level where the depolarized state became unstable and the membrane potential rapidly hyperpolarized. This hyperpolarization led to I_h activation and slow repolarization to the level where $I_{Na(p)}$ became activated and initiated the next burst. The frequency of this bursting depended on many intrinsic conductances, especially $g_{K(Ca)}$ and g_h [209]. The oscillatory patterns displayed by cortical neurons (slow 2-3 Hz bursting or fast 10-15 Hz run) during paroxysmal oscillation induced by high $[K^+]_o$ were found to depend on the absolute level of $[K^+]_o$ [248]. In the network model the sustained increased

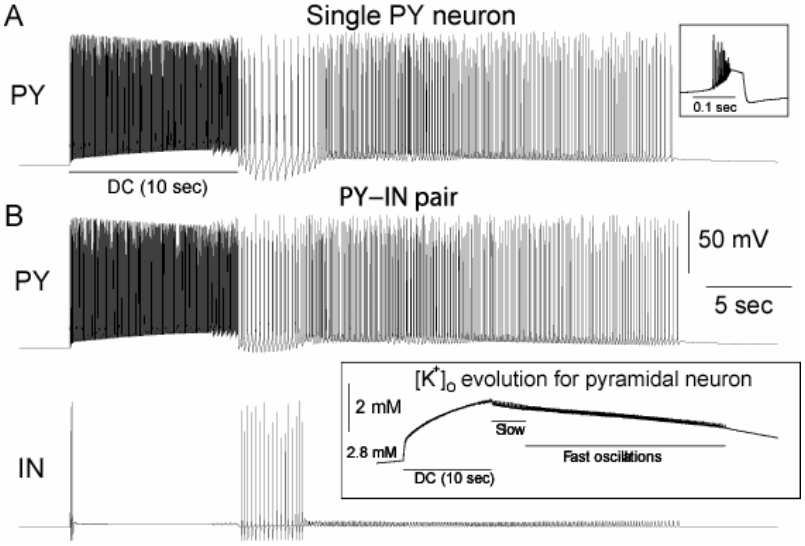

Figure 11. Neuron oscillatory activity induced by a current pulse. DC pulse (10 sec in duration, bar) was applied to the silent PY cell. Following high frequency firing, $[K^+]_o$ increased and maintained oscillations in PY neuron after DC pulse was removed. (A) Single PY neuron. Insert shows typical 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). (M. Bazhenov and I. Timofeev, unpublished).

the absolute level of $[K^+]_o$ [248]. In the network model the sustained increased level of $[K^+]_o$ caused a spatially inhomogeneous pattern of switching between epochs of slow bursting and fast runs, each lasting several seconds (Fig. 12). This study shows that hysteresis between slow and fast oscillations in a single neuron could serve as the basis for both the slow bursting and fast runs seen in cat neocortex during *in vivo* recordings [132].

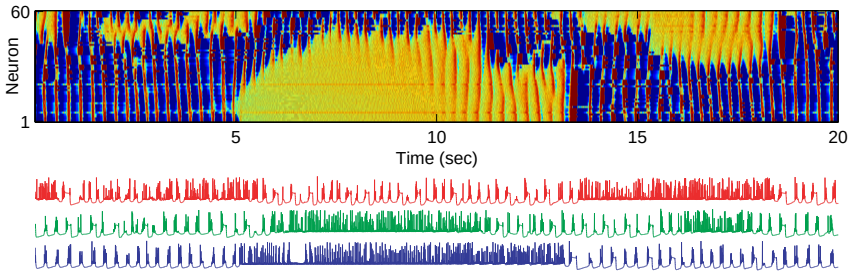

Figure 12. $[K^+]_o$ controls transitions between fast runs and slow bursting. Computational model showing hysteresis between regimes of fast and slow oscillations as a function of $[K^+]_o$, leading to spatially inhomogeneous patterns of slow (2-3 Hz) bursting and fast (~10 Hz) runs in the cortical network model of 60 PY cells and 15 INs. Electrical stimulation (20 sec) was used to create initial $[K^+]_o$ increase that triggered oscillations. The network was silent before stimulation. (F. Frohlich and M. Bazhenov, unpublished).

Cellular and network periodic bursting was found *in vitro* after increasing $[K^+]_o$ [228, 249, 250]. Traumatic brain injury leading to loss of K^+ conductance in hippocampal glia can result in the failure of glial K^+ homeostasis and abnormal neuronal function including seizures [251]. 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 [252]. In Kager et al., [253] periodic bursting after $[K^+]_o$ increase was described in a single cell; however, in this model the bursts occurred at very low frequency (one every 10-15 sec) which might be attributed to the lack of $I_{K(Ca)}$. Importance of low-threshold Ca^{2+} (T-type) current for generating spike-and-wave oscillations was suggested in [207]. In recordings from granule cells of the dentate gyrus of the 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 [249]. 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 [254]. In recordings from rat hippocampal slices with high $[K^+]_o$, the local generation of population bursts in CA1 was caused by intrinsically bursting pyramidal cells, which recruit and synchronize other neurons [228].

Conclusion

Penetrating wounds can induce acute seizures. Within the thalamocortical system these seizures originate in the neocortex. The primary cause of these seizures is an enhancement of intrinsic and synaptic excitability in the areas surrounding the traumatized cortex and a reduction of excitability in the partially deafferented cortex. It is most likely that these changes occur due to a local change in the balance of ion, extracellular mediator concentrations and deafferentation/ disfacilitation (resulting in neuronal hyperpolarization) due to the removal of excitatory afferents. The interaction between cortical areas with increased and decreased excitability creates conditions favorable for the development of acute seizures.

The mechanisms of chronic trauma-induced epileptogenesis are less clear. Deafferentation may trigger homeostatic plasticity mechanisms that enhance both intrinsic and synaptic excitability. Accordingly, the most deafferented area should exhibit the highest excitability. The remaining synaptic inputs to this area would induce overexcitation, thus triggering a seizure.

Usually, anti-epileptic drugs (other than those used for petit mal seizures) aim to increase inhibitory activity and to reduce the efficiency of sodium currents [255-257]. Both these measures decrease cortical excitability and, therefore, potentiate homeostatic plasticity. As a result the types of drugs applied have to be changed with a certain periodicity, and still some forms of epilepsy remain drug resistant. If the hypothesis that homeostatic plasticity may be a leading factor in trauma induced epileptogenesis is accepted, the treatment should be designed to reduce homeostatic mechanisms. This could be accomplished by the use of locally applied drugs that enhance the excitability of the traumatized cortex and/or local electrical stimulation with properties that would not induce kindling.

Acknowledgements

This study was supported by Canadian Institutes of Health Research (Grant MOP- 37862), Canadian Foundation for Innovation and the National Institute on Deafness and Other Communication Disorders, National Institutes of Health (Grant R01 DC006306). I.T. is Canadian Institutes of Health Research scholar.

References

1. Dinner, D. 1993, *The Treatment of Epilepsy: Principles*, Lea & Fibinger: Philadelphia. p. 654-658.
2. Kollevold, T. 1976, J Oslo City Hosp, **26**(12): p. 99-114.
3. Marcikic, M., A. Melada, and R. Kovacevic. 1998, Injury, **29**(8): p. 613-8.
4. Salazar, A., B. Jabbari, S. Vance, J. Grafman, D. Amin, and J. Dillon. 1985, Neurology, 1985. **35**(10): p. 1406-1414.
5. Pitkänen, A. 2001 *Focus on Epilepsy VI*. Mont-Tremblant, Quebec, Canada.
6. Engel, J., Jr., C. Wilson, and A. Bragin, 2003, Epilepsia, **44 Suppl 12**: p. 60-71.
7. Steriade, M., E.G. Jones, and D.A. McCormick. 1997, *Thalamus: organization and function*. Vol. 1. Oxford: Elsevier Science Ltd. 959.
8. Peters, A. and B.R. Payne. 1993, Cereb Cortex, 1993. **3**(1): p. 69-78.
9. Ahmed, B., J.C. Anderson, R.J. Douglas, K.A. Martin, and J.C. Nelson. 1994, J Comp Neurol, 1994. **341**(1): p. 39-49.
10. Jones, E.G. 1985, *The thalamus*. New York: Plenum.
11. Golshani, P., X.B. Liu, and E.G. Jones*.2001,* Proc Natl Acad Sci U S A, **98**(7): p. 4172-7.
12. Houser, C.R., J.E. Vaughn, R.P. Barber, and E. Roberts. 1980, Brain Res, 1980. **200**(2): p. 341-54.
13. Oertel, W.H., A.M. Graybiel, E. Mugnaini, R.P. Elde, D.E. Schmechel, and I.J. Kopin. 1983, J Neurosci, **3**(6): p. 1322-32.
14. Scheibel, M.E. and A.B. Scheibel. 1966, Brain Res, 1966. **1**(1): p. 43-62.
15. Yen, C., M. Conley, S. Hendry, and E. Jones. 1985, J Neurosci, **5**(8): p. 2254-2268.
16. Liu, X.B., R.A. Warren, and E.G. Jones. 1995, J Comp Neurol, 1995. **352**(2): p. 187-202.
17. Cox, C.L., J.R. Huguenard, and D.A. Prince. 1996, J Comp. Neurol., **366**(3): p. 416-430.
18. Landisman, C.E., M.A. Long, M. Beierlein, M.R. Deans, D.L. Paul, and B.W. Connors. 2002, J Neurosci, **22**(3): p. 1002-9.
19. Fuentealba, P., S. Crochet, I. Timofeev, M. Bazhenov, T.J. Sejnowski, and M. Steriade. 2004, Eur J Neurosci, **20**(1): p. 111-9.
20. Steriade, M. and I. Timofeev. 2001 Thalamus & related systems, **1**: p. 225-236.
21. Aladjalova, N.A. 1957, Nature, 1957. **4567**(11): p. 957-959.
22. Nita, D.A., S. Vanhatalo, F.D. Lafortune, J. Voipio, K. Kaila, and F. Amzica. 2004, J Neurophysiol, **92**(2): p. 1011-22.
23. Aladjalova, N.A., *Slow electrical processes in the brain*. 1962, Moscow: Acad Sci USSA. 239.
24. Steriade, M., D.A. McCormick, and T.J. Sejnowski. 1993, Science, 1993. **262**(5134): p. 679-85.
25. Steriade, M., A. Nuñez, and F. Amzica. 1993, J Neurosci, 1993. **13**: p. 3252-3265.
26. Steriade, M., I. Timofeev, and F. Grenier. 2001, J Neurophysiol, 2001. **85**(5): p. 1969-85.
27. Timofeev, I., F. Grenier, and M. Steriade. 2001, Proc Natl Acad Sci U S A, **98**(4): p. 1924-1929.
28. Steriade, M., A. Nuñez, and F. Amzica. 1993, J Neurosci, **13**: p. 3266-3283.
29. Timofeev, I. and M. Steriade. 1996, J Neurophysiol, **76**(6): p. 4152-68.
30. Timofeev, I., F. Grenier, M. Bazhenov, T.J. Sejnowski, and M. Steriade. 2000, Cereb Cortex, **10**(12): p. 1185-1199.

31. Sanchez-Vives, M.V. and D.A. McCormick. 2000, Nat Neurosci, **3**(10): p. 1027-34.
32. Hughes, S.W., D.W. Cope, K.L. Blethyn, and V. Crunelli. 2002, Neuron, **33**(6): p. 947-58.
33. Contreras, D., I. Timofeev, and M. Steriade. 1996, J Physiol, **494**(Pt 1): p. 251-64.
34. Timofeev, I., D. Contreras, and M. Steriade. 1996, J Physiol, **494**(Pt 1): p. 265-78.
35. Metherate, R. and J.H. Ashe. 1993, J. Neurosci., **13**(12): p. 5312-5323.
36. Massimini, M., R. Huber, F. Ferrarelli, S. Hill, and G. Tononi. 2004, J Neurosci, **24**(31): p. 6862-6870.
37. Cossart, R., D. Aronov, and R. Yuste. 2003, Nature, 2003. **423**(6937): p. 283-8.
38. Achermann, P. and A.A. Borbely. 1997, Neuroscience, **81**(1): p. 213-22.
39. Villablanca, J. and M.E. Salinas-Zeballos. 1972, Archives Italiennes de Biologie, **110**: p. 383-411.
40. Ball, G.J., P. Gloor, and N. Schaul. 1977, Electroencephalogr Clin Neurophysiol, **43**(3): p. 346-61.
41. Houweling, A.R., M. Bazhenov, I. Timofeev, M. Steriade, and T.J. Sejnowski. 2005, Cereb Cortex, **15**(6): p. 834-45.
42. Amzica, F. and M. Steriade. 1998, Electroencephalogr Clin Neurophysiol, **107**(2): p. 69-83.
43. Timofeev, I., F. Grenier, and M. Steriade. 2000, *Society for Neuroscience. 30 Annual Meeting*. 2000. New Orleans, La.
44. McCormick, D.A. and H.C. Pape. 1990, J Physiol, **431**: p. 291-318.
45. Leresche, N., S. Lightowler, I. Soltesz, D. Jassik-Gerschenfeld, and V. Crunelli. 1991, J. Physiol., **441**: p. 155-174.
46. Soltesz, I., S. Lightowler, N. Leresche, D. Jassik-Gerschenfeld, C.E. Pollard, and V. Crunelli. 1991, J. Physiol., **441**: p. 175-197.
47. Curró Dossi, R., A. Nuñez, and M. Steriade. 1992, J Physiol, **447**: p. 215-234.
48. Jahnsen, H. and R. Llinás. 1984, J Physiol, **349**: p. 205-226.
49. Timofeev, I., M. Bazhenov, T. Sejnowski, and M. Steriade. 2001, Thalamus & related systems, **1**(1): p. 53-69.
50. Pape, H.C. 1996, Annu Rev Physiol, **58**: p. 299-327.
51. Lytton, W.W., A. Destexhe, and T.J. Sejnowski. 1996, Neuroscience, **70**(3): p. 673-684.
52. Huguenard, J.R. 1996, Annu Rev Physiol, **58**: p. 329-48.
53. Steriade, M., R.C. Dossi, and A. Nunez. 1991, J Neurosci, **11**(10): p. 3200-17.
54. Williams, S.R., T.I. Tóth, J.P. Turner, S.W. Hughes, and W. Crunelli. 1997, J Physiol, **505**(3): p. 689-705.
55. Morison, R.S. and E.W. Dempsey. 1942, Am. J. Physiol., **135**: p. 281-292.
56. Morison, R.S. and D.L. Bassett. J. Neurophysiol., 1945. **8**: p. 309-314.
57. Contreras, D., A. Destexhe, T.J. Sejnowski, and M. Steriade. 1996, Science, **274**(5288): p. 771-774.
58. Kim, U., T. Bal, and D.A. McCormick. 1995, J Neurophysiol, **74**(3): p. 1301-1323.
59. Bal, T. and D.A. McCormick. 1993, J Physiol, **468**: p. 669-91.
60. von Krosigk, M., T. Bal, and D.A. McCormick. 1993, Science, **261**(5119): p. 361-4.
61. Steriade, M., M. Deschenes, L. Domich, and C. Mulle. 1985, J Neurophysiol, **54**(6): p. 1473-97.

62. Steriade, M. and R. Llinas. 1988, Physiol. Reviews, **68**(3): p. 649-742.
63. Steriade, M., E.G. Jones, and R. Llinas. 1990, *Thalmic oscillations and signaling*. The Neuroscience Institute Publications, New York: John Wiley & Sons. 431.
64. Steriade, M. and M. Deschénes. 1984, Brain Research Reviews, **8**: p. 1-63.
65. Steriade, M., L. Domich, G. Oakson, and M. Deschenes. 1987, J Neurophysiol, **57**(1): p. 260-273.
66. Bazhenov, M., I. Timofeev, M. Steriade, and T. Sejnowski. 2000, J Neurophysiol, **84**(2): p. 1076-87.
67. Bazhenov, M., I. Timofeev, M. Steriade, and T.J. Sejnowski. 1999, Nat Neurosci, **2**(2): p. 168-74.
68. Fuentealba, P., I. Timofeev, M. Bazhenov, T.J. Sejnowski, and M. Steriade. 2005, J Neurophysiol, **93**(1): p. 294-304.
69. Fuentealba, P., I. Timofeev, and M. Steriade. 2004, Proc Natl Acad Sci U S A, **101**(26): p. 9816-21.
70. Bal, T. and D.A. McCormick. 1996, Neuron, **17**: p. 297-308.
71. Budde, T., G. Biella, T. Munsch, and H.-C. Pape. 1997, J Physiol, **503**(1): p. 79-85.
72. Luthi, A., T. Bal, and D.A. McCormick. 1998, J Neurophysiol, **79**(6): p. 3284-3289.
73. Noda, H. and W.R. Adey. 1970, *J Neurophysiol*. **33**(5): p. 672-84.
74. Bressler, S.L. 1990, *Trends Neurosci*. p. 161-2.
75. Freeman, W.J. 1991, *Sci Am*. 1991. p. 78-85.
76. Bouyer, J.J., M.F. Montaron, and A. Rougeul. 1981, Electroencephalogr Clin Neurophysiol, **51**: p. 244-252.
77. Rougeul-Buser, A., J.J. Bouyer, and P. Buser. 1975, *Acta Neurobiol Exp (Warsz)*. p. 805-19.
78. Sheer, D.E. 1989, *Prog Clin Biol Res*. p. 79-94.
79. Gray, C.M., P. Konig, A.K. Engel, and W. Singer. 1989, *Nature*. p. 334-7.
80. Murthy, V.N. and E.E. Fetz. *Proc Natl Acad Sci U S A*. p. 5670-4.
81. Pfurtscheller, G. and C. Neuper. 1992, *Neuroreport*. p. 1057-60.
82. Singer, W. and C.M. Gray. 1995, Annu Rev Neurosci, 1995. **18**: p. 555-86.
83. Joliot, M., U. Ribary, and R. Llinas. 1994, Proc Natl Acad Sci U S A, **91**(24): p. 11748-11751.
84. Llinas, R. and U. Ribary. 1993, Proc Natl Acad Sci U S A, **90**(5): p. 2078-2081.
85. Steriade, M., F. Amzica, and D. Contreras. 1996, J Neurosci, **16**(1): p. 392-417.
86. Steriade, M., D. Contreras, F. Amzica, and I. Timofeev. 1996, J Neurosci, **16**(8): p. 2788-808.
87. Rulkov, N.F., I. Timofeev, and M. Bazhenov. 2004, *J. Comp. Neurosci.* **17**(2): p. 203-223.
88. Castelo-Branco, M., S. Neuenschwander, and W. Singer. 1998, J Neurosci, **18**(16): p. 6395-6410.
89. Timofeev, I. and M. Steriade. 1997, J Physiol, **504**(1): p. 153-168.
90. Calvin, W.H. and G.W. Sypert. 1976, J Neurophysiol, **39**(2): p. 420-34.
91. Gray, C.M. and D.A. McCormick. 1996, Science, **274**(4 October): p. 109-113.
92. Timofeev, I., F. Grenier, and M. Steriade. 2000, J Physiol (Paris), 2000. **94**(5-6): p. 343-355.

93. Steriade, M., I. Timofeev, N. Dürmüller, and F. Grenier. 1998, J Neurophysiol, **79**(1): p. 483-90.
94. Brumberg, J.C., L.G. Nowak, and D.A. McCormick. 2000, J Neurosci, **20**(13): p. 4829-43.
95. Wang, X.J. 1999, Neuroscience, **89**(2): p. 347-362.
96. Traub, R.D., E.H. Buhl, T. Gloveli, and M.A. Whittington. 2003, J Neurophysiol, **89**(2): p. 909-21.
97. Boucetta, S., S. Crochet, and I. Timofeev. 2003, *SFN annual meeting*. New Orleans.
98. Traub, R.D., M.A. Whittington, E.H. Buhl, J.G. Jefferys, and H.J. Faulkner. 1999, J Neurosci, **19**(3): p. 1088-1105.
99. Traub, R.D., N. Spruston, I. Soltesz, A. Konnerth, M.A. Whittington, and G.R. Jefferys. 1998, Prog Neurobiol, **55**(6): p. 563-75.
100. Traub, R.D., M.A. Whittington, I.M. Stanford, and J.G. Jefferys. 1996, Nature, **383**(6601): p. 621-624.
101. Lytton, W.W. and T.J. Sejnowski. 1991, J Neurophysiol, **66**(3): p. 1059-79.
102. Kopell, N., G.B. Ermentrout, M.A. Whittington, and R.D. Traub. 2000, Proc Natl Acad Sci U S A, **97**(4): p. 1867-1872.
103. Traub, R.D., A. Bibbig, A. Fisahn, F.E. LeBeau, M.A. Whittington, and E.H. Buhl. 2000, Eur J Neurosci, **12**(11): p. 4093-106.
104. Cunningham, M.O., M.A. Whittington, A. Bibbig, A. Roopun, F.E.N. LeBeau, A. Vogt, H. Monyer, E.H. Buhl, and R.D. Traub. 2004, Proc Natl Acad Sci U S A, **101**(18): p. 7152-7157.
105. Chrobak, J.J. and G. Buzsáki. 1996, J Neurosci, **16**(9): p. 3056-3066.
106. Collins, D.R., E.J. Lang, and D. Pare. 1999, Neuroscience, **89**(4): p. 1025-39.
107. Csicsvari, J., H. Hirase, A. Czurko, A. Mamiya, and G. Buzsaki. 1999, J Neurosci, **19**(1): p. 274-287.
108. Csicsvari, J., H. Hirase, A. Czurko, A. Mamiya, and G. Buzsaki. 1999, J Neurosci, **19**(16): p. RC20 (1-4).
109. Ylinen, A., A. Bragin, Z. Nadasdy, G. Jando, I. Szabo, A. Sik, and G. Buzsaki. 1995, J Neurosci, **15**(1 Pt 1): p. 30-46.
110. Jones, M.S. and D.S. Barth. 1999, J Neurophysiol, **82**(3): p. 1599-609.
111. Jones, M.S., K.D. MacDonald, B. Choi, F.E. Dudek, and D.S. Barth. 2000, J Neurophysiol, **84**(3): p. 1505-18.
112. Kandel, A. and G. Buzsaki. 1997, J Neuroscience, **17**(17): p. 6783-6797.
113. Grenier, F., I. Timofeev, and M. Steriade. 2001, J. Neurophysiol., **86**(4): p. 1884-1898.
114. Allen, P.J., D.R. Fish, and S.J. Smith. 1992,. Electroencephalogr Clin Neurophysiol, **82**(2): p. 155-9.
115. Fisher, R.S., W.R. Webber, R.P. Lesser, S. Arroyo, and S. Uematsu. 1992, J Clin Neurophysiol, **9**(3): p. 441-8.
116. Grenier, F., I. Timofeev, and M. Steriade. 2003, J Neurophysiol, **89**: p. 841-852.
117. Steriade, M., F. Amzica, D. Neckelmann, and I. Timofeev. 1998, J Neurophysiol, **80**(3): p. 1456-1479.
118. Grenier, F., I. Timofeev, S. Crochet, and M. Steriade. 2003, Neuroscience, **119**(1): p. 277-91.

119. Bragin, A., J. Engel, Jr., C.L. Wilson, I. Fried, and G. Buzsaki. 1999, Hippocampus, **9**(2): p. 137-42.
120. Bragin, A., J. Engel, Jr., C.L. Wilson, I. Fried, and G.W. Mathern. 1999, Epilepsia, **40**(2): p. 127-37.
121. Bragin, A., I. Mody, C.L. Wilson, and J. Engel, Jr. 2002, J Neurosci, **22**(5): p. 2012-21.
122. Draguhn, A., R.D. Traub, D. Schmitz, and J.G. Jefferys. 1998, Nature, **394**(6689): p. 189-192.
123. Traub, R.D., D. Schmitz, J.G. Jefferys, and A. Draguhn. 1999, Neuroscience, **92**(2): p. 407-426.
124. Schmitz, D., S. Schuchmann, A. Fisahn, A. Draguhn, E.H. Buhl, E. Petrasch-Parwez, R. Dermietzel, U. Heinemann, and R.D. Traub. 2001, Neuron, **31**(5): p. 831-40.
125. Galarreta, M. and S. Hestrin. 1999, Nature, **402**(6757): p. 72-5.
126. Galarreta, M. and S. Hestrin. 2001, Science, **292**(5525): p. 2295-9.
127. Galarreta, M. and S. Hestrin. 2001, Nat Rev Neurosci, **2**(6): p. 425-33.
128. Gibson, J.R., M. Beierlein, and B.W. Connors. 2005, J Neurophysiol, **93**(1): p. 467-480.
129. Gibson, J.R., M. Beierlein, and B.W. Connors. 1999, Nature, **402**(6757): p. 75-9.
130. Steriade, M. and D. Contreras. 1998, J Neurophysiol, **80**(3): p. 1439-1455.
131. Timofeev, I., F. Grenier, and M. Steriade. 1998, J Neurophysiol, **80**(3): p. 1495-1513.
132. Timofeev, I. and M. Steriade. 2004, Neuroscience, **123**(2): p. 299-336.
133. Steriade, M. 2003, *Neuronal substrates of sleep and epilepsy*., Cambridge (UK): Cambridge Univ. Press.
134. Pinault, D., N. Leresche, S. Charpier, J.M. Deniau, C. Marescaux, M. Vergnes, and V. Crunelli. 1998, J Physiol, **509**(Pt 2): p. 449-56.
135. Stafstrom, C.E. 2005, Epilepsy Currents, **5**(2): p. 69-71.
136. Steriade, M. 1974, Electroencephalogr Clin Neurophysiol, **37**(3): p. 247-63.
137. Bal, T., M. von Krosigk, and D.A. McCormick. 1995, J Physiol, **483**(3): p. 641-663.
138. Ajmone-Marsan, C. and B. Ralston. 1956, Electroencephalogr Clin Neurophysiol Suppl, **8**(4): p. 559-82.
139. Castro-Alamancos, M.A. 1999, J Neurosci, **19**(18): p. RC27.
140. Steriade, M. and D. Contreras. 1995, J Neurosci, **15**(1 Pt 2): p. 623-42.
141. Niedermeyer, E. 1999, *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, E. Niedermeyer and F. Lopes de Silva, Editors. Williams & Wilkins: Baltimor MD. p. 235-260.
142. Niedermeyer, E. 1999, *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, E. Niedermeyer and F. Lopes de Silva, Editors. Williams & Wilkins: Baltimor MD. p. 476-585.
143. Dichter, M.A. and G.F. Ayala. 1987, Science, **237**(4811): p. 157-164.
144. Galarreta, M. and S. Hestrin. 1998, Nat Neurosci, **1**(7): p. 587-94.
145. Nelson, S.B. and G.G. Turrigiano. 1998, Nat. Neurosci., **1**(7): p. 539-541.
146. Matsumoto, H. and C. Ajmone-Marsan. 1964, Experimental Neurology, **9**: p. 286-304.
147. Matsumoto, H. and C. Ajmone-Marsan. 1964, Experimental Neurology, **9**: p. 305-326.
148. Prince, D.A. 1978, Annu Rev Neurosci, **1**: p. 395-415.

149. Gutnick, M.J., B.W. Connors, and D.A. Prince. 1982, J Neurophysiol, **48**(6): p. 1321-1335.
150. Chagnac-Amitai, Y. and B.W. Connors. 1989, J Neurophysiol, **61**(4): p. 747-58.
151. Chagnac-Amitai, Y. and B.W. Connors. 1989, J Neurophysiol, **62**(5): p. 1149-62.
152. McNamara, J.O.1994, J Neurosci, **14**(6): p. 3413-25.
153. Traub, R.D., C. Borck, S.B. Colling, and J.G. Jefferys. 1996, Epilepsia, **37**(9): p. 879-91.
154. Abbott, L.F., J.A. Varela, K. Sen, and S.B. Nelson. 1997, Science, **275**(5297): p. 220-224.
155. Desai, N.S., L.C. Rutherford, and G.G. Turrigiano. 1999, Nat Neurosci, **2**(6): p. 515-520.
156. Desai, N.S., S.B. Nelson, and G.G. Turrigiano. 1999, Neurocomputing, **26-27**: p. 101-106.
157. Turrigiano, G.G., K.R. Leslie, N.S. Desai, L.C. Rutherford, and S.B. Nelson. 1998, Nature, **391**(6670): p. 892-6.
158. Watt, A.J., M.C. van Rossum, K.M. MacLeod, S.B. Nelson, and G.G. Turrigiano. 2000, Neuron, **26**(3): p. 659-70.
159. Murthy, V.N., T. Schikorski, C.F. Stevens, and Y. Zhu. 2001, Neuron, **32**(4): p. 673-82.
160. Topolnik, L., M. Steriade, and I. Timofeev. 2003, Cereb Cortex, **13**: p. 883-893.
161. Topolnik, L., M. Steriade, and I. Timofeev. 2003, Eur J Neurosci, **18**: p. 486-496.
162. Prince, D.A., K.M. Jacobs, P.A. Salin, S. Hoffman, and I. Parada. 1997, Can J Physiol Pharmacol, **75**(5): p. 500-7.
163. Jacobs, K.M. and D.A. Prince. 2005, J Neurophysiol, **93**(2): p. 687-696.
164. Jin, X., J.R. Huguenard, and D.A. Prince. 2005, J Neurophysiol, **93**(4): p. 2117-2126.
165. Li, H., A.E. Bandrowski, and D.A. Prince. 2005, J Neurophysiol, **93**(1): p. 146-156.
166. Crochet, S., S. Chauvette, S. Boucetta, and I. Timofeev. 2005, Eur J Neurosci, **21**(4): p. 1030-1044.
167. Massimini, M. and F. Amzica. 2001, J Neurophysiol, 2001. **85**(3): p. 1346-50.
168. Sakowitz, O.W., A.W. Unterberg, and J.F. Stover. 2002, Acta Neurochir Suppl, **81**: p. 221-3.
169. Moody, W.J., K.J. Futamachi, and D.A. Prince, 1974, Exp Neurol, **42**(2): p. 248-63.
170. Traynelis, S.F. and R. Dingledine. 1988, J Neurophysiol, **59**(1): p. 259-76.
171. McCormick, D.A. and D. Contreras. 2001, Annu Rev Physiol, **63**: p. 815-846.
172. Johnston, D. and T.H. Brown. 1981, Science, **211**(4479): p. 294-7.
173. Johnston, D. and T.H. Brown. 1984, Ann Neurol, **16**(71): p. S65-71.
174. Wong, R.K. and D.A. Prince. 1978, Brain Res, **159**(2): p. 385-90.
175. Timofeev, I., F. Grenier, and M. Steriade. 2004, J Neurophysiol, **92**(2): p. 1133-1143.
176. de Curtis, M., C. Radici, and M. Forti. 1999, Neuroscience, **88**(1): p. 107-17.
177. Timofeev, I., F. Grenier, and M. Steriade. 2002, Neuroscience, **114**(4): p. 1115-1132.
178. Esclapez, M., J.C. Hirsch, R. Khazipov, Y. Ben-AriI, and C. Bernard. 1997,. Proc Natl Acad Sci U S A, **94**: p. 12151-12156.

179. Prince, D.A. and K. Jacobs. 1998, Epilepsy Res, **32**(1-2): p. 83-92.
180. Cohen, I., V. Navarro, S. Clemenceau, M. Baulac, and R. Miles. 2002, Science, **298**(5597): p. 1418-21.
181. Fujiwara-Tsukamoto, Y., Y. Isomura, A. Nambu, and M. Takada. 2003, Neuroscience, **119**(1): p. 265-275.
182. Thompson, S.M. and B.H. Gähwiler. 1998, J Neurophysiol, **61**(3): p. 501-11.
183. Kaila, K., K. Lamsa, S. Smirnov, T. Taira, and J. Voipio. 1997, J Neurosci, **17**(20): p. 7662-72.
184. Taira, T., K. Lamska, and K. Kaila. 1997, J Neurophysiol, **77**: p. 2213-2218.
185. DeFazio, R.A., S. Keros, M.W. Quick, and J.J. Hablitz. 2000, J Neurosci, **20**(21): p. 8069-76.
186. Payne, J.A., C. Rivera, J. Voipio, and K. Kaila. 2003, Trends Neurosci, **26**(4): p. 199-206.
187. Pollen, D.A. 1964, Electroencephalogr Clin Neurophysiol, **17**: p. 398-404.
188. Giaretta, D., M. Avoli, and P. Gloor. 1987, Brain Res, **405**(1): p. 68-79.
189. Destexhe, A.1998, J Neurosci, **18**(21): p. 9099-111.
190. Matsumoto, H., G.F. Ayala, and R.J. Gumnit. 1969, Electroencephalogr Clin Neurophysiol, **26**(1): p. 120.
191. Neckelmann, D., F. Amzica, and M. Steriade. 2000, Neuroscience, **96**(3): p. 475-485.
192. Crunelli, V. and N. Leresche. 2002, Nat Rev Neurosci, **3**(5): p. 371-82.
193. Charpier, S., N. Leresche, J.M. Deniau, S. Mahon, S.W. Hughes, and V. Crunelli. 1999, Neuropharmacology, **38**(11): p. 1699-706.
194. Staak, R. and H.C. Pape. 2001, J Neurosci, **21**(4): p. 1378-84.
195. Deisz, R.A., J.M. Billard, and W. Zieglgansberger. 1997, Synapse, **25**(1): p. 62-72.
196. Jensen, M.S., E. Cherubini, and Y. Yaari. 1993, J Neurophysiol, **69**(3): p. 764-771.
197. Halliwell, J.V. 1986, Neurosci Lett, **67**(1): p. 1-6.
198. Schwindt, P.C., W.J. Spain, R.C. Foehring, C.E. Stafstrom, M.C. Chubb, and W.E. Crill. 1988, J Neurophysiol, **59**(2): p. 424-449.
199. Amzica, F., M. Massimini, and A. Manfridi. 2002, J Neurosci, **22**(3): p. 1042-1053.
200. Amzica, F. and M. Steriade. 2000, J Neurosci, **20**(17): p. 6648-65.
201. Timofeev, I., M. Bazhenov, T. Sejnowski, and M. Steriade. 2002, Proc Natl Acad Sci U S A, **99**(14): p. 9533-7.
202. Hutcheon, B., R.M. Miura, and E. Puil. 1996, J Neurophysiol, **76**(2): p. 683-97.
203. Hutcheon, B., R.M. Miura, and E. Puil. 1996, J Neurophysiol, **76**(2): p. 698-714.
204. Hutcheon, B. and Y. Yarom. 2000, Trends Neurosci, **23**(5): p. 216-22.
205. Ulrich, D. 2002, J Neurophysiol, **87**(6): p. 2753-9.
206. de la Peña, E. and E. Geijo-Barrientos. 1996, J Neurosci, **16**(17): p. 5301-5311.
207. Destexhe, A., D. Contreras, and M. Steriade. 2001, Neurocomputing, **38-40**: p. 555-563.
208. Paré, D. and E.J. Lang. 1998, Eur J Neurosci, **10**(10): p. 3164-70.
209. Bazhenov, M., I. Timofeev, M. Steriade, and T.J. Sejnowski. 2004, J Neurophysiol, **92**: p. 1116-1132.
210. Turrigiano, G.G. 1999, Trends Neurosci, **22**(5): p. 221-7.
211. Sharpless, S.K., 1969, *Basic Mechanisms of the Epilepsies*, W.A. Jasper H, and Pope A, Editor. 1969, Little Brown: Boston, MA. p. 329-348.

212. Sharpless, S.K. and L.M. Halpern. 1962, Electroencephalogr Clin Neurophysiol, 1962. **14**: p. 244-55.
213. Burns, B.D. 1951, J Physiol (Lond), **112**: p. 156-175.
214. Prince, D.A. and G.F. Tseng. 1993, J Neurophysiol, **69**(4): p. 1276-1291.
215. Hoffman, S.N., P.A. Salin, and D.A. Prince. 1994, J Neurophysiol, **71**(5): p. 1762-73.
216. Li, H. and D.A. Prince. 2002, J Neurophysiol, **88**(1): p. 2-12.
217. Bush, P.C., D.A. Prince, and K.D. Miller. 1999, J Neurophysiol, **82**(4): p. 1748-58.
218. Echlin, F.A., V. Arnet, and J. Zoll. 1952, Electroencephalogr Clin Neurophysiol, **4**: p. 147-164.
219. Henry, C.E. and W.B. Scoville. 1952, Electroencephalogr Clin Neurophysiol, **4**(1): p. 1-22.
220. Nita, D., I. Timofeev, and M. Steriade. 2004, *SFN annual meeting*. 2004. San Diego.
221. Zuckermann, E.C. and G.H. Glaser. 1968, Exp Neurol, **20**(1): p. 87-110.
222. Jensen, M.S., R. Azouz, and Y. Yaari. 1994, J Neurophysiol, **71**(3): p. 831-9.
223. Perez Velazquez, J.L. and P.L. Carlen. 2000, Trends Neurosci, **23**(2): p. 68-74.
224. Lipton, S.A. and P.A. Rosenberg. 1994, N Engl J Med, **330**(9): p. 613-22.
225. Yang, L. and L.S. Benardo. 1997, J Neurophysiol, **78**(5): p. 2804-10.
226. van den Pol, A.N., K. Obrietan, and G. Chen. 1996, J Neurosci, **16**(13): p. 4283-92.
227. Tasker, G.J. and F.E. Dudek. 1991, Neurochemical Research, **16**(3): p. 251-262.
228. Jensen, M.S. and Y. Yaari. 1997, J Neurophysiol, **77**(3): p. 1224-33.
229. Vale, C. and D.H. Sanes. 2000, J Neurosci, **20**(5): p. 1912-21.
230. Vale, C., J. Schoorlemmer, and D.H. Sanes. 2003, J Neurosci, **23**(20): p. 7516-24.
231. Lissin, D.V., S.N. Gomperts, R.C. Carroll, C.W. Christine, D. Kalman, M. Kitamura, S. Hardy, R.A. Nicoll, R.C. Malenka, and M. von Zastrow. 1998, Proc Natl Acad Sci U S A, **95**(12): p. 7097-102.
232. Leslie, K.R., S.B. Nelson, and G.G. Turrigiano. 2001, J Neurosci, **21**(19): p. RC170.
233. O'Brien, R.J., S. Kamboj, M.D. Ehlers, K.R. Rosen, G.D. Fischbach, and R.L. Huganir. 1998, Neuron, **21**(5): p. 1067-78.
234. Rao, A. and A.M. Craig. 1997, Neuron, **19**(4): p. 801-12.
235. Liao, D., X. Zhang, R. O'Brien, M.D. Ehlers, and R.L. Huganir. 1999, Nat Neurosci, **2**(1): p. 37-43.
236. Rutherford, L.C., A. DeWan, H.M. Lauer, and G.G. Turrigiano. 1997, J Neurosci, **17**(12): p. 4527-35.
237. Kilman, V., M.C. van Rossum, and G.G. Turrigiano. 2002, J Neurosci, **22**(4): p. 1328-37.
238. Wierenga, C.J., K. Ibata, and G.G. Turrigiano. 2005, *J Neurosci*. p. 2895-905.
239. Desai, N.S., R.H. Cudmore, S.B. Nelson, and G.G. Turrigiano. 2002, Nat Neurosci, **5**(8): p. 783-9.
240. Lynd-Balta, E., W.H. Pilcher, and S.A. Joseph. 2004, Neuroscience, 2004. **126**(1): p. 105-114.
241. Salin, P., G.-F. Tseng, S. Hoffman, I. Parada, and D.A. Prince. 1995, J Neurosci, **15**(12): p. 8234-8245.
242. Buckmaster, P.S., G.F. Zhang, and R. Yamawaki. 2002, J Neurosci, **22**(15): p. 6650-8.

243. Houweling, A.R., M. Bazhenov, I. Timofeev, M. Steriade, and T.J. Sejnowski. 2005, Cereb Cortex, **15**(6): p. 834-45.
244. Carmichael, S.T. and M.F. Chesselet. 2002, J Neurosci, **22**(14): p. 6062-70.
245. Herreras, O. and G.G. Somjen. 1993, Brain Res, **610**(2): p. 283-94.
246. Spain, W.J., P.C. Schwindt, and W.E. Crill. 1987, J Neurophysiol, **57**(5): p. 1555-1576.
247. Somjen, G.G. and M. Muller. 2000, Brain Res, **885**(1): p. 102-10.
248. Frohlich, F., M. Bazhenov, I. Timofeev, S. M, and T.J. Sejnowski. 2004, *SFN annual meeting*. 2004. San Diego.
249. Pan, E. and J.L. Stringer. 1997, J Neurophysiol, **77**(5): p. 2293-9.
250. Leschinger, A., J. Stabel, P. Igelmund, and U. Heinemann. 1993, Exp Brain Res, **96**(2): p. 230-40.
251. D'Ambrosio, R., D.O. Maris, M.S. Grady, H.R. Winn, and D. Janigro. 1999, J Neurosci, **19**(18): p. 8152-62.
252. Traub, R.D. and R. Dingledine. 1990, J Neurophysiol, **64**(3): p. 1009-18.
253. Kager, H., W.J. Wadman, and G.G. Somjen. 2000, J Neurophysiol, **84**(1): p. 495-512.
254. Bikson, M., S.C. Baraban, and D.M. Durand. 2002, J Neurophysiol. p. 62-71.
255. Brodie, M.J. and J.A. French. 2000, Lancet, 2000. **356**(9226): p. 323-9.
256. Brodie, M.J. and P. Kwan. 2001, CNS Drugs, **15**(1): p. 1-12; discussion 13-5.
257. Kwan, P. and M.J. Brodie. 2000, N Engl J Med, **342**(5): p. 314-9.