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MINIREVIEW

Inhibitory Transmission, Activity-Dependent Ionic Changes and Neuronal Network Oscillations

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Summary

Oscillatory network activity arises from interactions between synaptic and intrinsic membrane properties of neurons. In this review, we summarize general mechanisms of synchronous neuronal oscillations. In addition, we focus on recent experimental and computational studies which suggest that activity-dependent changes of ionic environment can affect both the synaptic and intrinsic neuronal properties and influence the network behavior. $GABA_A$ receptor ($GABA_AR$)-mediated signaling, that is based on Cl^- and HCO_3^- permeability, is thought to be important for the oscillogenesis and synchronization in cortical networks. A remarkable feature of GABAergic synapses is that prolonged $GABA_AR$ activation may lead to switching from a hyperpolarizing to a depolarizing response. This is partly due to a positive shift of the $GABA_AR$ reversal potential (E_{GABA}) that is generated by GABA-induced Cl^- accumulation in neurons. Recent studies suggest that activity-dependent E_{GABA} changes may have important implications for the mechanisms of gamma oscillations and seizure-like discharges. Thus, a better understanding of the impact of intracellular Cl^- dynamics on network behavior may provide insights into the mechanisms of physiological and pathological brain rhythms. Combination of experiments and simulations is a promising approach for elucidating which properties of the time-varying ionic environment can shape the dynamics of a given circuit.

Key words

Neuronal oscillations • Synchrony • GABAergic transmission • Computational model • HCO_3^- permeability • Cl^- accumulation • Intrinsic currents

Introduction

Rhythm generation is an ubiquitous property of nervous systems. Oscillatory activity of a large number of neurons occurs throughout various brain areas and is thought to underlie several physiological functions ranging from sensory information processing to cognition and motor control (Hooper 2001, Ward 2003). In recent years, cortical neuronal oscillations have been the subject of intense investigation. The attention of many scientists has been attracted to a specific activity pattern characterized by a fast synchronous neuronal activity (30-

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80 Hz; with average 40 Hz). This so-called gamma rhythm has been proposed to be essential for "binding" of sensory object features into a coherent conscious percept (Engel and Singer 2001). Moreover, gamma oscillations are suggested to play an important role in memory processes and induction of spike timing-dependent synaptic plasticity (Paulsen and Sejnowski 2000, Buzsáki and Draguhn 2004).

Oscillatory network activity generally arises from complex interactions between synaptic and intrinsic membrane properties of neurons. Synaptic and cellular mechanisms are continuously being modified. One modulatory mechanism is the time-varying ionic environment. In our review, after summarizing general mechanisms of synchronous oscillations, we will be focusing on recent experimental and computational studies which suggest that activity-dependent changes of intra- or extracellular ionic (Cl^-, K^+) concentration may influence synaptic and/or intrinsic electrical properties of neurons and thereby produce significant changes in network dynamics.

Oscillation and synchrony

Synchrony and rhythmicity are two different but often simultaneously occurring phenomena. A system is *rhythmic (oscillatory)* if the variables expressing its state are *periodic* (Ermentrout 2001). An oscillating system repeatedly returns to its initial conditions. However, a rhythmic system does not necessarily have to be synchronous and *vice versa*. In an oscillatory network there may be many neurons firing at different times but with the same period. (A special case of "firing rate synchrony" in a network with sparsely and aperiodically firing cells is described below.) In such a circuit the synchrony would arise if cells were firing with a relative phase of zero. On the other hand, a synchronized group of neurons may produce aperiodic (arrhythmic) output. In spite of the different meaning of synchrony and oscillation, there is a close connection in the nervous system between the two phenomena and their mechanisms. Synchrony can be brought about by oscillation. The *oscillation-based synchrony* appears to be the most energy-efficient mechanism for temporal coordination of neural activity (Buzsáki and Draguhn 2004). Thus, a fundamental issue of neuroscience is to understand how *synchronous rhythms* emerge in brain networks.

General mechanisms of neural oscillations

In recent years it has been shown that neuronal networks have a variety of mechanisms that contribute to rhythmic activity. These mechanisms may be divided into two main groups. Oscillatory electrical activity (repetitive firing or bursting) can be produced by *intrinsic biophysical mechanisms in individual cells* or by *network mechanisms* (Fig. 1). The two mechanisms are not mutually exclusive. Neurons can be classified as endogenous or conditional oscillators. *Endogenous oscillators* have an intrinsic ability to display spontaneous oscillations in the absence of any input. *Conditional* oscillators can fire in a rhythmic pattern if they receive an appropriate synaptic input. If neurons respond maximally to inputs (or oscillate spontaneously) within a well-defined frequency window we say that they exhibit *frequency preference*. The frequencies at which the response to input currents is maximal can be identified by a peak in the impedance curve, i.e. a *resonance* (Hutcheon and Yarom 2000). If a neural rhythm is critically dependent on a group of cellular oscillators we call these *pacemakers*.

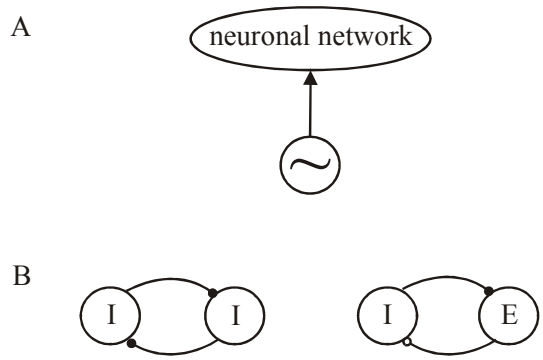

Fig. 1. *A.* Synchronous network oscillations can be induced by individual pacemaker cells carrying intrinsic oscillator properties. Pacemakers impose their own rhythm on the network. *B.* Network mechanisms of synchronous oscillations: chemical synapses may generate rhythmic network activity by reciprocal inhibition between interneurons (left) or feedback loop between excitatory and inhibitory subpopulations ('mixed' pyramidal-to-interneuron loop, right). Third possibility would be recurrent excitation between excitatory cells (not shown) but normal rhythms in cortical networks do not seem to depend on excitation alone. In addition to chemical transmission, electrical synaptic communication may promote synchrony in oscillating networks (not shown). E and I indicate groups of mutually connected excitatory and inhibitory neurons, respectively. Synaptic links that are important for mechanisms of synchronous oscillations are indicated by the connecting lines.

Mathematical analysis of 'reduced' neuronal models demonstrates that sustained oscillation of any kind needs two opposing processes: a fast autocatalytic (positive feedback) process and a slower restorative (negative feedback) process (Wang and Rinzel 1995). Rhythmic activity is generated if the two opposing processes alternatively dominate the system dynamics. *Fast autocatalysis* causes the rising phase and *slow negative feedback* produces the decay phase of the oscillatory cycle.

Cellular properties

In case of a *single cell* oscillation, positive feedback can be mediated by activation of inward (e.g. Na^+, Ca^{2+}) currents or cessation of outward (K^+) currents and negative feedback can be provided by either inactivation of inward currents or activation of outward currents. Hence, positive and negative feedback processes may comprise several components on different time scales that may endow neurons with various (endogenous or conditional) firing patterns including tonic repetitive firing or regular bursting (Canavier *et al.* 2001, Ramirez *et al.* 2004). Interestingly, a given set of ionic conductances can give rise to different discharge properties, depending on their relative strengths or their spatial distribution (Wang 2003, Prinz *et al.* 2004). On the other hand, computational modelling suggests that different combinations of intrinsic biophysical properties (and synaptic strengths) can generate very similar network activity patterns (Hooper 2004, Prinz *et al.* 2003).

Resonance in neurons arises from an interaction of passive (time-dependent low-pass filtering) and specific active (voltage-dependent high-pass filtering) membrane properties (Hutcheon and Yarom 2000, Pike *et al.* 2000). Importantly, the appropriate combination of low- and high-pass filtering mechanisms can give rise to resonators (band-pass filters), notch (band-stop) filters, and subthreshold oscillators that enable selecting inputs from a preferred frequency range (Buzsáki and Draguhn 2004).

It is often not possible to disentangle the cellular and network oscillatory mechanisms completely, because of their permanent interaction. Network dynamics is an emergent property of the *interplay between intrinsic and synaptic properties*. For example, whether a neuron is a pacemaker or not, is a result of the densities and kinetics of ionic channels that are continuously influenced by the synaptic and neuromodulatory 'milieu' (Ramirez *et al.* 2004). Thus, the contribution of pacemaker properties to the network activity pattern is not fixed but dynamically altered by heterogeneous mechanisms (Peña *et al.* 2004). There are several ways in which both network coupling and cellular mechanisms may give rise to rhythmic firing (Canavier *et al.* 2001). One example is a group of cells without intrinsic pacemaker properties that can be driven by phasic input from an endogenous oscillator neurons. Alternatively, synaptic inputs may 'tune' intrinsic properties of conditional oscillators so as to shift them into the oscillatory state. Even neuronal rhythms that are mainly driven by synaptic interactions (see below) may be enhanced by resonance mechanisms (Whittington and Traub 2003, Jonas *et al.* 2004).

Synaptic properties

The two opposing mechanisms of *oscillogenesis* can also be at work on a purely *network level*. For example, fast autocatalysis and slow negative feedback can be brought about by recurrent excitation and inhibition, respectively. Recent research has shed new light on details of synaptic mechanisms of oscillation-based *synchrony*. Basically, two synaptic network mechanisms of synchronization are possible: synchronization by chemical and/or electrical synapses. Given the two cell types in a neuronal circuit (excitatory principal neurons and inhibitory interneurons), three types of synchronization by chemical synapses may exist (Wang 2003) (Fig. 1B): recurrent excitation between excitatory cells, reciprocal inhibition between interneurons (interneuronal network model) and feedback loop between excitatory and inhibitory subpopulations ('mixed' pyramidal-to-interneuron loop model). However, computational and experimental studies indicate that normal synchronous rhythms in cortical networks do not depend on excitation alone, but rely critically on synaptic inhibition and/or on excitatory-inhibitory feedback loop (Wang and Rinzel 1993, Whittington *et al.* 1995, Wang and Buzsáki 1996, Fisahn *et al.* 1998, Traub *et al.* 2000; see also Fischer and Dürr 2003). In general, dynamics of a two-population network can be seen as a continuum between a purely interneuronal scenario and an excitatory-inhibitory loop scenario, depending on the relative degree and speed of excitatory transmission (Whittington *et al.* 2000, Traub *et al*. 2004, Brunel and Wang 2003, see below). In addition to chemical transmission, electrical coupling (*via* gap

junctions) between neuronal dendrites, as well as axons exists in the central nervous system. Electrical synaptic communication is known to be able to promote synchrony in oscillating networks (for review see Bennett and Zukin 2004). Neuronal modeling indicates that inhibitory and electrical synapses may act differently but synergistically to enhance neuronal synchronization (Kopell and Ermentrout 2004).

Structure always affects function. Therefore, network activity is affected not only by character and dynamics of synaptic connections but also by the synaptic coupling architecture (Strogatz 2001). An interesting hypothesis has recently been proposed that economical interneuronal wiring may be realized by so called 'small world' or 'scale-free' architecture (Buzsáki *et al.* 2004). Small world connectivity, characterized by a large number of local and a small population of long-distance interneurons (Barabási and Bonabeau 2003), could be an effective solution for synchrony-promoting network structure. Intriguingly, a new anatomical study has suggested that the mammalian dentate gyrus network is endowed with small world topology (Földy *et al.* 2005). Computer simulations show that specific changes in the network topology can contribute to transitions between different states of population activity (Netoff *et al.* 2004).

Inhibition-based oscillations

In vitro experiments (Whittington *et al.* 1995) suggest that interneuronal networks can sustain coherent gamma oscillations even when ionotropic excitatory postsynaptic potentials (EPSPs) are blocked (so called ING – interneuron network gamma). If the hippocampal interneurons in this pharmacologically isolated inhibitory network are tonically excited (e.g. by metabotropic glutamate receptor activation) they can entrain each other in ~40 Hz oscillation. Firing of a single uncoupled interneuron depends on the degree of tonic excitation as well as the duration of the relative refractory period. If the interneuron becomes synaptically coupled to other interneurons, its tonic firing is transformed into gamma rhythm by synchronous inhibitory postsynaptic potentials (IPSPs; cf. Fig. 2 in Whittington *et al.* 2000) mediated by $GABA_A$Rs. The ING model illustrates that synchronous oscillations with a specific frequency can be generated even without pacemaker cells carrying intrinsic oscillator properties (Jefferys *et al.* 1996, Fig. 1B). Computer simulations and experimental data suggested that the ING frequency depended, in part, on the size and time course of the $GABA_A$R-controlled conductance (Whittington *et al.* 1995, Traub *et al.* 1996, Wang and Buzsáki 1996). In more recent models, gap junctions and conduction delays were included and rapid IPSP decay time constants determined by paired recordings were used (Bartos *et al.* 2002). Coherent gamma oscillations were observed as an emergent result that depended on several factors, particularly the fast and large inhibitory conductance as well as the presence of conduction and synaptic delays. Bartos and colleagues argued that a fast inhibitory event, arriving with a specific delay, represents an effective synchronizing signal. Intriguingly, two theoretical studies supported the notion of delay-induced synchrony. Maex and De Schutter (2003) have shown that IPSP delay caused by axonal conduction and neurotransmission is a critical parameter for synchronization of inhibitory networks and the oscillation period of synchronously firing interneurons is approximately four times the IPSP delay. Likewise, quantitative analysis of dynamics in a noisy interneuron network has demonstrated that the oscillation period depends much more on the IPSP delay and rise time than on the decay time constant (Brunel and Wang 2003). Moreover, this study has expanded previous findings that *collective* synchronous oscillations can arise in noisy networks with stochastically and sparsely firing *individual* neurons (Brunel and Hakim 1999, Tiesinga and Jose 2000). Such a noise-dominated network displays so called "firing rate synchrony" (i.e. in each cycle, only a proportion of the cell population discharges) compared to the "spike-to-spike" synchrony that occurs in a low-noise network with single cells firing at rates similar to the collective rhythm frequency (Brunel and Wang 2003). Fast oscillations with irregular and rare discharges of single cells have been observed experimentally (Fisahn *et al.* 1998).

The ING oscillation reveals the synchronizing potential of reciprocal synaptic inhibition. However, its physiological meaning is not clear since in real networks both excitatory and inhibitory neurons usually contribute to the output activity. As already mentioned, another possible network mechanism for synchronous oscillations is the excitatory-inhibitory feedback loop that can lead to the so called PING (pyramidal-interneuron network gamma) oscillation (Whittington *et al.* 2000). In the PING model a rhythmic pattern emerges from the interplay between excitatory pyramidal neurons and interneurons. ING and PING mechanisms are not mutually exclusive but rather cooperative. Brunel and Wang (2003) have shown that in a noisy network

composed of both interneurons and principal neurons, excitatory connections tend to reduce network frequency and inhibitory connections tend to increase network frequency. Besides the balance between excitatory and inhibitory loops, the behavior of a two-population network depends on the ratio of excitatory and inhibitory synaptic time constants (Brunel and Wang 2003). Hence, in contrast to a purely inhibitory network (with irregularly and sparsely firing neurons), in a mixed network the synaptic decay time constants play a critical role in determining network activity.

Thus, interneuronal networks seem to play a crucial role in governing rhythmogenesis and synchronization. However, the emerging picture of the precise manner of interneuron involvement in diverse rhythms is "far more complex than originally suspected" (Whittington and Traub 2003) and many questions remain to be elucidated. For example, there is a broad spectrum of interneuron subtypes in the hippocampus and neocortex (McBain and Fisahn 2001). Different subclasses of hippocampal interneurons appear to participate in specific ways in different types of neuronal oscillations depending on the spatio-temporal compartmentalization of their input to principal cells (for summary of recent findings see Whittington and Traub 2003, Somogyi and Klausberger 2005, Mann *et al.* 2005).

Given the important role of inhibitory synapses for oscillogenesis and synchronization in cortical networks, it is important to know the mechanisms underlying various changes of GABAergic activity, including changes due to activity-dependent alteration of ion concentrations, in particular the intracellular Cl^- concentration ($[Cl^-]_i$).

Ionic plasticity of inhibitory transmission

In the adult mammalian nervous system, brief activation of postsynaptic $GABA_A$Rs leads to a fast hyperpolarization. In contrast, prolonged or repetitive activation of $GABA_A$Rs may evoke biphasic postsynaptic responses consisting of an initial hyperpolarization followed by a delayed depolarization. These biphasic GABA responses have been observed in several brain areas (see references in Staley and Proctor 1999). The depolarizing phase is strongly dependent on the HCO_3^- permeability of the $GABA_A$Rs. $GABA_A$ reversal potential (E_{GABA}) is determined by the reversal potentials of two anions, Cl^- and HCO_3^- (E_{Cl}, E_{HCO3}). According to Cl^- accumulation hypothesis (Kaila and Voipio 1987, Staley *et al.* 1995, Backus *et al.* 1998, Dallwig *et al.* 1999, Frech *et al.* 1999), Cl^- flux mediated by intensely activated $GABA_A$Rs or glycine receptors can substantially increase $[Cl^-]_i$ so that E_{Cl} is shifted in the positive direction (towards resting membrane potential, E_{rest}). Because of enzymatic regeneration (mediated by carbonic anhydrase, CA), the HCO_3^- gradient (E_{HCO3} ~ -10 mV) does not significantly change. As a consequence, E_{GABA} may become more positive than E_{rest}, changing the GABAergic response to depolarization. As an alternative or additional mechanism, HCO_3^--dependent extracellular potassium accumulation driven by network activity can evoke or enhance the depolarizing response by both direct membrane depolarization and reduction of Cl^- extrusion (Kaila *et al.* 1997). Another possible mechanism is that the depolarization arises from activation of a subset of $GABA_A$Rs with higher HCO_3^- permeability (Perkins and Wong 1996, Perkins 1999). Moreover, in neocortical pyramidal neurons *monophasic* depolarizing $GABA_A$ responses were observed that are due to the very negative E_{rest} (Gulledge and Stuart 2003). However, since E_{rest} *in vivo* is more positive as compared to *in vitro* situations (Paré *et al.* 1998, Bindman *et al.* 1988), these depolarizing $GABA_A$ responses might be a rather unphysiological situation *in vivo*. Some experimental and computational data indicate that in neuronal compartments receiving intense GABAergic inputs, $GABA_A$-mediated Cl^- accumulation may generate depolarization even if the GABAergic activity is not accompanied by large extracellular K^+ transient (Dallwig *et al.* 1999, Staley and Proctor 1999, Bracci *et al.* 2001, Jedlička and Backus 2005).

Acute E_{GABA} shift induced by Cl^- accumulation is an example of a short-term, ionic plasticity of GABAergic transmission (Rivera *et al.* 2005). Cl^- concentrations in neurons undergo both short- and long-lasting changes caused by activity-dependent ionic shifts and developmental changes in the expression of proteins (e.g. carbonic anhydrase, K^+-Cl^- cotransporter KCC2 and Na^+-K^+-$2Cl^-$ cotransporter NKCC1), respectively (Rivera *et al.* 2005, Yamada *et al.* 2004). Interestingly, in hippocampal pyramidal cells, a use-dependent E_{GABA} shift occurs in a compartment-specific manner. Selective activation of the dendritic $GABA_A$Rs can evoke significant depolarizing (even strongly excitatory) responses whereas perisomatic stimulation leads to much less positive E_{GABA} shift (Jackson *et al.* 1999, see also Vreugdenhil *et al.* 2005). Larger conductance/volume ratio in dendrites may enhance GABA-induced Cl^-

accumulation and depolarization (Staley and Proctor 1999). In pyramidal cells, simultaneous activation of their perisomatic and dendritic GABAergic inputs generates hyperpolarizing or moderately depolarizing postsynaptic responses that are usually inhibitory in nature. In contrast, in CA3 (stratum pyramidale-oriens) interneurons, hyperpolarizing GABAergic responses rapidly switch to depolarization (and usually excitation) after coincident perisomatic and dendritic stimulation (Lamsa 2000, Lamsa and Taira 2003). The difference between interneurons and pyramidal cells is hypothesized to be accounted for by differences in distribution or activity of anion transporters and/or CA. Kuner and Augustine (2000) have demonstrated that activation of $GABA_A$ inputs can bring about a local increase of $[Cl^-]_i$ that can spread into nearby regions of the cell and shift E_{GABA}. Thus, in addition to global changes of Cl^- concentration, local (compartmental, subcompartmental or even microdomain) alterations of $[Cl^-]_i$ may play either physiologically or pathophysiologically relevant roles (c.f. Hull and von Gersdorff 2004, Vreugdenhil *et al.* 2005). However, in comparison to intracellular Ca^{2+} concentration, in computational modeling, little attention has been paid to the dynamics of $[Cl^-]_i$ changes in neurons. Recently a model of $GABA_A$ synapses has been developed that can be inserted into neuronal models with detailed morphology. It can be used to simulate and analyze the interplay of various factors (e.g. localization of synapses, compartment size, frequency of $GABA_AR$ activation, $GABA_AR$ kinetics, Cl^- extrusion rate, diffusion of Cl^-, HCO_3^- permeability) that contribute to the spatial and temporal dynamics of $[Cl^-]_i$ and E_{Cl} (Jedlička and Backus 2005).

Insights into the mechanisms of E_{GABA} shift are important for a better understanding of a number of physiological and pathophysiological phenomena like spike timing-dependent synaptic plasticity (Woodin *et al.* 2003), neuronal discharges related to learning (Sun *et al.* 2001), epilepsy (Perez Velazquez 2003, Khalilov *et al.* 2003), addiction (Laviolette *et al.* 2004), pain (Coull *et al.* 2003) and oscillatory neuronal activity in general.

Activity-dependent E_{GABA} shift and network oscillations

As discussed above, hyperpolarizing IPSPs (hIPSPs) are considered to be essential for synchronous oscillations. Hence, it is reasonable to expect that depolarizing E_{GABA} shift in pyramidal dendrites and interneurons can affect network dynamics. Indeed, several experimental studies support this idea. Lamsa and Taira (2003) have found that an activity-dependent switch from hyperpolarization to depolarizing PSPs (dPSPs) at mature $GABA_A$ synapses is able to drive the local (pharmacologically isolated) CA3 interneuron network to massive population bursting. Surprisingly, these GABAergic bursts display short (duration ~ 500 ms) synchronous oscillations in the beta-gamma range. Thus, synchronous gamma rhythms can be generated in the CA3 interneurons although their $GABA_A$ coupling is depolarizing. This indicates that transient synchronous oscillations during bursts are produced by some mechanism other than generation of hIPSPs-based ING. Lamsa and Taira (2003) have shown that the rhythmicity in their interneuron network is dependent on gap junctions. They suggest that the degradation of the hIPSPs sets the temporal limits of an interneuron to participate in hIPSPs-mediated beta-gamma oscillations and promotes its involvement in dPSPs-dependent synchronous bursts of electrically coupled interneuron population. Interestingly, rhythmic activity in the thalamic reticular nucleus has also been attributed to depolarizing $GABA_A$ synapses (Bazhenov *et al.* 1999). Theoretical study by Rinzel *et al.* (1998) has shown that small changes in E_{GABA} may result in depolarization-mediated waves of activity in a network model of mutually connected inhibitory neurons exhibiting postinhibitory rebound. GABAergic inputs and intracellular/extracellular Cl^- concentration changes were shown to modulate synchronous neuronal activity in cells from several brain regions (Jarolimek *et al.* 1996, Hochman *et al.* 1999, Nakanishi and Kukita 2000, Marchetti *et al.* 2005).

Thus, E_{GABA} plasticity can influence the neural circuit behavior in complex and sometimes counterintuitive ways. However, the activity- and time-dependent changes of E_{GABA} are usually not incorporated in present models of oscillatory neural networks. Implementation of Cl^- dynamics in network models might bring novel insights into the synaptic and ionic mechanisms of synchronization and oscillogenesis. For example, the impact of E_{GABA} dynamics on network output can be investigated in a hippocampal ING-model (Bartos *et al.* 2002) by replacing $GABA_A$ synapses with constant reversal potential by synapses with adjustable Cl^- accumulation. In such a modified network model, consisting of single compartment interneurons, a sufficiently large positive E_{GABA} shift induces increase in

oscillation frequency and decrease in synchrony (Jedlička and Cuntz, unpublished). The simulations suggest that E_{GABA} change and subsequent disruption of hIPSPs-based gamma oscillation can be prevented by mechanisms that attenuate Cl^- accumulation in neurons (e.g. synaptic depression, faster $GABA_A$ conductance, rapid Cl^- pumps, placement of synaptic inputs to regions with small conductance/volume ratio). Providing the morphological and functional diversity of GABAergic cells, it is probable that the inclusion of various interneuron subtypes with specifically (perisomatically, dendritically, axo-axonic) targeting chemical and electrical synapses in cortical network models will reveal new network patterns with computationally rich properties.

Activity-induced $GABA_A$-mediated depolarization and excitation of interneurons may be an important antiepileptic mechanism since its overall consequence is disinhibition of interneuron network activity and enhanced inhibition of the glutamatergic principal neurons (Lamsa 2000). However, although E_{GABA} is usually more stable in pyramidal cells (Lamsa and Taira 2003), under certain conditions (e.g. tetanic stimulation) it can become excitatory and lead to epileptic-like neuronal discharges (Jefferys 2003). Thus, GABA activated $[Cl^-]_i$ plasticity may contribute also to pathological synchronous rhythms. In the hippocampal CA1 region, excitatory $GABA_A$R-mediated inputs participate in generation of slow posttetanic depolarization and subsequent seizure-like rhythmic activity (so-called afterdischarge, Taira *et al.* 1997, Fujiwara-Tsukamoto *et al.* 2003, 2004). The depolarization is partly due to $GABA_A$-mediated Cl^- accumulation in pyramidal neurons (Bracci *et al.* 2001, Isomura *et al.* 2003). Interestingly, the slow depolarization often carries gamma oscillations (Bracci *et al*. 1999) thus suggesting a transition link between tetanically-induced gamma oscillations and epileptic-like activity (Köhling *et al.* 2000, Jefferys 2003). Several other studies also indicate that GABA-mediated depolarization can contribute to epileptogenesis (c.f. Cohen *et al*. 2002, Perez Velazquez 2003, Kantrowitz *et al.* 2005, for review see Cossart *et al.* 2005).

Ionic environment and intrinsic conductances

Changes of ionic environment may affect network behavior not only through modulation of synaptic transmission but also by modification of intrinsic currents in neurons. It is known that alteration of the extracellular potassium concentration ($[K^+]_o$) can have an immense impact on different ionic channels conductances and thereby on the activity in neural circuits. For example, integrated experimental and computational approach of Bazhenov et al. (2004) illustrates how an increase of $[K^+]_o$ can generate periodic network bursting by modulating several intrinsic currents. In their neocortical network model that includes pyramidal cells and interneurons, $[K^+]_o$ is explicitly computed based on K^+ currents, K^+ pumps, glial buffering and lateral K^+ diffusion. The simulations indicate that a local $[K^+]_o$ increase (due to excessive neuronal firing or impaired K^+ regulatory system) along with lateral K^+ diffusion between neurons is able to promote paroxysmal rhythmic activity in the entire network. Furthermore, the model predicts that paroxysmal discharges after the elevation of $[K^+]_o$ depend on the cooperative effects of a few intrinsic conductances including persistent Na^+ current, high-threshold Ca^{2+} current and hyperpolarization-activated depolarizing current.

Conclusional remarks

Converging evidence from experimental and theoretical studies indicates that activity-dependent changes of ionic environment affect both the synaptic and intrinsic properties which shape the actual behavior of the neural network. Neural circuits are nonlinear systems exhibiting wide range of activity patterns that may be either highly variable and sensitive to slight parameter perturbations or, conversely, surprisingly stable and robust. Iterative interaction between experiments and simulations (Noble 2002) is a way to discover which details of synaptic transmission and cellular biophysics do matter for the dynamics of a given circuit. Recent studies suggest that short-term plasticity of inhibitory synapses, based on their Cl^- and HCO_3^- permeability, can have important implications for the mechanisms of physiological and pathological neuronal rhythms.

In view of nonlinear dynamics, synchronous oscillations represent a form of spontaneous order in time (Strogatz 2003). Thus, study of mechanisms underlying synchronization of brain rhythms contributes to our understanding how order emerges from the interaction of a vast number of dynamic elements.

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Note added in proof: Recently there have been published three new computational studies that investigate the complex role of E_{GABA} in network synchronization (Jeong and Gutkin 2005, Stiefel *et al.* 2005, Vida *et al.* 2005)