The Influence of Slow Calcium-Activated Potassium Channels on Epileptiform Activity in a Neuronal Model of Pyramidal Cells

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Abstract

An imbalance between excitation and inhibition can play an important role in the generation of epileptiform activity. Experimental evidence indicates that alterations of either synaptic activity or intrinsic membrane properties may contribute to this imbalance. The slow Ca^{2+} - activated K^+ currents (sI_{AHP}) limit neuronal firing rate and excitability and are therefore of great interest for their potential role in epileptogenesis. The sI_{AHP} is found in both excitatory and inhibitory neurons, and its effect on these neurons can influence the network behavior. Simulations show that the increased excitability caused by reduction of inhibition by the sI_{AHP} for inhibitory interneuron generates recurrent bursting activity.

Background and Significance

Neuronal hyperexcitability and epileptiform activity are associated with an imbalance between excitatory and inhibitory synaptic activity and/or alterations of neuronal intrinsic properties (Bernard et al., 2000; During et al., 1995; Olsen and Avoli, 1997; Treiman, 2001). GABAergic inhibition controls neuronal excitability in such a way that a change in GABAergic inhibition is thought to be important for many forms of human or experimental epilepsy (Bernard et al., 2000; Freund and Buzsáki, 1996; Prince, 1978; Treiman, 2001). There is evidence from *in vitro* experiments that reduced GABAergic inhibitory synaptic activity (Federico and MacVicar, 1996; McBain, 1994; Rodriguez-Moreno et al., 1997; Wong and Miles, 1994) or increased glutamatergic excitatory synaptic activity (Federicon and MacVicar, 1996; Johnston and Brown, 1981; Traub et al., 1993) leads to epileptiform activity.

The array of potassium channels expressed by a neuron is a major factor in determining its excitability. Studies of human epileptic hippocampus indicate that changes in the properties of some potassium channels may contribute to neuronal hyperexcitability and epileptogenesis (Beck et al., 1996; Biervert et al., 1998). The slow Ca^{2+}- activated K^+ current (sI_{AHP}) mediates the post-spike after hyperpolarization (AHP) that limits excitability of pyramidal neurons (Alger and Nicoll, 1980; Behr et al., 2000; Empson and Jefferys, 2001; Verma-Ajuja et al., 1995). Alger and Nicoll (1980) suggested that the Ca^{2+}- dependent K^+ current is important in preventing the development of seizure-like activity. In addition, Empson and Jefferys (2001) suggested that Ca^{2+} entry through L-type Ca^{2+} channels activates a K^+ current that helps terminate epileptiform activity.

While the studies summarized above suggest that sI_{AHP} controls the excitatory output of neuronal networks by altering intrinsic neuronal excitability, an unknown factor in these experiments is the role of interneurons. Interneurons also control the excitatory output of networks by providing feedback inhibition onto excitatory neurons. Interneurons, like pyramidal neurons, possess sI_{AHP} (Zhang and McBain, 1995; McQuiston and Madison, 1999). In contrast to pyramidal neurons, reducing sI_{AHP} and thereby increasing excitability in inhibitory interneurons would be expected to reduce rather than enhance the overall excitability of the network. When this added complexity is considered, it becomes less clear how various modulators may affect network behavior.

Experiments employing simultaneous intracellular recordings of pyramidal neurons and interneurons to determine how changes in sI_{AHP} may correlate with epileptogenesis would require a universally accepted model of epilepsy and the capability to perform complex data analysis. This type of experiment may be modeled using a small network of pyramidal cells and an

interconnected inhibitory interneuron. Using the computational approach will allow the simultaneous monitoring of individual neurons' membrane behavior as well as the behavior of the entire network. In addition, the individual conductance on each cell membrane can be modified and the resulting effect on network behavior tested. In this way, a carefully controlled study of the role of sI_{AHP} and its modulation in epileptogenesis can be performed. The results of this study may guide the design of biological experiments to verify where alterations or abnormal regulation of these important channels may occur in epilepsy, and may suggest key targets for therapeutic intervention.

Methods

We have built a circuit pyramidal cell model using the simulation software GENESIS (http://www.genesis-sim.org/GENESIS/). Three simplified pyramidal neurons and an interneuron later added are modeled in this study: two neurons synaptically connected with excitatory synapses forming a loop (neuron 1 and neuron 2 in Fig. 1), a neuron where random input is applied to generate action potentials (neuron 0 in Fig. 1), and an inhibitory interneuron (neuron 3 in Fig. 1) in a negative feedback loop with one of the modeled pyramidal neurons (neuron 2 in Fig. 1).

The generated action potentials stimulate one of the other neurons (neuron 1 in Fig. 1), which is connected to the other one (neuron 2 in Fig. 1) with an excitatory synapse as a recurrent loop. The synaptic inputs on each main dendrite of two pyramidal neurons are connected with an excitatory synapse (Fig. 1A). An inhibitory interneuron (neuron 3 in Fig. 1) forms a negative feedback loop with one of the two pyramidal neurons (neuron 2 in Fig. 1). This inhibitory interneuron synapses on the main dendrites of neuron 2 (Fig. 1B).

Each pyramidal neuron with 17 compartments is comprised of a soma, a main dendrite, and two branch dendrites. The soma and dendrite have a fast sodium (I_{Na}), delayed potassium (I_{KDR}), transient potassium (I_A), high-threshold calcium (I_{Ca}), and slow calcium activated potassium (sI_{AHP}) channels, and a short-duration voltage and calcium dependent potassium channel (I_{KC}). The equations for these channels are the same as in the Traub et al. (1991, 1994) multicompartmental CA3 pyramidal cell model. In this model the soma, main, and branch dendrites have excitatory and inhibitory synaptic channels, which connect two neurons as a loop. The soma and dendrites have a fast GABAergic inhibitory synapse and a slow GABAergic inhibitory synapse. The kinetics of these fast and slow GABAergic components are the same as for $GABA_A$ inhibitory and $GABA_B$ inhibitory synapses, respectively, in a model of piriform cortex pyramidal cells (Protopapas et al., 1998). The inhibitory interneuron has a soma with the

same channels as in the soma of two neurons synaptically connected with excitatory synapses. The soma, main, and branch dendrites have excitatory and inhibitory synaptic channels, which connect two neurons in a loop. The parameters for these excitatory and inhibitory synaptic conductance and cellular dimensions of the soma and dendrites are the same as in the reduced models of piriform cortex pyramidal cell in Protopapas et al. (1998).

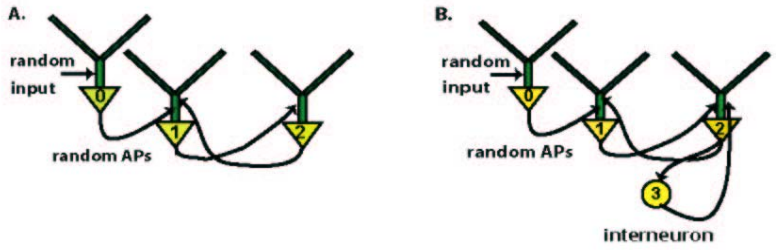

Figure 1. Schematic representation of neural connections. A. Neuron 1 and neuron 2 are connected with an excitatory synapse as a loop. Synaptic inputs are on the main dendrite of these two neurons connected with an excitatory synapse. B. An inhibitory interneuron in a negative feedback loop with the modeled pyramidal neuron 2 is added to the circuit in A. This inhibitory interneuron synapses on the main dendrite of neuron 2.

The synaptic connection between neurons is modeled by a synaptic channel, I_{syn} (Bhalla and Bower, 1993). The synaptic conductance is modeled as an alpha function with the maximum value of 0.5 nS. The synaptic weight represents the overall strength of a connection and the synaptic delay represents all delays between neurons. Simulations were performed for 10 sec using GENESIS version 2.2 on a LINUX operating system. The simulation time step is 0.05 ms, which is the same value as in the Traub et al. (1991, 1994) multicompartmental CA3 pyramidal cell model provided with GENESIS.

In order to examine the role of the sI_{AHP} on bursting activity caused by the increased excitability, simulations were performed with different values of the maximum conductance of the sI_{AHP} for the inhibitory interneuron. The synaptic weight and delay of the excitatory neuron sufficient to generate bursting activity without the inhibitory interneuron were used. For the inhibitory interneuron, the synaptic weight and delay that completely block bursting activity were used. Then with these synaptic weight and delay of the excitatory neuron and inhibitory interneuron, simulations were run for different values of the maximum conductance of the sI_{AHP}. The maximum conductance of the sI_{AHP} for the inhibitory interneuron, which synapses on the excitatory neuron in a negative feedback, was varied to investigate bursting activity caused by the increased excitability provided by reduced inhibition.

Results

In previous studies, we have demonstrated that a simplified pyramidal neuron model can produce bursting activity by changing the synaptic connectivity represented by the synaptic weight and delay in a circuit pyramidal cell model with neuronal connections as illustrated in Fig. 1 (Yang et al., 2001 and 2002). Figure 2 shows that bursting activity can be generated without the inhibitory interneuron. Figure 3 shows that bursting activity can be completely blocked by the inhibitory interneuron. We chose the synaptic weight and delay of the excitatory neuron, which generate bursting activity without the inhibitory interneuron, shown in Fig. 2. The synaptic weight and delay of the inhibitory interneuron, which completely block bursting activity shown in Fig. 3, were also chosen for the further simulations.

The present study with this circuit pyramidal cell model indicates that the sI_{AHP} of the inhibitory interneuron regulates bursting activity. Figures 4 and 5 show that the increased activity of the sI_{AHP} regenerates bursting activity. When the maximum conductance of the sI_{AHP} for the inhibitory interneuron, which synapses on the main dendrite of the excitatory neuron 2, is increased from 35.0 nS to 52.5 nS (50 % increase) bursting activity is regenerated (Fig. 4). Duration of the burst is 1.03 sec. When the maximum conductance of the sI_{AHP} for the inhibitory interneuron is increased to 70.0 nS (100% increase), recurrent bursting activity is also generated (Fig. 5). Duration of the burst is 1.23 sec, which is longer than in Fig. 4. The increased maximum conductance of the sI_{AHP} for the inhibitory interneuron produces reduction of inhibition of the negative feedback that results in the increased neuronal excitability of the pyramidal neuron. Then this increased excitability regenerates epileptiform activity in the pyramidal neuron. The duration of the burst is increased as the maximum conductance of the sI_{AHP} for the inhibitory interneuron increases.

In conclusion, simulations show that the slow Ca^{2+}-activated K^+ current (sI_{AHP}) regulates bursting activity in pyramidal neurons. The increased excitability caused by reduction of the inhibition provided by the sI_{AHP} for inhibitory interneuron generates recurrent bursting activity. The present study may provide the basis for future investigations into the cellular mechanisms of epilepsy.

A: The generated action potentials in neuron 0 in Fig. 1 from random inputs. B: The patterns of bursting activity in neuron 1 in Fig. 1. C: The patterns of bursting activity in neuron 2 in Fig. 1.

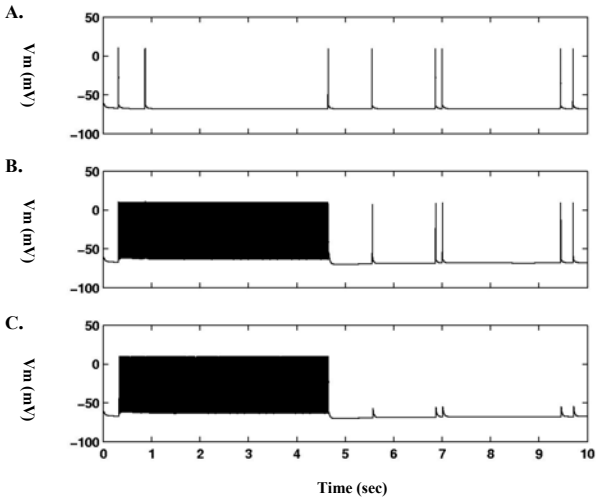

Figure 2. Traces of membrane potentials for all neurons. Bursting activity occurs in neuron 1 and neuron 2 when there is no inhibitory interneuron in the circuit pyramidal cell model (Fig. 1A).

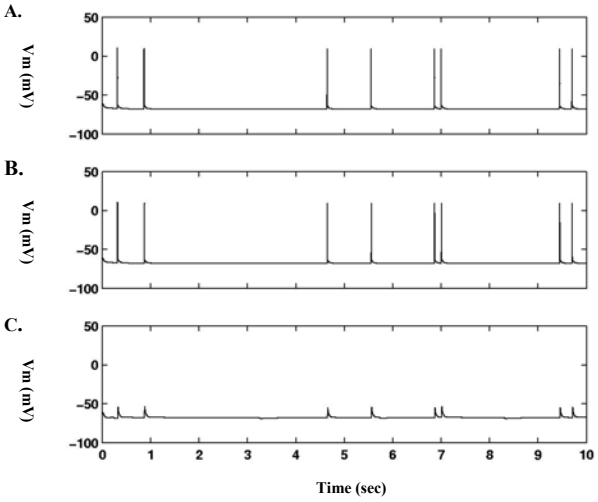

Figure 3. Traces of membrane potentials for all neurons. The excitatory synaptic weight and delay are the same as in Fig. 2. When the inhibitory interneuron is added to the excitatory neuron, inhibition blocks bursting activity in neuron 1 and neuron 2 (Fig. 1B).

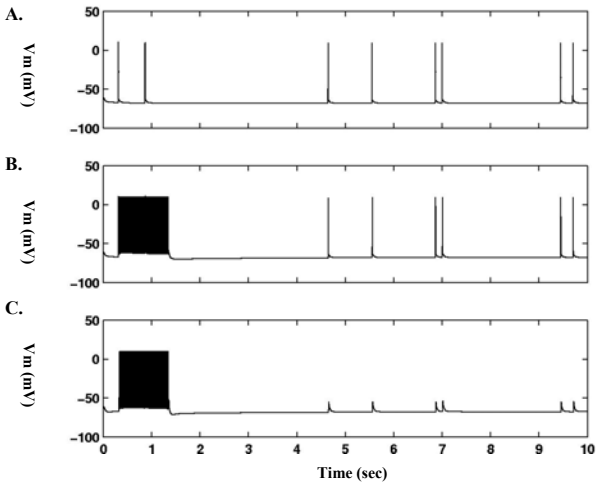

Figure 4. Traces of membrane potentials for all neurons. When the maximum conductance of the sI_{AHP} for the inhibitory interneuron is increased from 35.0 nS to 52.5 nS (50 % increase) with the same synaptic weight and delay of the excitatory and inhibitory neurons as in Fig. 3, recurrent bursting activity is generated in neuron 1 and neuron 2. Duration of the burst is 1.03 sec.

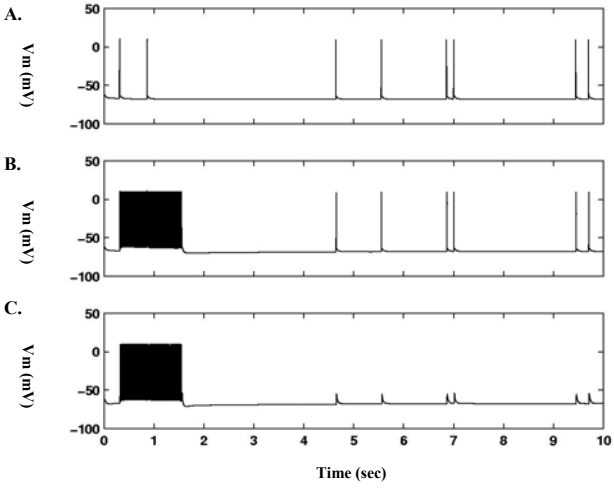

Figure 5. Traces of membrane potentials for all neurons. When the maximum conductance of the sI_{AHP} for the inhibitory interneuron is increased from 35.0 nS to 70.0 nS (100 % increase) with the same synaptic weight and delay of the excitatory and inhibitory neurons as in Fig. 3, recurrent bursting activity is generated in neuron 1 and neuron 2. Duration of the burst is 1.23 sec.

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