The Effect of Changes in the Inhibitory Interneuron Connectivity on the Pattern of Bursting Behavior in a Pyramidal Cell Model

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Abstract

Inhibitory interneurons play crucial roles in the regulation of patterns of activity in the hippocampus, and some types are thought to be vulnerable in epilepsy. The connections between excitatory and inhibitory synapses are important for generation of bursting activity in pyramidal neurons. The present study investigates the influences of changes in the connectivity of interneurons on the patterns of bursting in several excitatory connections using a multicompartmental pyramidal cell model. Simulations show that bursting activity depends upon changes in the connectivity of the inhibitory interneuron, and the location of the inhibitory synapses on excitatory neurons.

Key words: Experimental models of epilepsy; Bursting activity; Pyramidal neuron; Interneuron

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1 INTRODUCTION

Researchers have suggested that the connections between excitatory and inhibitory synapses are important for generation of bursting activity in pyramidal neurons (5; 10). Lamsa et al. (2000) examined the relative contributions of AMPA and $GABA_A$ receptors in network activity of CA3-CA1 pyramidal cells in the newborn rat hippocampus slices. They suggested that interneurons with synaptic $GABA_A$ synapses inhibit AMPA-R-mediated bursting activity in their slices. Velazquez and Carlen (1999) demonstrated that spontaneous bursting activity could be caused by excitatory inputs and GABAergic interactions among interneurons.
GABAergic inhibition has been investigated in human epilepsy and experimental models of epilepsy in a number of laboratories (1; 3; 4; 7). Cossart et al. (2001) demonstrated in their experimental models of epilepsy that spontaneous GABAergic inhibition is increased on the soma but reduced in the dendrites of pyramidal neurons. Such an increase of somatic inhibition could reduce epileptiform activity. In recent study, changes in the distribution and connectivity of interneruons in the epileptic dentate gyrus have been investigated (6). Magloczky et al. (2000) suggested that the distribution, morphology and synaptic connections in the epileptic human dentate gyrus differ from controls. This alteration of inhibitory interneurons in the epileptic human dentate gyrus is related to the balance between the excitatory and inhibitory inputs in the region.
The aim of this study is to investigate the influences of changes in the connectivity of inhibitory interneuron on the patterns of bursting in several excitatory connections in a neuronal circuit model of pyramidal cells. Several types of potential connections between two synaptically connected neurons with excitatory synapses are investigated. Then the inhibitory connection and the location of the inhibitory synapse are studied on those excitatory connections to investigate the effect of changes in the balance between excitatory and inhibitory synaptic connections.

2 METHODS

A reduced pyramidal model is built using the simulation software GENESIS (http://www.genesis-sim.org/GENESIS/). Three simplified pyramidal neurons and an interneuron are modeled in this study: two neurons synaptically connected with excitatory synapse as 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

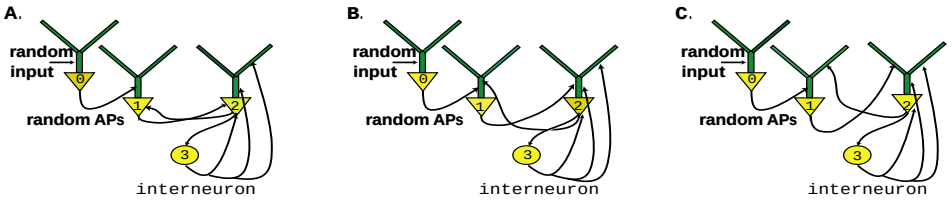

Fig. 1. Schematic representation of neural connections. There are several types of potential connections between two neurons connected with excitatory synapses. An inhibitory interneuron in a negative feedback loop with one of the modeled pyramidal neurons is added to these potential connections. This inhibitory interneuron then synapses on the soma, main dendrites, or branch dendrites of the modeled pyramidal neurons. A. Synaptic inputs are on the soma of two neurons. B. Synaptic inputs are on the main dendrite of two neurons. C. Synaptic inputs are on the branch dendrite of two neurons.

1 in Fig 1) which is connected to the other one (neuron 2 in Fig 2) with an excitatory synapse as a recurrent loop. There are several types of potential connections between two synaptically connected neurons with excitatory synapses. These potential connections include synaptic inputs on the soma, synaptic inputs on the main dendrite, and synaptic inputs on the neuronal branch dendrite of the two neurons, (Fig1A-1C). An inhibitory interneuron in a negative feedback loop with one of the two pyramidal neurons is added to those several potential connections. This inhibitory interneuron then synapses on the soma, main dendrites, or branch dendrites of the modeled pyramidal neurons (Fig. 1A-1C). Each cell is comprised of a soma, a main dendrite, and two branch dendrites, modeled with 15 compartments. The same channels in the soma of the Traub et al. (1991, 1994) multicompartmental CA3 pyramidal cell model are used in this study. In addition to those channels, the soma has a $GABA_A$ inhibitory synapse, which has relatively fast kinetics. The main and branch dendrites have an excitatory and a $GABA_B$ inhibitory synapse, which has much slower kinetics than $GABA_A$. The inhibitory interneuron has a soma with the same channels as in the soma of two neurons synaptically connected with excitatory synapses. The synaptic connection between neurons is modeled by a synaptic channel, Isyn (2). The synaptic conductance is

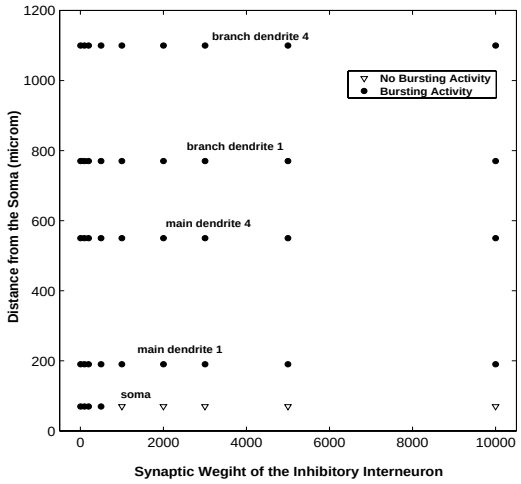

Fig. 2. Influence of the location and weight of the inhibitory synaptic connection on the pattern of bursting activity when synaptic inputs are on the soma of two connected neurons with excitatory synapse (Fig 1A). The synaptic weight and delay for the excitatory synapse are 950 and 5 msec, which generate the bursting activity with no inhibitory interneuron, respectively. The synaptic delay of the inhibitory interneuron is 5 msec. When interneuron synapses on the only soma of one of the two neurons connected with excitatory synapse there is no bursting activity if the synaptic weight of interneuron is larger than 900.

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. Interspike interval (ISI) analysis was used for examination of bursting patterns to define a burst. Simulations were performed for 10 sec using Genesis version 2.1 on a LINUX operating system. The simulation time step was 0.05 msec which is the same value in the Traub et al. (1991, 1994) multicompartmental CA3 pyramidal cell model provided with GENESIS.

3 RESULTS

The effect of inhibition is stronger when the synaptic inputs are close to the soma of the excitatory neurons. The synaptic weight of the interneuron has to be increased to produce the same effect if the inhibitory synapse is on the main or branch dendrites. When the synaptic inputs are on the soma of the two neurons connected with an excitatory synapse (Fig. 1A) inhibition affects on bursting activity only if interneuron synapses on the soma of one of the two neurons connected with excitatory synapse (Fig. 2). Figure 3 shows that when the synaptic inputs are on the main dendrite of the two neurons connected

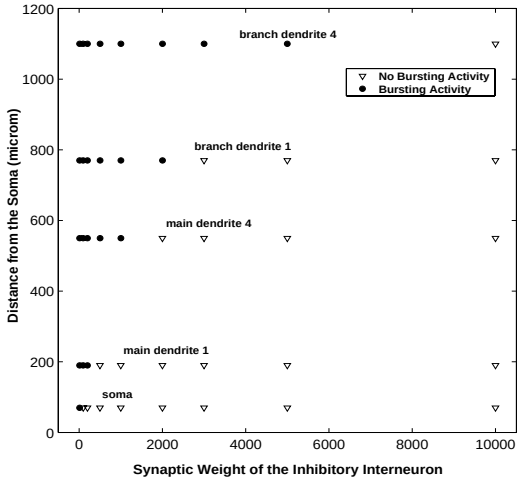

Fig. 3. Influence of the location and weight of the inhibitory synaptic connection on the pattern of bursting activity when synaptic inputs are on the main dendrite of two connected neurons with excitatory synapse (Fig 1B). The synaptic weight and delay for the excitatory synapse are 950 and 5 msec, which are the same as in Fig. 2, and generate the bursting activity with no inhibitory interneuron, respectively. The synaptic delay of the inhibitory interneuron is 5 msec. The inhibitory effect is stronger when the inhibitory synapse is close to the soma. The synaptic weight of interneuron needs to be increased to produce the same effect when the inhibitory synapse is on the main or branch dendrite.

with excitatory synapses (Fig. 1B), the inhibition effect is stronger when interneuron synapses on the soma than dendrites of one of excitatory neurons. Figure 4 also shows that the inhibition effect is stronger if the interneuron synapses on the soma than on the dendrites of one of the excitatory neurons when the synaptic inputs are on the branch dendrite of the two neurons connected with an excitatory synapse (Fig. 1C). The alteration of the synaptic weight of interneurons for busting activity is likely to be compensatory changes in excitatory synaptic inputs. The synaptic weight has to be increased as excitatory synaptic inputs move close to the soma in order to produce the same effect of inhibition. The values of median and standard deviation of interspike intervals (ISIs) are used to determine bursting activity including no bursting activity and repetitive bursting activity (results not shown).

4 CONCLUSIONS

Simulations show that bursting activity depends upon the synaptic weight and synaptic delay of the inhibitory interneuron and changes in the connectivity of the excitatory neuron as well as the inhibitory interneuron in a pyramidal cell

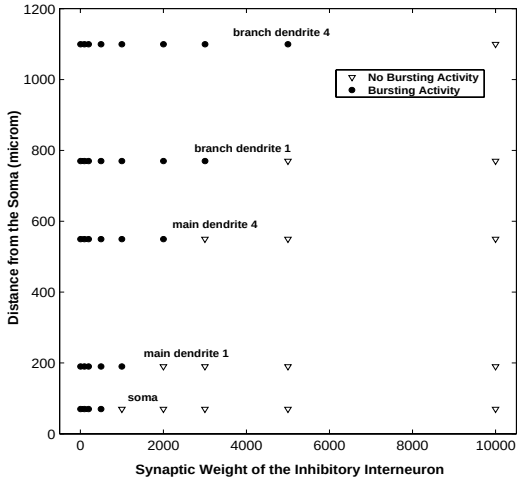

Fig. 4. Influence of the location and weight of the inhibitory synaptic connection on the pattern of bursting activity when synaptic inputs are on the branch dendrite of two connected neurons with excitatory synapse (Fig 1C). The synaptic weight of the excitatory synapse is increased to 9000 and the delay of the excitatory synapse is 5 msec, the same as in Fig. 2 and Fig. 3, in order to generate the bursting activity with no inhibitory interneuron. The synaptic delay of the inhibitory interneuron is 5 msec. The inhibitory effect is stronger when the inhibitory synapse is close to the soma. If the inhibitory synapse is on the main or branch dendrite than soma the synaptic weight of interneuron has to be increased to produce the same effect.

model. The inhibition effect is stronger when the interneuron synapses on the soma than on the dendrites of one of two excitatory neurons. The alteration of the synaptic weight of interneuron on bursting activity could be compensatory for changes in excitatory synaptic inputs.

5 ACKNOWLEDGMENTS

This research was supported by NIH grant NS38958.

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