Intrinsic desynchronization properties of neurons containing dendritic rapidly activating potassium currents

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February 21, 2003

Abstract

In this work, we argue that some neurons may posses intrinsic properties that bias them from getting activated by synchronous synaptic input, and thereby prevent them from participating in the synchronous activity. In biophysical simulations, we show how dendritic K_A channels can act as amplitude dependent filters that permit desynchronized EPSPs to pass relatively unaffected but reduce high amplitude population EPSPs produced by synchronized inputs. We further propose that modulation of these potassium currents may change the level of reduction of synchronized inputs. The results may also have implications for pathological states of synchronization like epilepsy.

1 Introduction

Synchronized neural activity has been experimentally observed in EEG and local fieldpotentials of cortical and subcortical regions. It has been discussed in a multitude of functional contexts, regarding 1) the efficacy of bringing post synaptic target neurons to firing *e.g.* (Llinas *et al.* 2002); 2) spinal motor neuron activation *e.g.* (Baker *et al.* 1999); 3) dynamic linking of cell assemblies *e.g.* (Singer 2001, Llinas *et al.* 2002); 4) induction of long-term potentiation *e.g.* (Wigström and Gustafsson 1985).

Synchronous neural activity also has a pathological side, for instance in epilepsy. The epileptiform activity typically shows large synchronizations that spread during a seizure. Normal tissue by necessity thus possesses mechanisms to control such activity. But even normal tissue can display epileptiform activity if sufficiently many neurons, a cubic millimeter or so, are activated simultaneously (Lindström S, personal comm.). One obvious mechanism to control activity is by inhibition via interneuron activity. Inhibition, however, is very effective in producing synchronization. Could there be additional mechanisms to control the degree of synchronization between neurons?

In this work, we argue that some neurons may posses intrinsic properties that bias them from getting activated by synchronous synaptic input, and thereby prevent them from participating in the synchronous activity. In biophysical simulations, we show how dendritic K_A channels can act as amplitude dependent filters that permit desynchronized EPSPs to pass relatively unaffected but reduce high amplitude population EPSPs produced by synchronized inputs. We further propose that modulation of these potassium currents may change the level of reduction of synchronized inputs.

K_A currents are present in neocortical pyramidal cells (Zona 1988) as well as in hippocampal pyramidal cells (Nakajima *et al.* 1986, Johnston *et al.* 2000). Traditionally, the transiently activated and rapidly inactivated potassium current K_A has been described as a "delay" current (Johnston and Wu, 1995). In current clamp, a depolarizing current injection in the soma may show a fast depolarization followed by a delay before the action potential is generated. This delay is caused by the activation of K_A. K_A has however also been found in dendrites of pyramidal cells (Johnston *et al.* 2000). This opens the possibility that K_A may affect the integrative properties of dendrites. We are in this work focusing on K_A channels of the high threshold type. Due to the voltage dependence of the current, small amplitude EPSPs generated by desynchronized synaptic input may not reach potentials sufficiently depolarized to activate the current. For synchronized input however, the population EPSP may be depolarized enough to activate the current. The outward current will counteract the inward synaptic current, and lead to a loss of amplitude of the EPSP, and thus a smaller input to the soma, thereby reducing the drive towards spiking. Therefore, the more synchronized the input to a cell, the less likely it will be to respond to the synaptic input by spiking.

2 Modeling methods

Biophysical multi-compartmental models of a dendritic branch were used. The models use Hodgkin-Huxley representations of intrinsic currents. The morphology was reduced to 50 compartments for the dendrite. Simulations were done using the simulation package GENESIS. Data from a number of experimental studies on K_A currents were compared.

3 Results

In an initial study, variable degree of synchronization was represented by a variable amplitude of the resulting population EPSP. We studied how EPSPs of various amplitudes are transmitted in a dendritic cable. The results show that attenuation is larger for larger amplitudes of the EPSP, figure 1. In the figure, data from four different experiments (Connor and Stevens 1971, Traub *et al.* 1991, McCormick and Huguenard 1992, Yamada *et al.* 1989) were compared. As can be seen, all representations of K_A show an effect, but to variable degrees. We also studied how reduction

depends on the size of the K_A conductance by varying the size of the K_A maximal conductance, figure 2 left. The test further covers varying the relative size of the synaptic conductance and the K_A conductance. It also shows how the presence of a modulator would affect the reduction. The larger conductance produces a larger attenuation, as expected.

In experiments, the absolute potential of the activation curve and the time constant curve is uncertain: it depends on the electrode junction potential, temperature, holding current *etc.* We have studied how shifting the K_A relative to the voltage axis affects the reduction magnitude, figure 2 right. For sufficiently large inputs, the curves show a maximum of attenuation, located for the 10 mV shift.

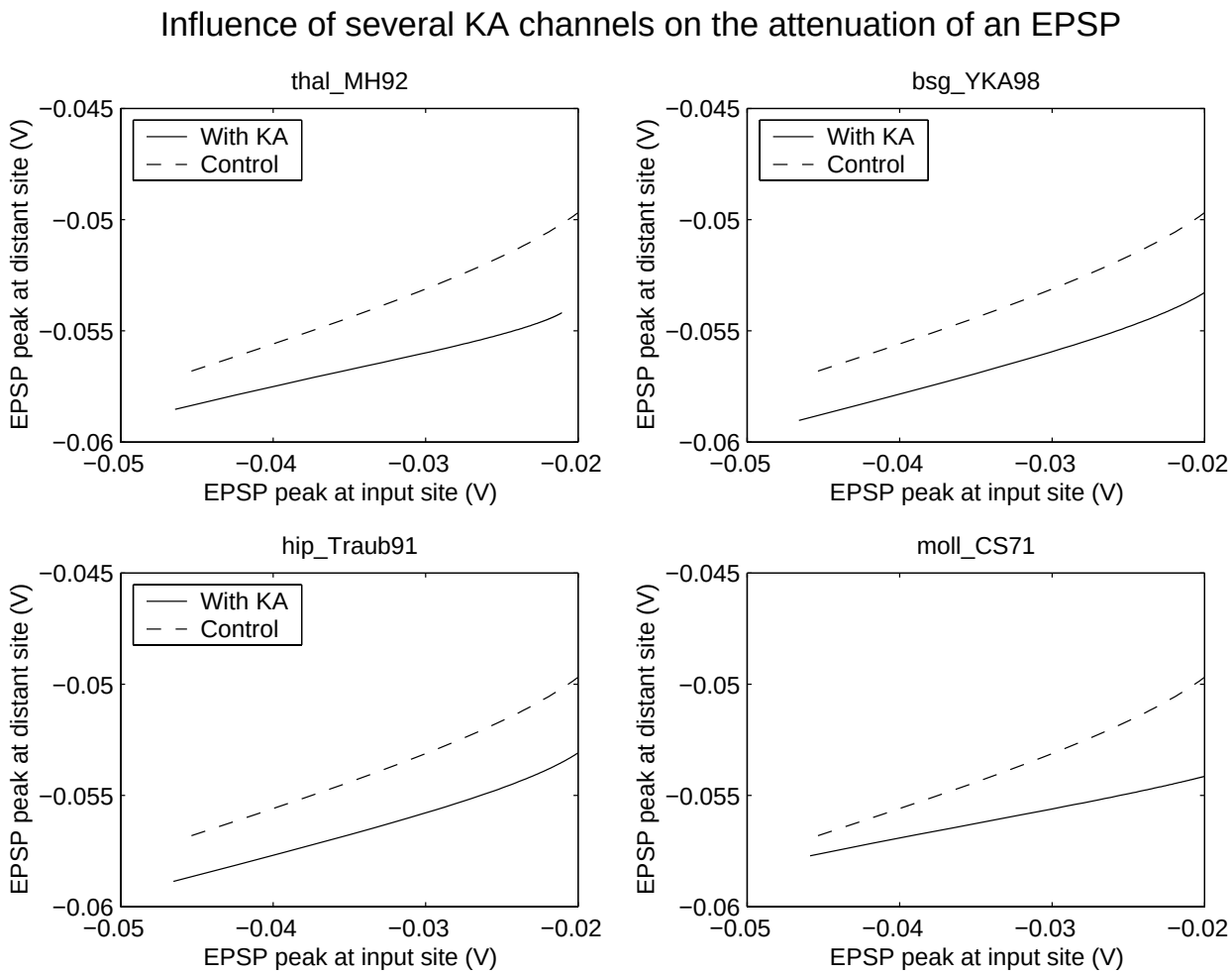

Figure 1: Four different K_A representations were tested. In each plot, the EPSP peak voltage at the recording site is plotted versus the peak voltage at the site of synaptic input. The result for control (without K_A, upper curve) as well as including K_A (lower) is shown. In each case, the effect of K_A is larger for high amplitude EPSPs. thal_MH92 = McCormick and Huguenard 1992, bsg_YKA98 = Yamada *et al.* 1989, hip_Traub91 = Traub *et al.* 1991, mol_CS71 = Connor and Stevens 1971.

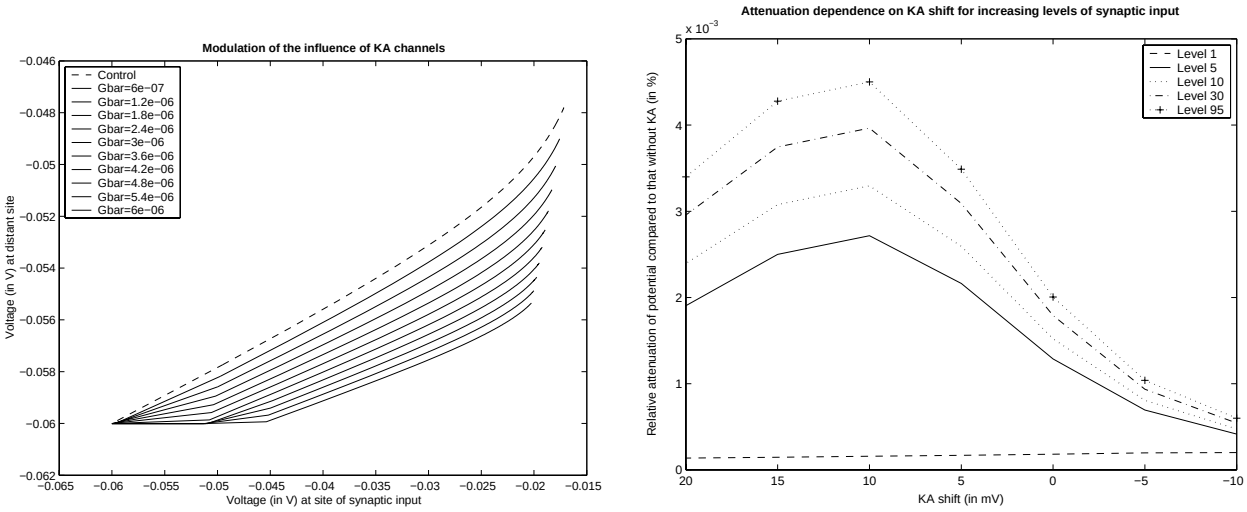

Figure 2: LEFT: The hippocampal K_A current maximal conductance was varied. Legend and curves go orderly from top to bottom. Modulation effects would be represented by higher modulation producing lower conductance, *i.e.* a shift upwards. Note that for high conductances, the EPSP is totally shunted. RIGHT: Relative percent attenuation $(V_{control} - V_{KA})/(V_{KA} - V_{rest})$ is plotted versus voltage shift of K_A for the hippocampal K_A current. This current has intersection point at -60m̃V. As can be seen, attenuation depends on the size of the synaptic conductance, *i.e.* the EPSP amplitude.

4 Discussion

In the near future, we plan to study how a population of synapses brings a pyramidal cell to firing depending on the degree of synchronization between the synaptic inputs. We also will study a network of pyramidal cells and compare the degree of synchronization depending on the level of modulation of the K_A current. We will further study the difference between using the rapidly inactivating current K_A and a more slowly inactivating current like K_D.

Cholinergic modulation reduces the K_A current (Nakajima *et al.* 1986). Based on this finding, we hypothesize that modulation of potassium currents may influence the degree to which a cell reduces synchronous synaptic activation. This is consistent with the observation that activation of the mesencephalic reticular formation, producing a cholinergic input to cortical areas, gives sharper synchronization (Singer 2002), and that the administration of the cholinergic antagonist scopolamine reduces synchronization (Singer 2002). Furthermore, in hippocampal slices, administration of muscarine, a substance that also blocks K_A, raises excitability of pyramidal cells (Nakajima *et al.* 1986), enhances spike reliability and shortens spike latency of O/A interneurons (Grinspan *et al.* 2002). An increased spike probability and firing precision would improve synchronization in a network. In the work by Grinspan *et al.* , no change in input resistance was observed, consistent with a dendritic localization of the currents affected by muscarine. Finally, consistent with the involvement of K_A currents in regulating synchronization, the antiepileptic drug lamotrigine reduced epileptiform discharges induced by 4-AP application (*i.e.* blocking of K_A) in *in vitro* neocortical slices (Zona *et al.* 2002). Lamotrigine increases a 4-AP sensitive transient outward current without affecting a late TEA-sensitive outward current. These results thus relate our findings both to synchronization in general and to epilepsy in particular.

Not all regions, however, show signs of synchronized neural activity. For instance, during working memory tasks prefrontal cortex activity is desynchronized (Compte *et al.* 2003). Desynchronized activity has commonly been a requirement in models of working memory function *e.g.* (Fransén and Lansner 1995) and more specifically in so called bump models *e.g.* (Tegnér *et al.* 2002). In these models, desynchronized activity has been ensured using slow EPSP decay time con-

stants (Fransén and Lansner 1995, Tegnér *et al.* 2002) and saturating synaptic activation (Fransén and Lansner 1995). It is tempting to speculate that, in addition to these network mechanisms, the neurons might have intrinsic properties such as the one proposed in this work, to prevent them from participating in synchronized activity.

5 Acknowledgments

This work was supported by the Swedish Research Council, grant no VR 621-2001-3035.

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