Role of A-type potassium currents in excitability, network synchronicity and epilepsy

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Abstract

A range of ionic currents have been suggested to be involved in distinct aspects of epileptogenesis. Based on pharmacological and genetic studies, potassium currents have been implicated, in particular the transient A-type potassium current (K_A). Epileptogenic activity comprises a rich repertoire of characteristics, one of which is synchronized activity of principal cells as revealed by occurrences of for instance fast ripples. Synchronized activity of this kind is particularly efficient in driving target cells into spiking. In the recipient cell, this synchronized input generates large brief compound EPSPs. The fast activation and inactivation of K_A lead us to hypothesize a potential role in suppression of such EPSPs. In this work, using computational modeling, we have studied the activation of K_A by synaptic inputs of different levels of synchronicity. We find that K_A participates particularly in suppressing inputs of high synchronicity. We also show that the selective suppression stems from the current's ability to become activated by potentials with high slopes. We further show that K_A suppresses input mimicing the activity of a fast ripple. Finally, we show that the degree of selectivity of K_A can be modified by changes to its kinetic parameters, changes of the type that are produced by the modulatory action of KChIPs and DPPs. We suggest that the wealth of modulators affecting K_A might be explained by a need to control cellular excitability in general and suppression of responses to synchronicity in particular. We also suggest that compounds changing K_A-kinetics may be used to pharmacologically improve epileptic status.

Keywords

Introduction

In epileptogenesis, a range of ionic currents have been implicated, among these potassium currents (Timofeev et al., 2004; Birnbaum et al., 2004). For instance, it is well known that application of the K-channel blocker 4-AP induces seizures (Voskuyl and Albus, 1985), but as glutamate also is released the interpretation is complicated. However, more specific support that in particular the transient A-type potassium current (K_A) may be involved comes from studies where seizures were induced by application of the selective K_A blocker scorpion toxin PiTx-Kα (Juhng et al., 1999). Furthermore, in the methylazoxymethanol model of cortical malformations and epilepsy (Castro et al., 2001), the hippocampal

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heterotopia showed loss of the K_A-current. Moreover, the heterotopia also lacked expression of functional Kv4.2 potassium channels, which is one of the genes coding for K_A currents in brain (Yuan et al., 2005, Chen et al., 2006). Finally, temporal lobe epilepsy has been reported in a patient with a genetic Kv4.2 truncation mutation (Singh et al., 2006).

K_A has fast activation and relatively fast inactivation. As viewed from the soma, it belongs to the threshold currents activated near the spiking threshold and in this respect it produces the well known delay of an action potential. K_A is present in pyramidal cell dendrites (Hoffman et al., 1997; Korngren and Sakmann, 2000), where it affects the backward spread of action potentials, as well as integration of EPSPs (Hoffman et al. 1997, Ramakers and Storm 2002, Kim et al. 2007). Importantly, it also has the property to suppress rapid large compound EPSPs (Urban et al., 1998). Such EPSPs may be present during fast ripples. Fast ripples are discrete high frequency oscillations (HFOs) in the range 200-600 Hz, which have been recorded in human mesial temporal epilepsy (Bragin et al., 1990), and will be further discussed below. Epileptogenic activity, and in particular fast ripples are characterized by spiking at high synchronicity levels (Bragin et al. 2000, 2002, 2005, Lasztóczi et al. 2004). Such activity will at target cells produce synchronous compound EPSPs characterized by fast rise times, large amplitudes and short duration. We hypothesized that the properties of K_A, with its fast activation, would be suitable to suppress this voltage profile more than one from less synchronous input. Less synchronized activity would due to its higher DC-level and smaller and slower EPSP-fluctuations also trigger the relatively slower K_A inactivation and thereby prevent the current from suppressing the EPSP. *In vivo*, action potentials most commonly arise from brief dendritic depolarizations reflecting synchronous synaptic inputs (Azouz and Gray, 1999, 2003). K_A may therefore reduce how effective synchroneous input is in generating action potentials in a neuron. Availability and integrity of dendritic K_A currents may thus be an important component regulating recruitment of neurons into seizure activity.

Fast ripples are field oscillations between 200-600 Hz with a broad peak in the power spectrum around e.g. 250 Hz (Engel et al. 2009) or 350 Hz (Dzhala and Staley 2004). These events, recorded from human focal epileptic brain, occur mostly in regions of primary epileptogenesis and rarely in regions of secondary spread (Jirsch et al., 2006). The phenomena is suggested to depend on simultaneous onset of activity in excitatory synaptic circuits (Bragin et al. 2000, Grenier et al., 2003, Dzhala and Staley 2004). It is evident that principal neurons can not sustain firing at these high rates, as found by Lasztóczi et al. (2004) and disussed by Foffani et al. (2007) and one suggestion has been that there may exist populations of neurons firing at lower subharmonics and that the populations alternate and thereby together generate this high frequency (Staley 2007). Moreover, the frequency of fast ripples may not be the main factor distinguishing a fast ripple from e.g. a ripple (Engel et al. 2009) and frequencies of fast ripples may reach into the interval commonly attributed to ripples. Furthermore, increases in synchronicity appear to precede increases in frequency (e.g. transitions into fast ripples) shortly before onset of epileptogenic activity (Lasztóczi et al. 2004). Moreover, neurons are more synchronized in fast ripples than in ripples (Lasztóczi et al. 2004, Engel et al. 2009). We have for these reasons focused on the increase in synchronicity and studied whether K_A is differentially more activated by fast ripples than ripples. To evaluate whether such a dynamic perspective would work quantitatively, we performed biophysical simulations. It may be noted that we will not deal with the synchronizing mechanism *per se*, in which inhibition from interneurons have been suggested to play a major role, but investigate the response of a neuron to synchronized input, and thereby the mechanism of recruitment of principal neurons into seizure activity.

Methods

Neuron model

The model used in this work was based on the model by Migliore et al (1999) which was downloaded from the ModelDB (Hines et al., 2004) database http://senselab.med.yale.edu/modeldb. This model has been used by Hoffman, Migliore, Poolos et al. in work on CA1 pyramidal cell dendrite processing, specifically the role of the K_A and h-currents in backpropagating action potentials. During initial tests, it was found that the Na-current conductance had to be reduced in the dendritic compartments by 1/8 and enhanced in the soma compartments by 5.6 (giving a relative conductance difference of 45) to ensure that synaptically induced action potentials were induced in the soma and not in the dendrites. This is consistent with combined experimental and computational findings where an approximately 50 times higher Na-channel density at the site of initiation of action potentials has been found (Meeks and Mennerick 2007; Kole et al. 2008). Moreover, to simplify our analysis of dendritic processing, we did not make the distinction as in the original model between distal and proximal characteristics of K_A, but used only the distal model throughout the dendrite. In a subsequent sensitivity test where effects of additional currents were analyzed, the influence of another threshold current, the h-current, as well as the influence of a persistent sodium current, were studied. The model had a resting potential of -65mV which well corresponds to values found in vivo (Crochet et al., 2006). The EPSP amplitude in the soma remaining for a synaptic input at 171μm was 41%. This corresponds well to experimental findings of 38% remainder for *lacunosum moleculare* inputs on CA1 pyramidal cells (Inoue et al., 2001) as well as 78%-29% remainder in CA1 cells for inputs at 100μm and 300μm respectively (Magee, 2000).

Model of synaptic input

CA1 pyramidal cells have several thousand synapses distributed over the dendritic tree. The proportion of neurons, and thus also synapses, that are active at any point in time is generally low, and this is particularly true for hippocampus (Buzsaki et al. 1983, Frank and Brown 2001). Thus, ten synaptic inputs were included in the neuron model, representing the synapses that become activated at a particular period in time in a restricted part of the dendrite. For each synapse, we generated Poisson distributed synaptic events at 12Hz. The simulation was run for 1.5 s leading to 17 synaptic inputs for the case of full synchronicity. Synaptic inputs of kainate/AMPA-type had a rise time constant of 1.5ms and a decay time constant of 2.5ms and were positioned on the apical dendrite 171μm from the soma. Experimentally, EPSP amplitudes as measured in the soma vary greatly and range from 0.13-2.8mV (Markram et al., 1997) and 0-4mV (Thomson et al., 1995). We used inputs generating 3.1mV in the soma which thus were 7.5mV in the dendrite at the point of input (leading to the reduction factor 0.41 discussed above). For the case with K_A present, the synaptic inputs were increased 41% to compensate for the hyperpolarizing effect of K_A. The different levels of synchronicity were modeled according to Charcos Lloréns and Fransén (2004). Briefly, different inputs were separated with a Poisson distribution within a time window, and the relative size of the window in relation to the base frequency of 12 Hz determines the degree of synchronicity.

Model of fast ripples

Although much is known about the phenomenology of fast ripples, the mechanisms behind them are not known. We therefore modeled them following two different experimental models, one *in vivo* and one *in vitro*.

Case 1. The model is based on studies of fast ripples generated in a slice preparation (Dzhala and Staley 2004). To model fast ripple input to the target neuron, the model uses a sequence

of ISI intervals from data of spontaneously generated burst-like discharges in individual neurons evoked in high potassium concentration (Dzhala and Staley 2004) with the following consecutive intervals: 3.8, 4.5, 4.9, 6.8, 7.2, 8.6, 9, 10, 10, 10 ms. The corresponding ISI series from spontaneous burst-type intervals for control levels of potassium concentration were: 5, 7, 9, 10, 10, 10, 10, 10, 10, 10ms (Dzhala and Staley 2004). This input was used to represent normal spiking patterns not associated with epileptogenic activity. If K_A works selectively to suppress epileptogenic activity, it is not expected to be significanlty activated by this kind of input. A real neuron is assumed to have many such inputs of the type described above spread over the dendritic tree. In the model, ten synaptic inputs were provided at five different locations of the dendritic tree. In the control case the ten synaptic time series were evenly spaced with a time delay of 2.5 ms, leading to the average delay between bursts of 6ms as reported by Dzhala and Staley (2004), see also Supplementary figure 1. For the fast ripple the delay was decreased to 0.15ms, consistent with the observed decrease towards zero delays in high potassium (Dzhala and Staley 2004).

Case 2. Input from a ripple versus input from a fast ripple. Ripples in awake animals range from 80-200 Hz (Ylinen et al. 1995) and are, contrary to fast ripples, associated with normal brain activity. A ripple episode commonly consist of some 4-16 cycles of oscillations (Ylinen et al., 1995, our estimate). A neuron participates (spikes) on average in 11% of the cycles, and at most in 40% (Ylinen et al., 1995). Focusing on the neurons making up the core of a ripple, we have assumed neurons participate in 25% of the cycles and produce a total of 4 spikes each. Assuming individual neurons fire at 50 Hz during the ripple, a 25% involvement gives an ensemble frequency of 100 Hz containing 16 cycles if neurons fire in four groups 90 degrees out of phase. The target neuron was subjected to 50 synaptic inputs, 10 each on 5 different dendrite locations, with the temporal structure just described, see Supplementary figure 2. Moreover, the 10 inputs at a site were evenly spaced by 1.1ms (Ylinen et al. 1995). Fast ripples are more synchronized than ripples (Lasztóczi et al. 2004; Engel et al. 2009). Assuming a four times higher frequency during a fast ripple compared to a rippe (e.g. 400 Hz and 100 Hz resp.) a spacing of 1.1ms in a ripple would correspond to a spacing of 0.27 ms in a fast ripple. Thus, to test the synchronicity aspect of a fast ripple, a "synchronized" ripple was used. In this case, the time lag between the 10 spikes within one cycle of a ripple was reduced to 0.3 ms. We subsequently studied whether K_A would be more activated and thereby to a larger extent suppress activity of a fast ripple.

Results

In order to investigate the potential capacity of K_A to differentially suppress EPSPs depending on their level of synchronicity, the neuron model was subjected to 11 runs each of a particular level of synchronicity. In table 1 we show the median time between EPSPs as a function of the synchronicity level. We measured the number of spikes produced by the input as a measure of K_A suppression. The rationale behind this choice is that, even though we are considering K_A as a postsynaptic dendritic excitability factor, network activity mediated by action potentials is the ultimate component of epileptogenic activity. The neuronal transformation of inputs into spiking is therefore a key element.

Differential suppression

The effect on the postsynaptic dendritic membrane for inputs of three different levels of synchronicity in the absence of K_A is shown in figure 1A. It can be seen that with decreasing levels of synchronicity, amplitude and rate of rise of the compound EPSP decreases but variability increases. In 1B we show the soma membrane spiking pattern at these levels of synchronicity in the absence of K_A. In figure 1C K_A is present. The different panels show number of spikes produced and one can infer how many are suppressed at different levels of

synchronicity. In figure 1D we summarize the neuron response with and without K_A present. Error bars are based on 20 repetitions of the procedure with different starting random seeds. In general, without K_A, higher levels of synchronicity generate more spikes, consistent with the general properties of a neuron as discussed in the introduction. But, with K_A present, there is a substantial suppression of efficacy of inputs for high degrees of synchronicity in the interval 90-100%. The level 90% correspond to EPSPs separated by a median of 0.7ms and an interval ranging from 0.1ms to 2.2ms (10% and 90% of the events respectively). The particular shape of the curve, particularly of the peak, depends on the synaptic strength, which is further studied in the supplementary material. Thus, as can be seen from figure 1, whereas K_A, as a potassium current, will always be suppressive, it has a selective effect on the synchroneous input that otherwise is so powerful in activating a neuron.

K_A current amplitude and activation

To further analyze the contribution of K_A in this differential suppression, we show in figure 2 the activation, inactivation and current through K_A at two different levels of synchronicity. We compare two cases, fully synchronized and 80% level of synchronicity. For comparison, the two instances shown produced the same peak potential, figure 2 (top) around 17ms. As can be seen, K_A gives more current (second trace), opens more (third trace) and is less inactivated (bottom trace), at the higher level of synchronicity. Note that this is true even though the case of less synchronized input leads to spiking of the cell (around 18ms). The figure also shows that this is a dynamic effect caused by the interaction between the activation and the inactivation dynamics. More specifically, this is seen by replacing the instantaneous activation and inactivation with their steady-state values (dashed traces) computed using the membrane potential and steady-state activation/inactivation curves (shown in supplementary figure 3). Using steady-state values, differences in kinetics between activation and inactivation are removed. This can be seen most clearly for the relatively slower inactivation (trace D, in particular between 4ms-10ms) which at steady-state balances out activation (trace C) yielding very little current (trace B). Further analysis of the dynamics of K_A confirmed that the inactivation is particularly important in the suppression, it must be fast enough but not as fast as the activation. This influence of the inactivation time constant is further studied in relation to modulatory effects on K_A described below.

Slope of compound EPSP

One major difference between the fully synchronized and the 80% level of synchronicity is the slope (derivative) of the rising phase of the EPSP, inset figure 2 (top) and figure 1A. To further analyze the influence of the derivative on the differential activation of K_A, we conducted voltage clamp simulations providing triangular ramps as inputs to the location of the synaptic input, figure 3A. To enable comparisons of cases of different derivatives, we kept the area of the triangular voltages constant as higher potential and longer time always gives more activation and more current. As can be seen in figure 3B, higher derivatives produced higher activation of K_A. These differences can be seen both in the amplitude of the current, and in the integral of the current. Thus, in general, inputs of higher synchronicity produce compound EPSPs with higher derivatives, which as shown here activate K_A more.

Spatial extent of K_A activation

In addition to its sensitivity to the derivative of the voltage, K_A as a voltage gated channel, is sensitive to membrane potential. EPSPs propagating in the dendrite decay with distance from the point of synaptic input and we were interested to study the spatial region of activated K_A currents. In figure 4A we show the membrane potential at input site. The EPSP appears around the time point 10ms and the backpropagating action potential around 20ms. In figure 4B we show the current of K_A at several locations around the point of synaptic

input. It can be seen that the peak of K_A current is relatively local, about a third of the peak remaining 46μm more proximally, but that points even 100μm away are activated. In the figure, around the time point 20ms, it can also be seen how K_A is affected by a backpropagating action potential. Even though the backpropagating action potential amplitude and rate of rise is larger than the EPSP, it is preceded by the EPSP which produces a partial inactivation of K_A.

Selectivity of the suppression of synchronous input

K_A is modulated by a range of factors, affecting the conductance of the current as well as its activation and inactivation characteristics, and we will return to this in the discussion. One potential consequence of such changes are changes in the suppression profile of different synchronicity levels. We have studied the effects on the inactivation time constant produced by auxillary subunits of K_A, KChIPs and DPPs (Nakamura et al., 2001a; Gutman et al., 2005; Jerng et al. 2004, 2007). In figure 5 we show the effect on suppression by using different K_A inactivation time constants. As can be seen in figure 5, both the selectivity of suppression with regard to high levels of synchronicity (interval of high suppression, position of the peak of activation), as well as the degree of suppression of lower levels of synchronicity (level of suppression at independent input, rate of decline at intermediate levels of input) are attenuated. We will return to the modulatory action on inactivation kinetics in our analysis of suppression of fast ripples below. Furthermore, auxillary subunits as well as modulators like PKA and PKC produce shifts in the steady-state activation and to a lesser extent also the inactivation curves (Hoffman and Johnston, 1998; Nakamura et al., 2001a; Gutman et al., 2005; Jerng et al. 2004, 2007). When auxillary subunits produce a hyperpolarizing shift, the produced K_A current is increased (data not shown). Conversely, PKA and PKC produce shifts in the depolarizing direction, leading to an effective reduction of K_A current and as a consequence a loss of differential suppression (data not shown). The results thus show that the suppressive characteristics of K_A may be changed, and we argue potentially may be adjusted to functional demands of the network.

Suppression of epileptogenic activity

As discussed in the introduction, experimental observations indicate the appearance of fast ripples at or before the onset of seizures. We have investigated to what extent K_A is able to suppress a fast ripple. In the first study, we generated input to a neuron from *in vitro* data on spontaneous bursts in individual neurons (Dzhala and Staley 2004) generated either in control or high concentrations of potassium, the latter used as a model of epiletogenic activity. Figure 6 shows the result comparing activity produced in control levels of potassium to those of "fast ripples" generated in high levels of potassium, the latter case tested both with and without K_A present. As can be seen, K_A does not suppress input in the control condition, but it does so for the fast ripple case. The fast ripple case without K_A shows that without K_A the cell spikes as in the control condition. Thus, a neuron containing K_A would to a lesser extent participate in the fast ripple event, and spread of the fast ripple event might therefore be reduced or prevented.

In the second case, we started from a model based on *in vivo* data on ripples (Ylinen et al. 1995). From this we generated fast ripples by increasing the synchronicity, consistent with the observation by Lasztóczi et al. (2004) and Engel et al. (2009). We tested both input at a frequency of 50 Hz and of 100 Hz, effectively representing oscillations of higher harmonics like 100 and 200 Hz as suggested by Staley (2007) and discussed in the introduction. As can be seen in figure 7, the control case with input replicating a ripple does not get suppressed, but input from the more synchronized fast ripple is suppressed if K_A is present. These results are also consistent with the findings of figure 1 showing differential suppression for comparable spike ISIs in the window 90% (no suppression)-100 % (total suppression). We

were also interested to study the modulatory influence by e.g. KChIPs and DPPs on the suppression of fast ripples found. In Table 2 we summarize our findings. Enhanced modulation (reduced inactivation time constant) leads to a reduced current as the inactivation kinetics approaches that of activation (as discussed in figure 2) and thereby to reduced suppression of fast ripples. Decreased modulation on the other hand leads to increased current and as a result suppression that also affects ripple activity.

As mentioned, the genesis of fast ripple events is not known. If a group of neurons would receive several inputs within a small window of time (due to random fluctuations or some particular process), it is conceivable that they might spike and that the synchroneous activity thereby could spread to other neurons. We investigated whether K_A would oppose such a single synchroneous input. Analyzing data from figure 1 at the synchronicity level 98%, the probability of the first spike of the input is 0.15, the probability of a spike following the second input is 0.35 and for the third it is 0.3. Thus, the first input is more suppressed than the following two. Thus, K_A is not only able to suppress trains of inputs, but also single ones. K_A may therefore also be part in preventing the initiation of fast ripples and seizures.

Discussion

In this work, we have shown that the K_A current selectively suppresses synchronized inputs. This property may be particularly important in the context of epileptogenesis, where synchronized activity e.g. in the form of fast ripples is observed at the onset of seizure activity. Preventing the spread of highly synchronized input may be an important mechanism in the control of seizures.

Neocortical pathological ripples

We have here used a model of a CA1 pyramidal cell. However, K_A is also present in neocortical pyramidal cells (Korngreen et al., 2000; Schaefer et al., 2003; Yuan et al., 2005). Moreover, although there are differences between the pathological high frequency ripples observed in neocortex commonly denoted "neocortical ripples" compared to those observed in hippocampal strucures termed "fast ripples", there are also commonalities. Grenier et al. (2003) present evidence that neocortical ripples occur at the time of transition to ictal events. There is furthermore a strong correlation between neuronal excitation and the intensity of neocortical ripples (Grenier et al., 2003). More specifically, neocortical ripples during seizures involve coordinated action potentials in a majority of neurons synchronized on the millisecond scale (Grenier et al., 2003). Our results based on hippocampal fast ripples may therefore be of more general nature.

Separate roles for inhibition and K_A

In this work the focus is on the spread of synchroneous activity among excitatory neurons. We have thus studied the response of a neuron to synchronized input and not dealt with the synchronizing mechanism *per se*, in which inhibition from interneurons has been suggested to play a major role (Maglóczky and Freund 2005). Moreover, activity of interneurons may also play a minor role in the generation of ripples and fast ripples. More specifically, during ripples, interneurons were reported to fire at higher frequencies than that of the ripples, and there was no clear modulation of firing by ripples (Grenier et al., 2003), eg the interneurons are not directly pacing the ripples. On the other hand, neocortical ripples during nonseizure states depend on IPSPs (Grenier et al., 2003). Thus, whereas inhibition from interneurons may play a major role during seizures, synchronized activity of principal cells may be more important for the initial spread of activity.

Synchronization in non-rhythmic events

Synchronous activity is not only present during oscillations, but may also be present during non-rhythmic events relevant for epilepsy. Large field potential spikes, for instance, reflect epileptic network activity (Ulbert et al., 2004). Comparisons of human intracranial EEG recordings and spontaneous events in *in vitro* slice preparations taken from the same patient show they have spike and waves events resembling each other (Cohen et al 2002). In these slices, intracellular recordings show high degrees of synchronization during the spike and wave events. Thus, in both rhythmic and non-rhythmic events, synchronized neuronal firing is present and this synchronous input may be particularly effective in recruiting additional neurons.

Amplitude of compound EPSP

Our results show that the differential suppressive effect of K_A increases with increasing EPSP amplitude. Compound EPSPs generated by multiple inputs in concert may indeed reach large amplitudes. For instance, amplitudes of sharp waves of 8mV have been recorded intracellularly (Maier et al., 2003). In pathological circuits comprising the start of epileptic activities, synaptic efficacies may be even larger. K_A may therefore be particularly important in preventing hyperexcitability under those circumstances.

Role of modulators of K_A

A number of different substances modulate K_A, for instance PKA (Hoffman and Johnston, 1998), PKC (Hoffman and Johnston, 1998), MAPK (Yuan et al., 2002), arachidonic acid (Colbert et al., 1999; Ramakers and Storm, 2002), adenyl cyclase activating peptide (Han et al., 2005; 2006) and frequentin (Nakamura et al., 2001b), for a review, see Jerng et al. (2004). Furthermore, potassium channels colocalize with membrane proteins, notably the Kv channel-interacting proteins (KChIP) and dipeptidyl peptidase-like proteins (DPP), e.g. DPP6 and DPP10 (for a review, see Jerng et al. 2004). The presence of KChIPs and DPPs in neurons enhances the surface expression of K_A. Moreover, it has been shown that KChIPs produce substantial changes in K_A characteristics, e.g. shifting the steady-state activation and inactivation curves 10′s of millivolts as well as changing inactivation kinetics (Nakamura et al., 2001a; Gutman et al., 2005; Jerng et al. 2007). Moreover, DPPs produce a hyperpolarizing shift of steady-state curves and a more rapid inactivation kinetics (Jerng et al. 2007). There may be several reasons for this complex regulation of K_A. 1) General excitability, the control of the threshold for action potential generation, latency of spike, or number of spikes produced by somatic input. 2) Backpropagation of action potentials, specifically a control of spread of backpropagating action potentials. 3) Interaction with incoming EPSPs and potentially synaptic plasticity. 4) Modulation of efficacy of synchronized input, in particular, modulating the degree of specificity of this suppression, as shown in figure 5. Our results also suggest that effects from PKA and PKC would work in the detrimental direction whereas KChIPs and DPPs would enhance the suppressive effects of K_A on hypersynchroneous activity.

A vicious circle involving K_A

We have in this work discussed how reduction of K_A may be a risk factor in epilepsy. However, the opposite may also be true. In hippocampal tissue after pilocarpine induced seizures, CA1 pyramidal neuron dendrites showed decreased availability of the A-type potassium channel due to transcriptional and posttranslational processes (Bernard et al., 2004). Furthermore, after convulsant drug pentylenetetrazole treatment (Tsaur et al., 1992; Francis et al., 1997), Kv1.2 and Kv4.2 mRNAs were reduced. Thus, there seems to be a bidirectional relationship between seizures on the one hand and expression and electrophysiological properties of K_A on the other, and thus a possibility of a vicious circle.

Anticonvulsants and K_A

Preventing or reversing the vicious circle of K_A run-down may be a key objective in treatment of seizures. Indeed, several anticonvulsants have been shown to enhance K_A currents; lamotrigine (Zona et al., 2002, but see Huang et al. 2004), valproate (Walden et al., 1993) and carbamazepine (Zona et al., 1990). Conversely, $GABA_B$ activation reduces potassium currents by shifting their activation in the positive direction (Saint et al., 1990). This interaction could work via the suppressive effect of AA on K_A (Ramakers and Storm 2002) activated by phospholipase A_2 activation downstream of $GABA_B$. This suppression of K_A could be one explanation for less good results of GABA enhancing compounds on some patients. $GABA_B$ activation could on the one hand lead to a beneficial direct hyperpolarization of the neuron, but on the other hand also an indirect enhancement of temporal summation capacity and an increased sensitivity to synchroneous activation. In this work, we have investigated the potential link between K_A and neural responsiveness to synchroneous synaptic input. Based on the results in this work, the prediction would be a decrease in synchronicity following administration of these compounds. Indeed, lamotrigine, which enhances K_A (Zona et al. 2002) reduces population spikes (Langosch et al., 2000) and population spikes have been suggested to be a sign of neuronal synchrony (Andersen et al., 1971). Furthermore interictal spikes are reduced by lamotrigine (Marciani et al., 1996) and the addition of lamotrigine decreases EEG ictal and interictal abnormalities (Akman et al., 2003). A second antiepilepticum, valproate, has been shown to reduce the frequency of extracellularly recorded spontaneous interictal bursts (Albus et al., 1998).

Properties of potassium current enhancers

Observations in epileptic patients of increased excitability due to compromized potassium currents have lead to the recent development of potassium current enhancers (Retigabine and Flupirtine enhancing the M-type (KCNQ/Kv7) channel, Nicorandil enhancing an adenosine triphosphate sensitive potassium (K+ATP) channel and Chlorzoxazone as an opener of a calcium sensitive potassium current), and with their anti-epileptic properties evaluated in Kobayashi et al. (2008). However, K-current enhancing drugs may not always give the desired effect. Resting membrane potential changes induced by a K-current enhancer may be counteracted by homeostatic mechanisms (Marder and Goaillard, 2006) either reducing other K-currents or enhancing depolarizing currents. Likewise, influences on average firing frequency may be balanced out in the long run. Based on the work presented here, pharmacological interventions that affect the neurons response to highly synchronized inputs but less so for intermediate or unsynchronized inputs are suggested.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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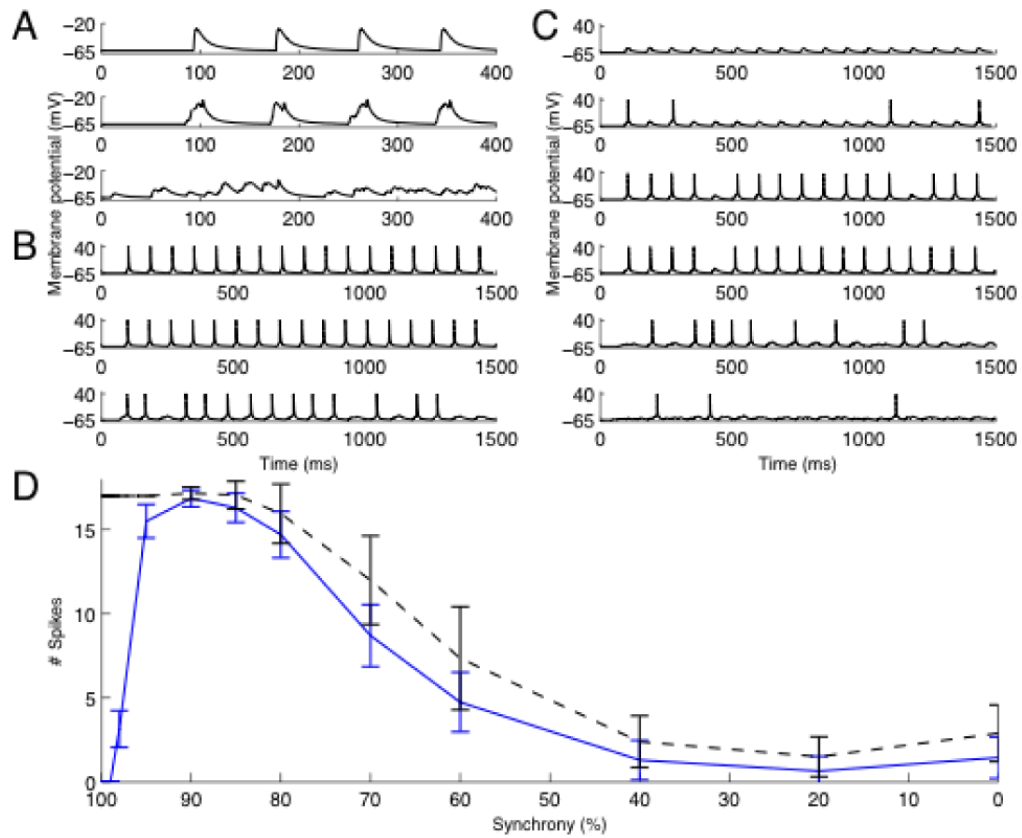
Fig 1.
Differential suppression of synchronous input. A. Synaptic input. The figure shows from top
the membrane potential at input site with 100%, 90% and independent input respectively. B.
The membrane potential in the soma without K_A present. The graphs shows from top
simulations with 100%, 90% and 70% synchronous input. C. Membrane potential in soma
with K_A present. The graphs shows from top the simulation with 100%, 98%, 95%, 90%,
70%, and 40 % synchronous input. D. Synchronized input is strongly suppressed by K_A. The
figure shows the number of spikes produced for different synchronicity levels. The black
line represents baseline (control without K_A) and the blue line with K_A present. Note the
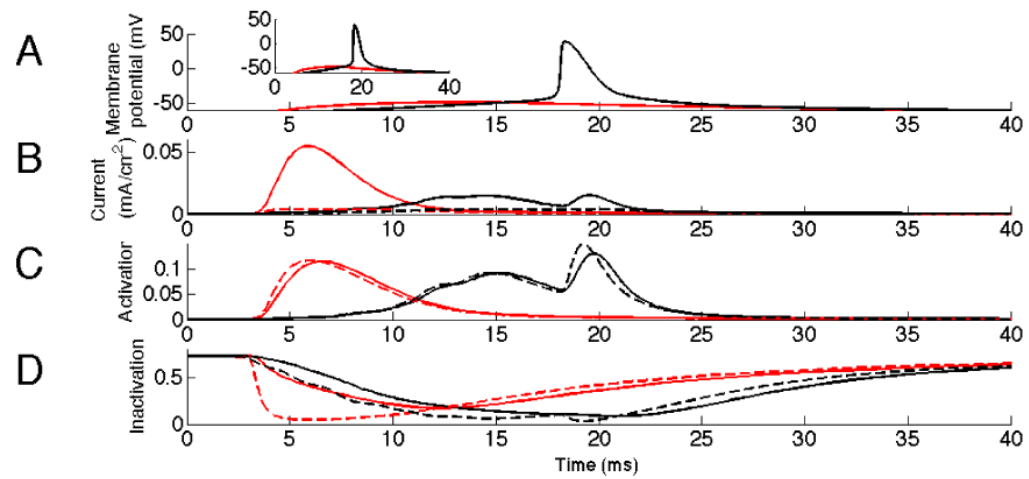pronounced suppression in the interval 100-90%.

Fig. 2.
Activation of K_A by synchronized versus semi-synchronized input. Synchronous input (100%), in red, activates K_A more than semi- synchronous input (80%), in black. The dashed lines represent values of K_A steady-state activation and inactivation at the membrane potentials dictated by A. A: Membrane potential in the soma. Inset shows initial slope of EPSP more clearly. B: Current through K_A at input site. Note the difference in current around 6 ms. C: Inactivation of K_A at input site. The interval 2-10 ms shows that the effect seen in B originates from the dynamics aspects of K_A. D: Activation of K_A at input site. Note the difference in inactivation around time of input 2-10ms.
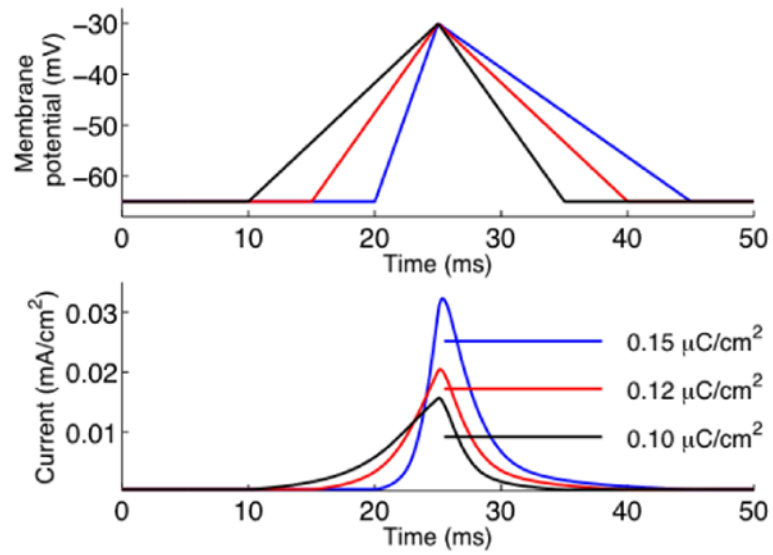
Fig. 3.
Sensitivity to voltage slope. The top graph shows voltage clamp command of different initial slope but same area. The bottom graph shows the corresponding current through the K_A channel. Note the difference in the peak current at 25 ms. The legend indicates the integral of the current for each protocol.
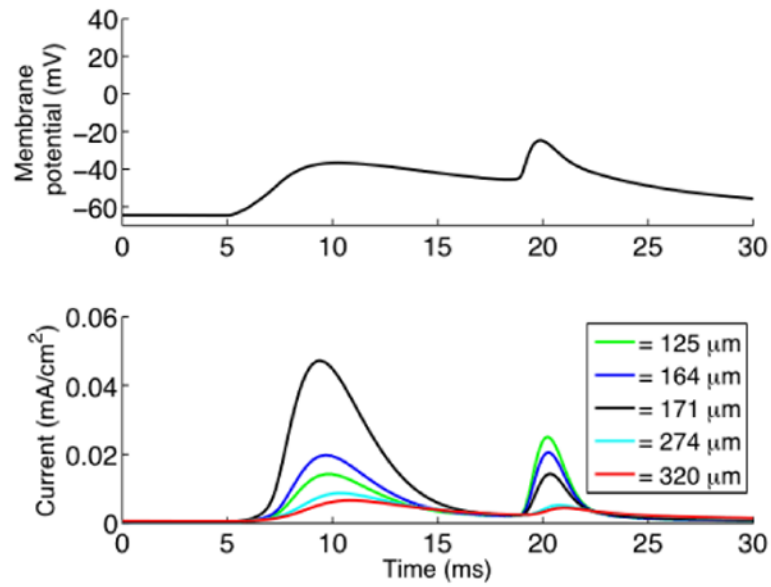
Fig. 4.
Distance-dependent K_A activation. The top graph shows the membrane potential at input site (171μm from soma) with a 92% level of synchronous input. The first event is the EPSP and second is the backpropagating action potential. The bottom graph shows the current through the K_A channel. The current was measured at five different locations 125μm, 164μm, 171μm, 247μm and 340μm from the soma.
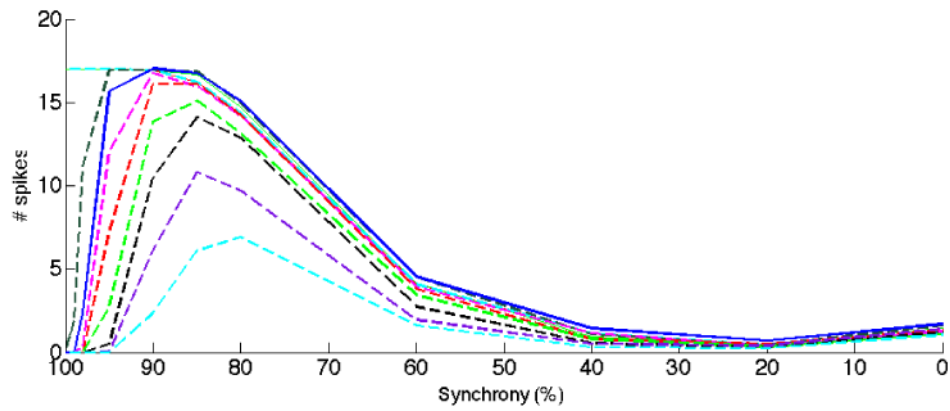
Fig. 5.
The selectivity to synchronized input varies when K_A dynamics is modified. The inactivation time constant was changed representing modulatory influences of e.g. auxillary proteins. As in figure 1, the solid blue curve is the result with standard values of K_A. The magenta, red, light green, black purple and cyan curves represent decreasing inactivation time constant in steps of 1ms. Dark green and solid cyan curves represent increasing inactivation time constant in steps of 1ms. Note the significant difference in reduction of synchronized input, effectively covering the interval 95-80%.
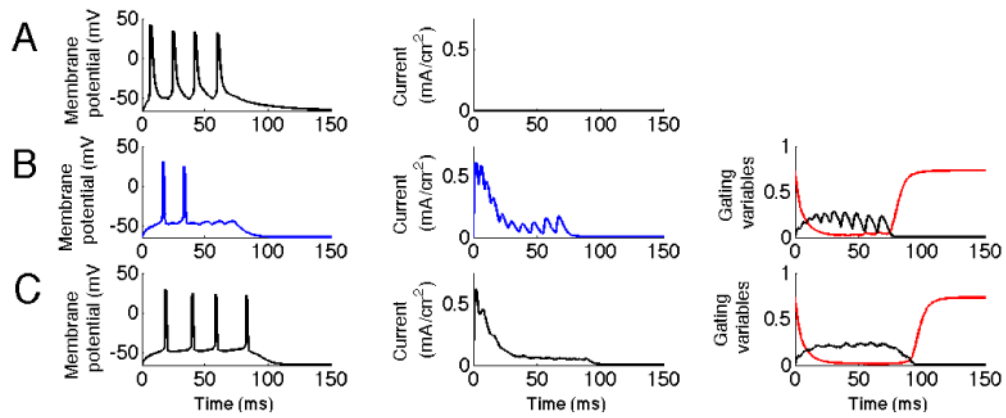
Fig. 6.
K_A reduces response to fast ripple input. The first column represents the membrane potential of the soma. The second column represents the current through the K_A channel measured at the location of the synaptic input. The third column represents the gating variables of the K_A channel. The black line represents activation and the red line inactivation. A. Fast ripple with no K_A present. Input represents higher synchronicity levels present during high potassium concentration conditions. B. Fast ripple with K_A present. Note the reduction in number of action potentials generated due to the increase in K_A current. The plot of gating variables show that this input leads to a larger degree of activation, particularly at its peaks and to a lesser degree of inactivation, particularly for later inputs. C. Control input representing lower synchronicity present in control concentration of potassium.
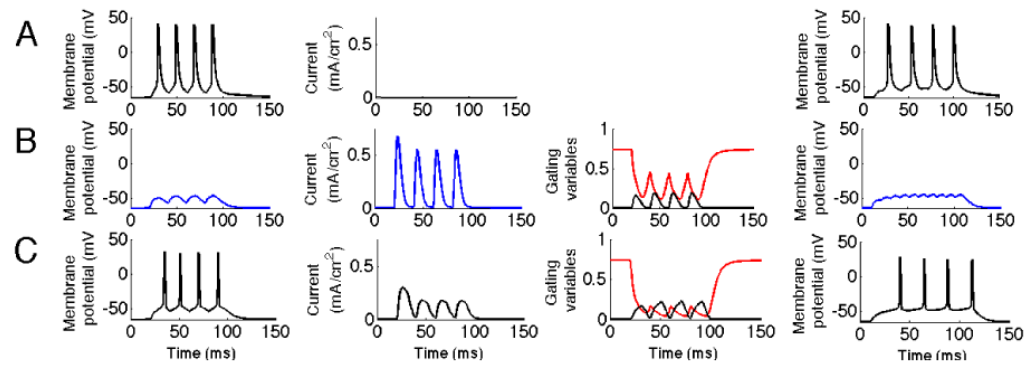
Fig. 7.
K_A reduces response to fast ripple input. The three first columns correspond to the simulation when the input frequency was 50 Hz and the fourth column a case with 100Hz input. The first column represents the membrane potential of the soma. The second column represents the current through the K_A channel measured at the location of the synaptic input. The third column represents the gating variables of the K_A channel. The black line represents the activation and the red line inactivation.A. Fast ripple input with no K_A present. B. Fast ripple input with K_A present. Note the significant reduction in spike activity. It can be seen that the inactivation is lower than in the control case C, particularly in its troughts. C. Ripple input. K_A does not suppress input representing ripple activity.

Table 1

Time between inputs

	100%	90%	70%	40%	Independent
median	0	0.67	2.01	2.68	6.71
10%	0	0.096	0.29	0.57	0.96
90%	0	2.15	6.45	12.9	21.5

The table shows time (in ms) between synaptic inputs for a select number of synchronization levels of figure 1. In the table, median refers to the median value in the distribution of input intervals produced, 10% refers to the shortest intervals and 90% covers almost all of the intervals produced.

Table 2

Effects on fast ripples from changes in inactivation kinetics

	50Hz			100Hz		
	-	c	+	-	c	+
Without K_A	4	4	4	4	4	4
Fast ripple input	0	0	3	0	0	3
Ripple input	3	4	4	2	4	4

Number of spikes produced following fast ripple input (case 2), c control, standard value of the inactivation time constant i.e. same data as in figure 7 first and fourth column, + enhanced modulation by reducing the inactivation time constant by 4 ms representing enhanced KChIP/DPP modulation, - reduced modulation by increasing the inactivation time constant by 4 ms representing reduced KChIP/DPP modulation.