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INHIBITION CAN DISRUPT HYPERSYNCHRONY IN MODEL NEURONAL NETWORKS

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Abstract

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1. Model neuronal network simulations were performed using a reduced Traub neuronal network model. In the absence of inhibition the network produced synchronous population bursting.
2. Bursting of individual neurons was dependent on 1 or more of the following: build-up of charge in the dendritic compartment, prolonged current flow through simulated NMDA associated channels, current flow through T channels. Interburst interval duration and consequent burst frequency was dependent on the density of slow after-hyperpolarizing potassium channels.
3. Addition of an inhibitory interneuron population projecting to $GABA_A$ receptors resulted in rapid desynchronization of the population, generally after only 1-2 cycles. This effect was found to be due to reduced participation in the individual population burst and to the need for multi-synaptic activation of the individual neuron in the presence of inhibition.
4. This desynchronizing effect could be offset by increasing the strength of interburst hyperpolarization either through increased density of I_{AHP}, or through the addition of a separate inhibitory interneuron pool projected to $GABA_B$ receptors.
5. These data suggest that the synchronizing effects of inhibition may vary depending on circumstances – with desynchronization being dominant in cases characterized by large population bursts such as those seen in epilepsy.

Keywords: computer models, epilepsy, inhibition, oscillations.

Abbreviations: alpha-amino-3-hydroxy-5-methyl-ioxyzole-4-propionic acid (AMPA) gamma-aminobutyric acid (GABA), afterhyperpolarizing 'small K' current (I_{AHP}), inhibitory post-synaptic potential (IPSP), N-methyl-D-aspartate (NMDA)

Introduction

The role of $GABA_A$-receptor-projecting inhibitory interneurons (henceforth $GABA_A$ interneurons) in normal functioning of the cortex and in epilepsy remains unclear (Thompson 1994). Early work demonstrated how loss of $GABA_A$ activity might produce hypersynchrony

in the hippocampus by making it easier for a single pyramidal neuron to be activated by a single presynaptic neuron (Miles and Wong 1987a, Miles and Wong 1987b, Traub and Miles 1991). In particular, Traub and colleagues (1987) demonstrated that the presence of $GABA_A$ inhibition would transform network behavior from hypersynchrony (full pyramidal cell participation in each population burst), to a faster frequency synchronous pattern with many fewer pyramidal cells participating in each cycle (Traub et al. 1987).

Conversely, other studies have shown that $GABA_A$ input could act to synchronize activity (Lytton and Sejnowski 1991, Cobb et al. 1995, Kopell and LeMasson 1994). Several factors permit this synchronizing role. Pyramidal cells are capable of some degree of inhibitory rebound, allowing classically inhibitory input to produce facilitatory drive onto these cells. Interneuron projections tend to be onto proximal apical dendrites or pyramidal somata, allowing them a greater influence on activity at the soma and axon hillock. Inhibitory inputs are characterized by far lower convergence ratios than excitatory inputs, suggesting that the single interneuron might be influential in producing synchronization in a set of pyramidal cells to which it diverges (Cobb et al. 1995, Sik et al. 1994).

The authors decided to explore the apparent contradiction between synchronizing and desynchronizing roles by evaluating the effect of inhibitory activity in the reduced Traub network model proposed by Pinsky and Rinzel (1994). The authors were able to confirm Traub's original observation of reduction of hypersynchrony in the presence of $GABA_A$ inhibition. The authors have extended these observations by demonstrating that $GABA_A$ inhibition can produce full desynchronization and by exploring the interplay of $GABA_A$ inhibition with $GABA_B$ and with the intrinsic voltage-sensitive channels I_T and I_{AHP}.

Methods

Model neurons were adapted from the two compartment reductions of Traub hippocampal pyramidal cell (Traub et al. 1991), developed by Pinsky and Rinzel (1994). The use of two compartment neurons in the models reduced the computational load, while maintaining the essential responses of the elements being modeled. Simulations were run in NEURON (Hines 1989).

A large number (> 1000) of simulations were run with various parameters and network

designs. Most of the networks had 2 types of model neurons: glutamatergic excitatory pyramidal cells, and $GABA_A$ interneurons. Some simulations also had a separate population of $GABA_B$-receptor-projecting inhibitory interneurons. The glutamatergic cells and the $GABA_B$ interneurons were modeled as 2 compartments, a soma and a dendrite (Fig. 1A). The $GABA_A$ neurons were modeled as a single compartment.

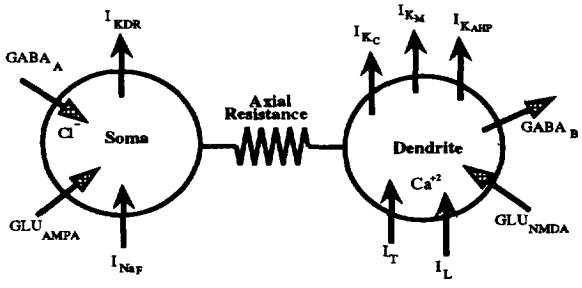

Fig. 1 Schematic of two compartment model pyramidal neuron showing the location of the voltage- and transmitter-dependent channels.

Compartmental Model

Both compartments had the same dimensions (length = 20μ; diameter = 10μ). The somatic compartment contained fast sodium (I_{Na}) and delayed rectifier potassium (I_{Kdr}) conductances. The maximum conductance ($\bar{g}$) values were 30 mS/cm^2 and 15 mS/cm^2, respectively. The dendritic compartment had two calcium currents, an L-type ($\bar{g}$ = 10 mS/cm^2) and, in some simulations, a T-type ($\bar{g}$ = 1 mS/cm^2), and three K^+ conductances, a calcium-sensitive, voltage-dependent current, I_C, with a $\bar{g}$ of 15 mS/cm^2, a calcium-dependent current, I_{AHP}, with a $\bar{g}$ of 1-4.5 mS/cm^2 , and an I_M, with a $\bar{g}$ of 3-6 mS/cm^2. The input resistance at steady state was 160 MΩ. Membrane resistance was 10 kΩ-cm^2, and the capacitance was 3 μF/cm^2 to give a membrane time constant of 30 ms. These values, as well as individual channel parameterizations were taken from Traub et al. (1991). In addition, I_T has been shown to exist in hippocampal cells (Avery and Johnston 1996). The I_T model used was taken from thalamic modeling studies (Lytton et al. 1996, Lytton and Sejnowski 1992). Random variability in a range from 2.5% to 10.0% was added to channel

parameters.

Synaptic Parameters

$GABA_A$, $GABA_B$, AMPA and NMDA were modeled using a 2-state model (Destexhe et al. 1994a, Destexhe et al. 1994b, Lytton 1996). Activity in the network was initiated by brief (2-4 spikes 50-100 msecs) high potency activation (5 nA) of a sub-population of the excitatory cells (10-20%). AMPAergic strength between neurons was sufficient so that one excitatory neuron could directly cause another to fire. Typical strengths were 50 nS, 100 nS, 5 nS, 5 nS, and reversal potentials were 0 mV, 0 mV, -75 mV, -90 mV for AMPA, NMDA, $GABA_A$, $GABA_B$, respectively. Synaptic strength was randomly varied by $\pm 5\%$.

Network Design

Network synaptic interconnections were randomly assigned. The density of synapses decreased exponentially, while conduction/synaptic delay increased linearly, over distance from the pre-synaptic cell in the 1-dimensional architecture. The network was divided into density zones (Traub et al. 1987). Excitatory neurons projected over greater distance and traversed a greater number of density blocks, when synapsing onto other excitatory cells, than did projections that emanated from or terminated on inhibitory interneurons. The interactions were distributed over the density blocks. For example, in many simulations a neuron would synapse onto 15% of other excitatory cells with 4 density blocks in a network with 500 excitatory neurons. It would synapse onto 75 cells: 48 (64%) in the closest block on either side (block 0), 18 (24%) in block 1, 7 (9%) in block 2 and 2 (3%) in block 3. Networks ranging in size from 100-500 neurons were assayed. When interneurons were included, they were 10-30% of the total population. Connections between inhibitory neurons were represented. The findings reported here did not appear sensitive to network size.

Results

Over 1200 simulations were assayed involving a variety of network connectivities. All networks involved pyramidal neurons with excitatory synaptic connections between them. The effect of inhibition was assessed by simulating interneurons with various levels of connectivity with the pyramidal neurons and with each other. The results presented were generally ro-

bust to small changes in connectivity parameters. This paper presents the effect of $GABA_A$ inhibition on pyramidal neurons both without and with the low-threshold spike generating T-channel. In addition, results pertaining to changes in intrinsic afterhyperpolarization and the effects of $GABA_B$ inhibition are presented.

Bursting in Individual Pyramidal Neurons

Synchronous population bursting was readily produced with a variety of network architectures and different intrinsic neuron properties. In general, population bursting depended on the ability of individual neurons to burst (Fig. 2A). Three different aspects of neural dynamics were useful in producing the transient depolarization required to create a burst morphology. First, as previously shown, the presence of a separate dendritic compartment with calcium entry provides a store-house for charge that can gradually dissipate via the soma (Baer et al. 1995, Traub and Llinas 1979). Second, bursting could be supported synaptically due to the prolonged current entry characteristic of synaptic activation via NMDA receptors. The duration of bursts, as well as the duration of the interburst interval, was found to depend on the density of the slow-decaying, after-hyperpolarizing currents I_{AHP} and I_M. Third, some of the simulations utilized a the low-threshold calcium channel (T channel) that has been shown to underlying bursting in thalamus and other cell types (Coulter et al. 1989, Crunelli et al., 1989, Jahnsen and Llinas 1984, Lytton and Sejnowski 1992, Wang et al. 1991). In most simulations, small constant current injections were given to produce repetitive bursting in the individual neurons. Inhibitory interneurons were non-bursting (Fig. 2B).

Network Synchrony Disrupted by $GABA_A$ Inhibition

Networks maintained prolonged synchronous bursting after an initial stimulus was applied to a sub-population of the cells with no $GABA_A$ interneurons present (Fig. 3A). Bursting was initiated with simultaneous activation of a subpopulation of the neurons which can be seen as a line of simultaneously firing cells at the beginning of the simulation (small oblique arrows). Frequency typically declined slightly for the first few cycles before stabilizing, in this case going from 5.7 Hz to 4.1 Hz. Burst frequency in most simulations was 4-8 Hz. Frequency was largely dependent on the strength of I_{AHP}, a calcium-dependent potassium channel, and the dynamics of calcium elimination. Increasing the time constant of calcium

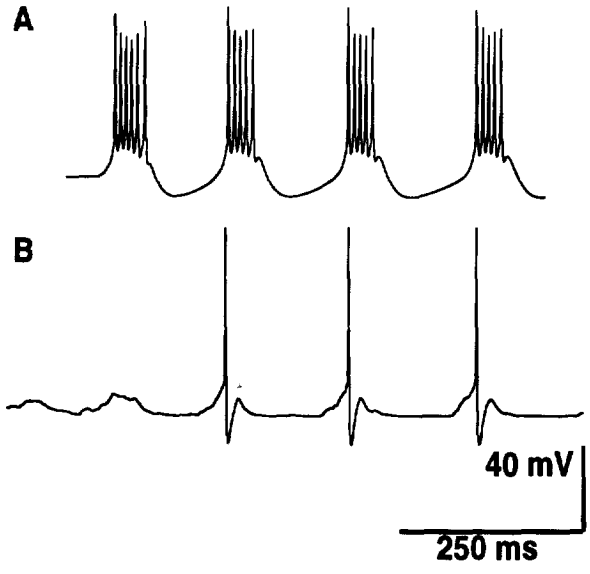

Fig. 2 Single neuron activity during a network simulation. A. Bursting in 2-compartment pyramidal neuron with I_T. B. Firing pattern of a model $GABA_A$ interneuron. This neuron type does not burst.

elimination led to a prolonged afterhyperpolarization that would delay the next burst. The introduction of $GABA_B$ interneurons in the network could also slow bursting considerably due to its long duration of action.

With the addition of $GABA_A$, synchronous population bursting was disrupted (Fig. 3B). Following activation of the subpopulation, an initial population burst can be seen (first vertical arrow). The density of this burst was considerably less than in the control due to the presence of the inhibition. A still more diffuse second burst could also be seen (second arrow) and close inspection revealed evidence of clustering suggestive of a third burst as well (third arrow). The frequency of this diffuse bursting was 9.4 Hz, over 50% faster than that seen on initiation in the control.

Two major factors appeared to be responsible for the desynchronizing effect of $GABA_A$.

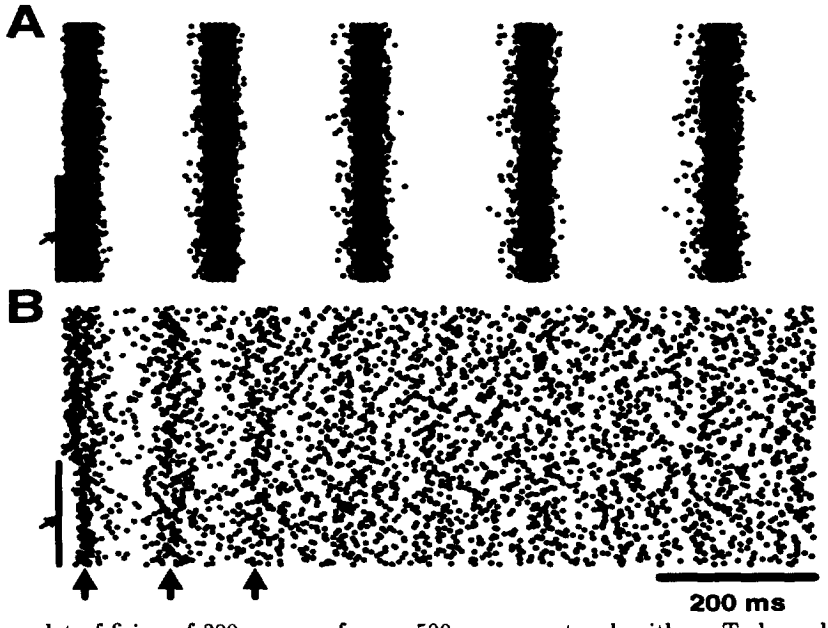

Fig. 3 Raster plot of firing of 300 neurons from a 500 neuron network with no T channel present. Initially 120 neurons were activated and fire simultaneously (oblique arrow). A. In the absence of $GABA_A$ inhibition prolonged synchronous bursting at 5 Hz with a gradually increasing interburst interval. B. With $GABA_A$ added ($\bar{g}$=5 nS), the first population burst is much less dense (left vertical arrow) and subsequent bursts become quite diffuse (second and third arrows).

First, while all of the neurons were involved in a single burst in the control (Fig. 3A), the reduction in overall excitability allowed only a subset of neurons to be involved in the desynchronized case (Fig. 3B). Therefore, in the control, the relative refractory periods of all of the neurons were coordinated, causing them to burst together again at the termination of this period. Second, since monosynaptic excitatory input into an individual pyramidal neuron was made strong enough to fire the cell, firing cascades took place in the tight temporal cluster of a rapidly expanding domino-effect. With sufficient divergence from individual pyramidal cells, this spread of excitation would quickly involve the entire population. With the addition of inhibitory input, coincident feedforward excitation and inhibition often resulted in a combined postsynaptic potential that was subthreshold for firing. In such cases, coincident

multisynaptic input was required to produce firing, a lower probability event. Assuming that there is some regularity of firing of individual neurons, but that phase is in general somewhat random, this requirement for coincident presynaptic firing will tend to obscure the underlying regularity of the single units, producing less regular firing in the population.

Synchrony Disruption Still Seen in Models Using I_T

A well-documented mechanism for burst synchronization in thalamus is the low-threshold spike, a calcium-mediated burst that follows a preceding hyperpolarization (Jahnsen and Llinas, 1984). Since this inhibition-responsive channel has also been described in hippocampus and other cortical areas, the authors decided to assess what effect it might have on inhibition-mediated desynchronization in the present model. I_T, the low-threshold calcium channel responsible for the low-threshold spike, requires prior deinactivation in order to open (Crunelli et al. 1989, Coulter et al. 1989, Suzuki and Rogawski 1989). Therefore, burst activity can occur in response to a preceding inhibitory postsynaptic potential (IPSP) (Lytton et al. 1996). Since chloride reversal potential for $GABA_A$ (-75 mV) was at a value that would produce about 50% deinactivation in I_T, this interaction might be expected in the network. This response would be expected to give $GABA_A$ a synchronizing effect that would work against the desynchronization seen in Fig. 3.

The authors assayed model networks with neurons with high enough I_T density to permit spontaneous bursting of a single neuron even in the absence of external stimulation. Population burst frequency was faster, the pattern of population bursting was different and the coherence of the bursts was less than seen in the previous figure (Fig. 4A). Nonetheless, addition of $GABA_A$ into the network still resulted in a desynchronizing effect (Fig. 4B). In contrast with Fig. 3, the initial population burst in the inhibited case is actually tighter than that seen in the control and the initial intra-population-burst interval is longer (210 msec compared to 120 msec). Therefore, the alteration in population burst density and synchronization of the relative refractory period which were causative factors in inhibitory desynchronization in Fig. 3 do not appear to play as large a role initially, although they do appear to be present in subsequent population events.

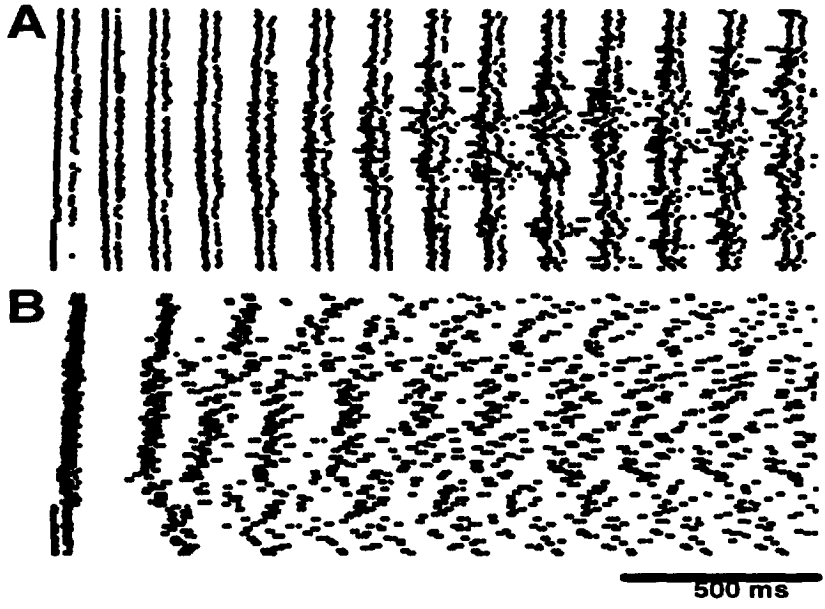

Fig. 4 Synchronization in a 100 neuron network with neurons made spontaneously active with I_T. 15 neurons were activated to initiate activity. A. Control simulation shows synchronized oscillation. An initial dominant frequency of 8.2 Hz gradually slows to 6.2 Hz. Each burst was made up of two components separated by about 40 ms. B. Identical simulation except for addition of $GABA_A$ ($\bar{g}$=0.5 nS). Disruption of synchrony is seen.

Enhanced Refractory Period Opposes Desynchronizing Effects

Since synchronization depended on the relative refractory period, the authors hypothesized that neuromodulators or other synaptic effects that enhance this refractoriness would tend to offset the desynchronizing effects of $GABA_A$ (Fig. 5). This enhancement could be effected in the model either through augmentation of the intrinsic potassium channel I_{AHP} (Fig. 5B), or through addition of another network element which would produced prolonged hyperpolarization, namely $GABA_B$ (Fig. 5C). The $GABA_B$ synchronization in Fig. 5C was transient; sustained synchronization could be obtained by using still higher $GABA_B$ conductance values.

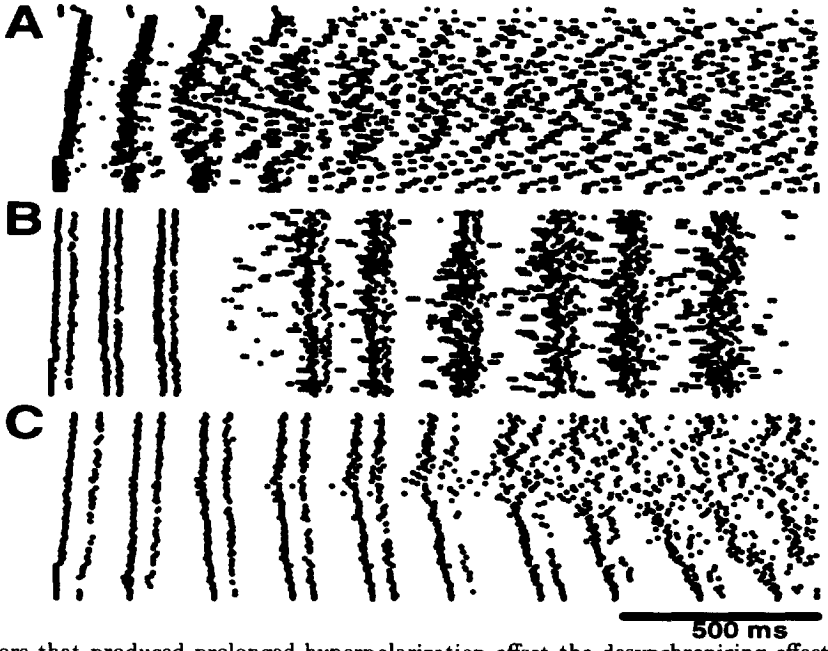

Fig. 5 Factors that produced prolonged hyperpolarization offset the desynchronizing effect of $GABA_A$. Each network was run with 110 neurons with initial activation in 20. A. Desynchronization of network activity in the presence of $GABA_A$. B. Adding an additional set of inhibitory neurons that project to $GABA_B$ receptors results in increased synchrony. C. Increasing I_{AHP} density from 1 mS/cm^2 to 2 mS/cm^2 in the absence of $GABA_B$ also produced increased synchrony.

Discussion

These simulations confirm the earlier findings of Traub and colleagues (Traub and Miles 1991) that suggest that loss of inhibition may predispose to hypersynchronous activity of an epileptiform nature. In this paper, the authors have largely explored this relationship from the alternative point of view emphasized by other authors (Golomb and Rinzel 1993, Golomb et al. 1994, Kopell and LeMasson 1994), demonstrating how increasing $GABA_A$ activation can be variably disruptive to what would otherwise be a hypersynchronous process. The relatively rapid action of $GABA_A$ allows it to disrupt the structure of the individual population burst, producing this desynchronizing effect. This desynchronizing effect was

seen even in the presence of I_T, a hyperpolarization-responsive calcium channel which would be expected to give inhibition a synchronizing role.

Possible Mechanisms of the $GABA_A$ Desynchronizing Effect

As noted in the results section, $GABA_A$ disrupted the population burst, allowing fewer neurons to fire and thereby leaving more neurons that were primed to fire during the interburst interval. Related to this was the fact that increased inhibitory tone prevented a single pyramidal neuron from immediately causing firing in a postsynaptic neuron. The regularity of firing of the individual neurons will be reflected in the population so long as a single neuron can trigger a population spike. The requirement for coincident synaptic activation in the presence of inhibition will tend to obscure this regularity since the phases of the individual neurons will generally drift apart due to parameter variation. Coincident presynaptic firing will be sensitive to this drift.

In contrast to previous studies (Golomb et al. 1994, Golomb and Rinzel 1993), the authors did not find evidence for a break-up of synchronized activity into smaller phase-locked subpopulations. This break-up phenomenon has been seen most clearly in networks made up entirely of inhibitory neurons but is also seen in networks with mixed and excitatory elements (Kopell and LeMasson 1994) . The occurrence of subpopulations in the Kopell and LeMasson model was dependent on I_H producing firing at a subharmonic of the incoming IPSP frequency. Absent this conductance, phase-locked subpopulations were not seen in the present model.

In addition to these effects, more subtle alterations also seemed to affect synchrony. In the simulations where NMDA-mediated bursting dominated (Fig. 3), burst timing was dependent on the rate of depolarization produced by the preceding AMPA activation necessary to relieve the magnesium blockade and allow NMDA activation. Variability in timing of the $GABA_A$ activation was therefore magnified by its effect on the depolarization necessary to permit the NMDA burst. Small delays in feedforward and feedback $GABA_A$ activation translated into large delays in the onset of the burst.

In the network containing I_T (Fig. 4), $GABA_A$ was expected to produce greater synchrony

since divergent output from a single interneuron could potentially simultaneously deinactivate T channels in follower pyramidal neurons and produce a synchronous population burst. Instead, the desynchronizing effect of $GABA_A$ was still present. The several effects described certainly all played a role in preserving $GABA_A$ desynchronization. Additionally, the authors hypothesize that while large hyperpolarizing forces would be expected to augment synchrony, smaller hyperpolarizations that would lead to cumulative T channel deinactivation over time might show a magnification of variance effect similar to that described above for the NMDA case and similar to that seen with I_H in previous models (Kopell and LeMasson 1994). Thus, minor deinactivation would not lead directly to a burst but would tend to prime the postsynaptic neuron to a variable degree.

Another relatively minor effect that disrupted synchrony occurred due to the fact that chloride, the $GABA_A$ ion, has a less negative reversal potential than does potassium, the predominant conductance during the interburst interval. Therefore $GABA_A$ postsynaptic potentials became depolarizing during the intense hyperpolarization of the interburst interval. Although the magnitude of this current was insufficient to overcome the effect of maximal I_{AHP} or $GABA_B$ activated current, this activation appeared to play some role in augmenting excitatory activation towards the end of the interburst interval, leading to the earlier occurrence of bursting.

Does $GABA_A$ Synchronize or Desynchronize?

One objective of this study was to evaluate an apparent paradox: some research describe interneurons as having a synchronizing influence on pyramidal neurons while others describe them as having a desynchronizing influence. The synchronizing role has been ascribed to $GABA_A$ interneurons in a setting where synchronous inhibitory inputs occur on a background of diffuse excitatory input (Lytton and Sejnowski 1991, Cobb et al. 1995). This contrasts markedly with the setting where desynchronization has been described: epileptiform models where overexcitation leads to high degrees of synchronization. Thus, the seemingly contradictory roles of $GABA_A$ interneurons do not conflict but simply reflect the operations of a modulatory mechanism in two very different situations. In a desynchronized system, $GABA_A$ interneurons can serve a pacemaker role and increase synchrony (Lytton

and Sejnowski 1991). In the setting of excessive synchrony with large epileptiform population bursts, $GABA_A$ could disrupt simultaneous firing through the mechanisms described here.

Prolonged Hyperpolarization Tends to Synchronize

The rapid action of $GABA_A$ inputs is in marked contrast to the very prolonged inhibition produced by $GABA_B$ activation or by the intrinsic effects of slowly decaying potassium channels such as I_{AHP}. While $GABA_A$ is desynchronizing, these slower hyperpolarizing mechanisms tend to reinforce synchronization by enforcing a prolonged relative refractory period that tends to phase set all the neurons identically (Fig. 5) .

The role of $GABA_B$ interneuron activity in epilepsy and normal cortical function are still poorly understood. It has been suggested that $GABA_B$ activation may only take place under conditions associated with excessive activity. This may be due both to a higher threshold for driving the subpopulation of interneurons projecting onto $GABA_B$ receptors and to a cooperative effect requiring intense synaptic activation at the receptor itself (Thompson 1994, Destexhe and Sejnowski 1995). Therefore, $GABA_B$ activation might be regarded as a safety valve that activates only when excitatory cells are overdriven. A similar function could also be imputed to the intrinsic afterhyperpolarizing currents, such as I_{AHP}, that will tend to be heavily activated with the massive calcium influx that would occur with excessive activation. While these mollifying influences might protect pyramidal neurons from excitotoxicity, the downside of this overdrive protection might be an increased tendency to synchrony that results in epilepsy.

Conclusions

Inhibitory $GABA_A$ activity may play opposite roles in modulating synchrony depending on whether it occurs against a desynchronized background or against the hypersynchrony characteristic of epilepsy. In the latter case it would be expected to disrupt large population bursts and produce relative desynchronization. Conversely, the more prolonged hyperpolarization due to $GABA_B$ activation would be expected to enhance synchrony in either setting.

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