The contributions of different interneuron types to the activity patterns and plasticity of pyramidal cells in the hippocampus

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Cortical areas typically contain a single type of principal neuron; this excitatory population gives rise to most of the output projections from an area, and their spiking activities are believed to carry the vast majority of the information represented there. The relative uniformity of principal neurons may be contrasted with the great variety of (mostly inhibitory) interneurons which accompany them. Different classes of interneurons have been distinguished based on several criteria, including dendritic and axonal arborization, cellular and subcellular target selectivity, neurochemical marker content, receptor types and electrophysiological characteristics. Accordingly, the various interneuron types have been proposed to play different roles in modulating the activity and plasticity of principal cell populations. However, despite our growing knowledge of interneurons, quantitative efforts to understand their functioning and the consequences of their interactions with principal cells through computational modeling have been quite limited. Here we describe our efforts to create simple compartmental models of some basic types of hippocampal interneuron, which are then used in network simulations to explore the ways in which they modulate activity in the somata and dendrites of CA1 pyramidal cells. Simulations were performed in the GENESIS environment.

We have focused on two very distinct classes of CA1 interneuron: basket cells, which receive inputs from a variety of sources and target the perisomatic region of pyramidal neurons, and oriens - lacunosum moleculare (O-LM) interneurons, which provide mostly feedback inhibition to the distal apical dendrites of pyramidal cells. Basket cells are assumed to modulate the spiking activity of their target pyramidal cells, while O-LM cells are thought to be ideally placed to modulate the strength and plasticity of input from the perforant path, which also targets the distal dendritic region of CA1 pyramidal neurons.

Based on their morphology and membrane properties, hippocampal interneurons are thought to be electrotonically compact, and were therefore modeled using a single neuronal compartment. In agreement with earlier studies, we found that conventional Hodgkin-Huxley type Na^+ and delayed rectifier K^+ channels were sufficient to reproduce the fast-spiking

physiological phenotype and the measured firing rate - injected current relationship of basket cells. In contrast, O-LM cells display relatively complex behavior under standard voltage- and current-clamp conditions, and have been shown to contain a large set of voltage-gated and/or Ca-dependent ion channels, somewhat similar to pyramidal cells. We show that many of these channels have essential contributions to the observed physiological characteristics of O-LM neurons. In particular, action potential shape and amplitude seem to depend on at least 6 distinct currents: a transient Na^+ current, a high-threshold Ca^{2+} current, two delayed rectifier K^+ currents, an A-type transient K^+ current, and a Ca-dependent voltage-gated (C-type) K^+ current. The characteristic "sag" response to hyperpolarizing current steps depends on the presence of the h-type (hyperpolarization-activated mixed) cation current, which also contributes to the resting potential of the cell, along with the A-type K^+ current. In fact, these two currents appeared to play a major role in determining the baseline excitability of the O-LM cell. Spike frequency adaptation in the model was due to the presence of the Ca-activated slow K^+ current K(AHP). We also found that the observed preference of O-LM cells for low firing frequencies (relative to, say, basket cells) does not appear to result from the action of any single ion channel. Rather, several different channels, including K(AHP), the high-threshold Ca^{2+} channel, and an experimentally identified slower type of delayed rectifier K^+ channel had independent as well as synergistic contributions to this slow phenotype.

We also tested the frequency preferences of our interneuron models using oscillatory input currents. In agreement with experimental observations, we found that our O-LM model cell fired one action potential per cycle when the frequency of the oscillatory component of the input was in the theta (4-10 Hz) range, but that it skipped several cycles between spikes for inputs at higher frequencies (e.g., those in the gamma frequency range). In contrast, our model basket cell could easily follow oscillations in the gamma frequency range.

Our model of the CA1 pyramidal cell was a modified version of Traub et al.'s (1991) CA1 model. The main difference is the presence in our model of transient Na^+ and delayed rectifier K^+ currents in the dendrites as well as the soma, which enables action potentials to backpropagate into the dendrites.

After we have confirmed the validity of our single-cell models, we looked at the interactions between these interneurons and small populations of CA1 pyramidal cells. In agreement with earlier models, we found that a population of reciprocally interconnected fast-spiking (basket-type) interneurons could naturally oscillate and synchronize in the gamma frequency range, and these basket cells could entrain pyramidal cells through fast inhibitory synapses to fire – albeit at relatively low frequencies – preferentially near a particular phase of the basket cell oscillation. Excitatory input from the pyramidal cells to the basket cells decreased the coherence of the basket cell oscillation, and eliminated any rhythmicity in the spiking activity of individual pyramidal cells, while maintaining the phase relationship between pyramidal and basket cell populations.

As expected, inhibitory input to the distal apical dendrites resulting from O-LM cell activity had a much smaller direct effect on the somatic voltage and spiking activity of pyramidal cells than somatic input from basket cells. However, when (tonic, random) excitatory input to pyramidal cells was provided solely through the perforant path, pyramidal cell spiking was strongly modulated by O-LM cell activity. This effect was mediated by the shunting of perforant path EPSPs through the activation of dendritic GABA(A) conductances by the

O-LM cell input. This shunting effect depended on the relative timing of the two inputs; a more than twofold reduction in EPSP amplitude could be achieved by relatively widespread dendritic inhibition if O-LM cell activity preceded the perforant path input by about 5-15 ms. This inhibitory effect was specific to input through the perforant path, since inputs to other (more proximal) parts of the cell, such as those mediated by the Schaffer collaterals, were essentially unaffected.

Finally, we have also started to investigate the effects of dendritic inhibition on the backpropagation of action potentials into distal parts of the dendritic tree. In our model, strong, synchronous inhibitory input to a large segment of the apical dendrites was required to cause backpropagating action potentials to fail. The timing of inhibition was also found to be critical; importantly, due to the slow kinetics of O-LM cell-mediated inhibition on pyramidal cells, O-LM cell spiking had to *precede* the somatic action potential in the pyramidal cell by at least 1-2 ms (and no more than about 25 ms) to be able to block action potential backpropagation in the dendrites. This result indicates that direct inhibitory feedback to a pyramidal cell through O-LM cell activation occurs almost certainly too late to interact with the backpropagating spike within the same pyramidal neuron. On the other hand, such feedback through O-LM cells could effectively suppress the efficacy and plasticity of perforant path inputs to pyramidal cells which fire slightly later than those which activated the O-LM cell feedback. This mechanism may thus provide an ideal substrate for competitive learning.