SLOW AND FAST INHIBITION AND H-CURRENT INTERACT TO CREATE A THETA RHYTHM IN CA1 IN VITRO.

Horacio G. Rotstein [1], Martin J. Gillies [2], Corey D. Acker [3], John A. White [3], Miles A. Whittington [2], Nancy Kopell [1]

[1] Department of Mathematics and Center for Biodynamics, Boston University, Boston, MA, 02215
[2] School of Biomedical Sciences, University of Leeds, Leeds LS2 9NQ, UK.
[3] Department of Biomedical Engineering and Center for Biodynamics, Boston University, Boston, MA, 02215

Gillies et al. [1] have shown the existence of atropine-resistant theta frequency oscillations in slices of the CA1 hippocampal area in the presence of metabotropic glutamate. These oscillations require reduced AMPA receptor activation, and can be seen in the presence of a total blockade of the latter. A critical class of cells of this oscillatory network is a subset of inhibitory interneurons in stratum oriens (O-LM cells), which have been shown to cause long-lasting (tau $\sim$ 30ms) $GABA_A$ receptor based IPSPs in post-synaptic cells. In the CA1 network, the O-LM cells project to the distal apical dendrites of the pyramids, and the field theta is associated with currents in these dendrites. In vitro, in the absence of external input, the field theta is not compatible with field gamma, which occurs when the pyramidal somata fire.

We describe a model of this mechanism for theta, focusing on the activity of the O-LM cells (O) and other inhibitory neurons (I). We model the O cells using persistent Na and h currents, whose blockade destroys the oscillations, in addition to the standard transient Na, delayed rectifier K and leak currents. The I cells are modelled as standard Hodgkin-Huxley neurons. Both type of cells have standard $GABA_A$ IPSPs but the O cells IPSPs last longer than those corresponding to the I cells.

Our simulations show that the firing frequency of a tonically driven O-LM cell depends on both the drive and the conductance of the h-current, being an increasing function of

each. This is confirmed by our analytical results. We show that a network consisting only of O-LM cells does not robustly synchronize at theta frequencies but it can do so by getting common input from basket (I) cells. We present the results of our simulations that are in a very good agreement with the experimental results presented by Gillies at al. We also provide heuristic explanations for our findings.

Using numerical and analytical techniques we study the dynamics of the O cells, In particular we study the role of the persistent Na and h currents in determining the firing frequency of the O cells. We show that in most of the interspike interval the dynamics of the single O cell model can be described by a sequence of 2 dimensional systems involving the dominant currents in different time subintervals. One of such reduced systems involve the leak and delayed rectifier K current, and describes the response of the system to hyperpolarization. Once the delayed rectifier K current wears off, the leak, persistent Na and h currents are dominant. For a given tonic drive, the next firing time after a spike event is determined by a balance between the leak and persistent Na currents, and the slowly increasing h current modulates this balance.

Following the same reasoning but considering the hyperpolarization of a single O cell as an IPSP produced by another O cell, we construct a time response curve (TRC) by calculating the firing time $\bar{t}_1$ after a spike occured at t_1 as a function of $\Delta t = t_2 - t_1$ where t_2 is the perturbation time by the second O cell. With the help of the TRC for two O cells we construct a map on the difference in spike times between the O cells. This tool allows us to predict that two O cells will not synchronize unless the initial Δt is very small. Heuristic theoretical considerations and simulations show that synchronization of the O cells can be achieved in a network including I cells in addition to O cells.

References

[1] M. J. Gillies, R. D. Traub, F. E. N Le Bleau, C. H. Davis, T. Gloveli, E. H. Buhl, and M. A. Whittington. A model of atropine-resistant theta oscillations in rat hippocampal area CA1. *J Physiol (Lond)*, 543:779–793, 2002.