GABAergic modulation of theta activity in the septohippocampal system

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Theta rhythm (3-8 Hz) is a prominent physiological activity in the hippocampal formation of rodents and is a typical activity in other mammals prevalent during rapid eye movement sleep and several distinct behaviors during arousal. There are opposing views concerning the source of this rhythmic activity. While several physiological and computational studies point out that the septum is the source of hippocampal theta (as the intactness of septal neurons firing in the theta band seems to be necessary), other studies suggest intrahippocampal mechanisms and the involvement of the entorhinal cortex. A weak synthesis of these investigations is that there is an accumulating evidence that a simple circuitry consisting of only one or two populations of neurons can not account for the broad spectrum of physiological behavior observed during theta activity, multiple populations are implicated.

In our study we used detailed compartmental modeling technique to describe interactions between three hippocampal and a single septal neuron population. Hippocampal neuron populations were CA1 pyramidal cells, basket neurons and oriens interneurons (Fig. 1). Although more populations are likely to participate in the generation and maintainance of theta activity (for instance calretinin containing interneurons), we focused on whether verified anatomical connections and physiological behavior of the modeled cell types enable them to reproduce the observed timing of action potentials of these cells [2, 3, 6]. As *in vitro* studies suggested that atropine resistant type of theta activity, which is particularly relevant as in behaving animals theta rhythm persists if muscarinic receptors are blocked by atropine, can be elicited in a CA1 slice preparation [3] in the first set of simulations the hippocampal populations were modeled. Recent studies suggested that basket cell inhibitory postsynaptic potentials (IPSPs) can elicit rebound spikes in pyramidal neurons [1]. Therefore we explored under what conditions such a rebound activation can be elicited and found that a physiologically realistic convergence on pyramidal cells was sufficient (Fig. 2). Thus, disinhibion of pyramidal neuron was neccessary for action potential generation. This disinhibition was provided by the oriens interneurons (figure not shown). O–LM neurons are known to be able to generate intrinsic low frequency oscillations. As these cells innervate parvalbumin positive neurons [4] they are able to carry out the disinhibition of pyramidal cells (Fig. 3). Synchronization of the O–LM neuron population was achieved only in the case when pyramidal cell-to-O–LM neuron connections were taken into account (figure not shown)

Although $\mathrm{GABA_A}$ synapses are neccessary for theta activity in the hippocampus, the role of GABAergic transmission is poorly understood. In our further investigations we were interested in the dependence of theta activity on GABAergic synaptic transmission.

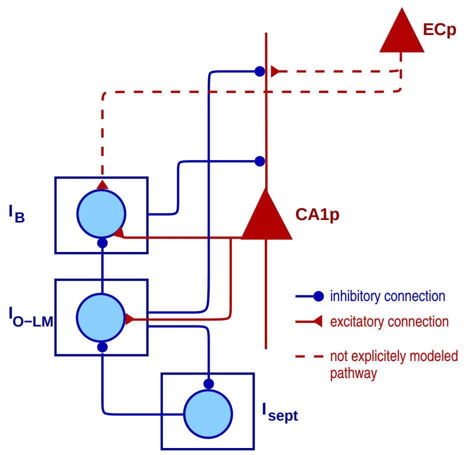

Figure 1: Neuron populations and structure of connections. I_b: basket neurons, I_{o-lm}: oriens–lacunosum-moleculare neuron (O–LM neuron), $CA1_p$ pyramidal cell, I_{sept}: septal GABAergic neuron. Box around the cell denotes a neuron population. A single basket neuron established connections up to 60 neurons of the same population, while 10 – 14 basket neurons innervated a single pyramidal neuron. O–LM neuron to basket cell connections were in the range of 50 synapses established by an O–LM neuron.

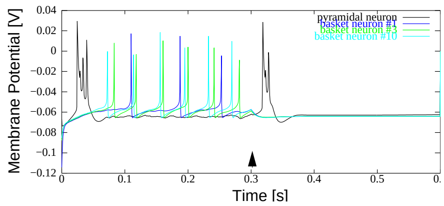

Figure 2: Simulation of rebound spike elicited in the pyramidal cells (black line) by IPSP of a basket neuron network (green and blue lines). 20 randomly chosen basket neuron converged on a single pyramidal cell (synaptic conductance was 1.3 nS, site of termination was on the proximal apical dendrite of the pyramidal neuron). Basket cell firing was blocked by lowering the constant depolarizing current on every basket neuron (*arrowhead*). Silence of basket neurons reliably caused action potential generation in the pyramidal neuron.

For this purpose computational methods in combination with physiological techniques in *in vivo* conditions were used. The GABA allosteric modulator inverse benzodiazepine-antagonist FG-7142 was used to pharmacologically modulate the synaptic transmission in the septohippocampal circuitry. FG-7142 was shown to induce or enhance theta activity both in the CA1 region of the hippocampus and septum as revealed by EEG and autocorrelation of spike trains, respectively (Fig. 4A).

Autocorrelograms revealed a switch from non-periodic to a theta-periodic behavior in neurons characterized as non-theta cells. This result shows that the classification of septal neurons as theta- and non-theta cells [5] can only be sound with a given strength of synaptic transmission but not with changing ones. We used the septal GABAergic neuron model and the three-neuron population hippocampal CA1 model to simulate the effect of modulation of GABAergic transmission. The septal GABAergic neuron model posessed intrinsic firing properties in the theta band [7]. We took into account the effect of FG-7142 with a lower conductance of the chloride channels in the $GABA_A$ synapses. In our control simulations we found that using a randomly connected network different neurons could show distinct forms of behavior (Fig. 4). While one part of the network fired periodically the other part fired irregularly. With a given network structure, a neuron

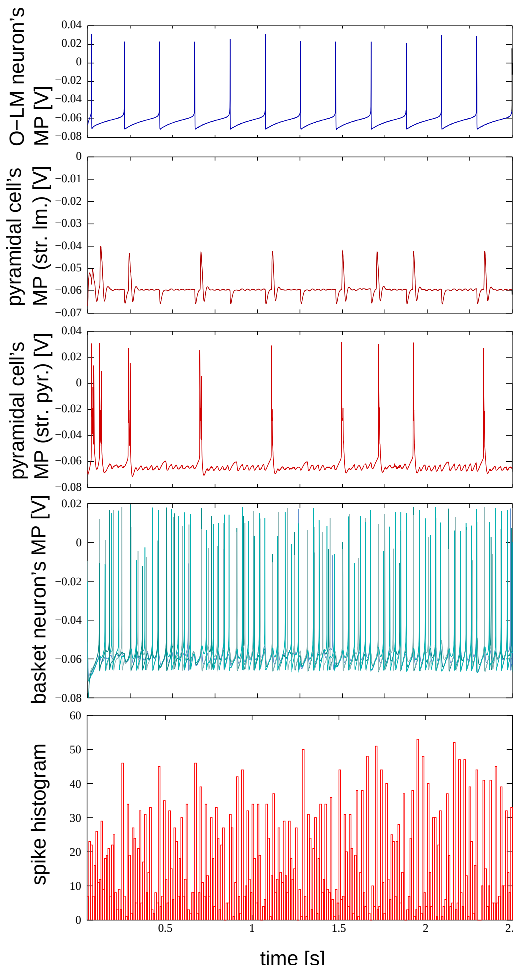

Figure 3: Theta frequency oscillation in the hippocampal CA1 region. In this specific simulation 100 basket neurons, one O–LM neuron and one pyramidal cell was used. Using a single oriens neuron it indirectly triggers theta-frequency firing of the pyramidal neuron by evoking depolarizing afterpotentials. Backpropagation of action potentials into the dendrites and emergence of calcium spikes are observable (dispite of the action potentials of basket neurons). Note, that under physiological conditions the pyramidal cell is not able to generate action potentials in every theta cycle. In this simulation pyramidal neuron-to-O–LM neuron interaction was not implemented.

was characterized by this behavior and this characteristic behavior depended on network structure (figure not shown). This result was in accordance with previous experimental observations [5]. Systematically changing the synaptic conductance resulted in more and more periodically firing septal neurons (figure not shown). This observation can be easily explained by the fact that lower conductance means less perturbation to a given cell. Although weakening the coupling between septal neurons caused the neurons to fire more periodically the periodicity of single cells was not expressed in the coherence of the oscillation: the network synchrony did not rise significantly. Finally, implementing the septohippocampal projection we suggest that increased theta activity following the application of FG-7142 is a result of more regularly firing O–LM neurons.

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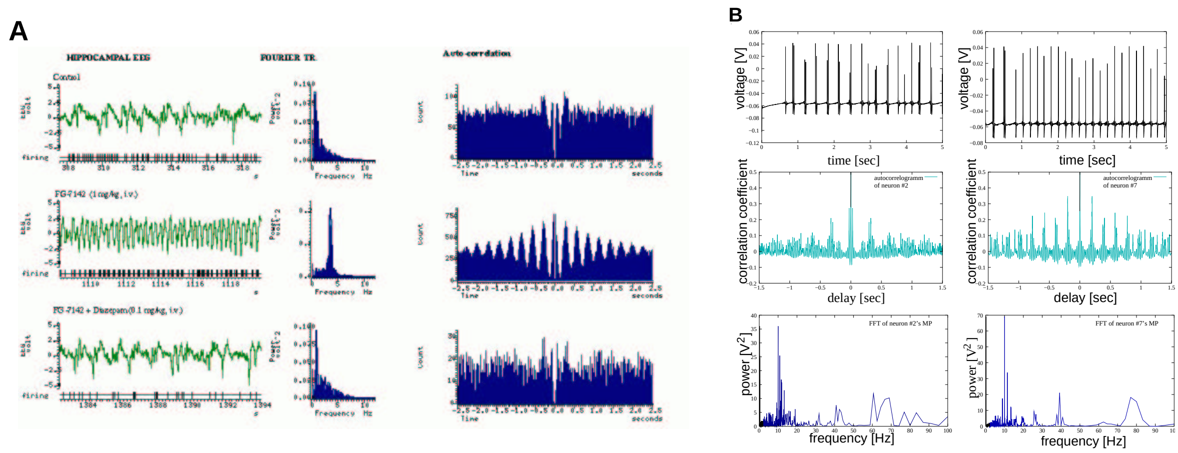

Figure 4: **A**, Effect of FG-7142 (*center*) and diazepam (*bottom*) on the septohippocampal system. Both field potentials in the CA1 region (*left panel* power spectum on the *middle panel*) and septal unit recording (*right panel*) shows enhanced theta modulation of activity after treatment with FG-7142 and attenuation of theta activity after application of diazepam. **B**, Physiological behavior of single neurons in a simulated randomly connected network. The simulation was conducted with 100 septal GABAergic neurons, every neuron received 40 contacts from the other septal neurons. As a result of heterogeneity single neurons showed markedly different forms of behavior. Both highly coherent priodic oscillation (*right panel*) and non-periodic behavior could be observed. (*upper row:* membrane potentials (MPs) of septal neurons, *middle row:* autocorrelograms of MPs, *bottom row:* power spectra of MPs)

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