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Changes of GABAergic Inhibition Substantially Modulate the Neuronal Firing in the Initial Period of High-Frequency Stimulation

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***Abstract*—High-frequency stimulation (HFS) of pulses has been used to treat some neurological disorders, but its action mechanisms are not completely clear. Here we built a computational model to investigate the role of GABAergic inhibitions on neuronal reactions in the initial period of orthodromic HFS in rat hippocampal CA1 region. Results showed that the computational simulation reproduced the neuronal responses in real rat experiments. The change of GABA-A current from inhibition to excitation and the partial inactivation of sodium channels induced by HFS inputs resulted in a triphasic change of the firing of pyramidal cells: inhibition-excitation-inhibition. The study provides new clues to reveal the mechanisms of HFS.**

I. Introduction

Deep brain stimulation commonly utilizes HFS to treat neurological disorders with its underlying mechanisms unclear. Previous studies have reported that the inhibition of GABAergic synapses can be altered by HFS, even be transformed to excitation [1]. We hypothesized that this alteration of GABAergic inhibitions could play a significant role during HFS. Thus, we built a computational model involving GABAergic networks and an accumulation mechanism of intracellular chloride ($[Cl^-]_i$) in post-synaptic neurons, to investigate the effect of the change of GABA-A inhibitions on neuronal firing during the initial period of HFS.

II. Method and Materials

The computational model of local neuronal circuit of hippocampal CA1 region was built by NEURON simulation package. It consisted of 100 pyramidal cells (PC), 2 basket cells (BC), 1 bistratified cell (BSC), 1 axonic cell (AAC) and 1 oriens moleculare cell (OLM) [2]. A HFS sequency (0.3 mA, 100 Hz, 250 ms) was applied at the afferent fiber, the Schaffer collaterals (SC) of the circuit (Fig. 1A). The integrated extracellular potential, membrane potentials of BSC and PC, the post-synaptic current and $[Cl^-]_i$ of GABA-A synapses, and the inactivation variable of sodium channel (*h*_Na) of PC soma were obtained.

III. Result and Discussion

The integrated potential of simulation recording (Fig. 1B *top*) was consistent with the experimental recording (Fig. 1B *bottom*, from reference [3]). In both recordings, the first pulse of HFS induced a large orthodromic population spike (OPS), but the following several pulses did not. Afterwards, OPSs reappeared with various amplitudes. The underlying process was that the BSC fired intensively following each pulse of HFS (Fig. 1C) thereby resulting in an increase of $[Cl^-]_i$ and a change of GABA-A current from inhibition to excitation (Fig. 1D). At the meantime, the *h*_Na of PC soma decreased under the HFS inputs (Fig. 1E), causing a decrease of PC excitability due to the inactivation of sodium channels. These factors together resulted in the firing pattern of single PC (Fig. 1F) that was similar to the integrated extracellular potential (Fig. 1B), i.e., inhibition-excitation-inhibition.

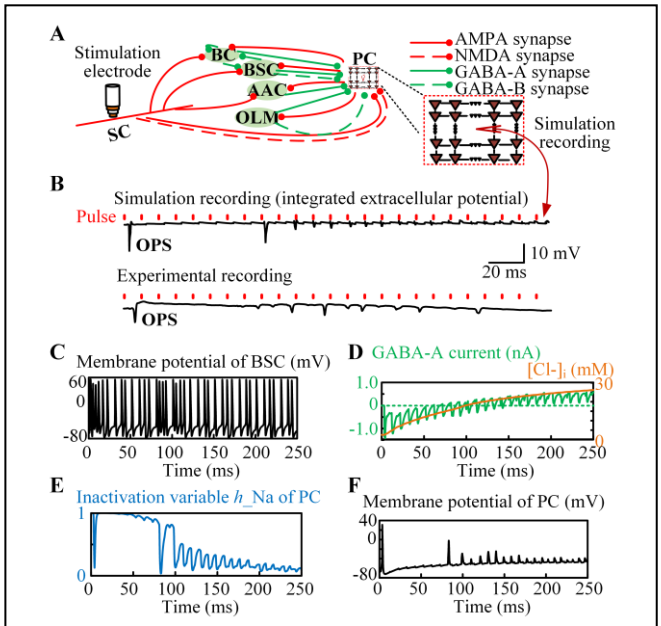

Figure 1. (A) Schematic diagram of CA1 network model. (B) Simulation versus experimental recording. (C) Membrane potential of BSC. (D) GABA-A current (in green) and $[Cl^-]_i$ (in orange). (E) Inactivation variable of sodium channels (*h*_Na) at soma of PC. (F) Membrane potential of PC.

The above results suggested that changes of GABAergic inhibition can substantially modulate the downstream neuronal activity in the initial period of HFS, which may be important for adaptive closed-loop stimulations.

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