Short- and long-term neuronal plasticity in hippocampal CA1 region of rat

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I: **Huang FS**, Meng K, Tang JS. Properties of paired-pulse firing thresholds and the relationship with paired-pulse plasticity in hippocampal CA3–CA1 synapses. *Eur J Neurosci. 2007 Jun; 25(11):3253-63.*

II: **Huang FS**,Tang JS. Variability of AMPA-EPSCs at CA3-CA1 synapses. *Manuscript.*

III: Li R, **Huang FS**, Abbas AK, Wigström H. Role of NMDA receptor subtypes in different forms of NMDA-dependent synaptic plasticity. *BMC Neurosci. 2007 Jul 26;8:55.*

IV: **Huang FS**, Abbas AK, Li R, Afanasenkau D, Wigström H. Bidirectional synaptic plasticity in response to single or paired pulse activation of NMDA receptors. *Neurosci Res. 2010 67: 108-116.*

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Abstract

The brain is highly plastic, displaying both short- and long-term changes, resulting from developmental processes as well as learning and memory. Moreover, short-term plasticity such as paired pulse facilitation and depression (PPF, PPD) have long been used to monitor the presynaptic versus postsynaptic changes occurring during more lasting processes such as long-term potentiation and depression (LTP, LTD). Many issues remain unresolved, e.g. how PPF and PPD are related to the probabilistic features of synaptic transmission, an issue which has also methodological aspects. Regarding LTP and LTD, it is still uncertain how Ca^{2+} via NMDA receptors (NMDA-R) produces either increases or decreases of synaptic strength.

Experiments were performed on hippocampal slices from 1-21 day-old Sprague-Dawley rats. Intracellular recordings were obtained from visually identified CA1 pyramidal cells using whole-cell patch clamp technique. Extracellular recordings were obtained under low magnification optical resolution by assessing field potentials evoked in the synaptic layer. AMPA-R and NMDA-R mediated responses were assessed in parallel via early and late measurements of composite excitatory postsynaptic potentials (EPSPs).

I first examined short-term plasticity in the millisecond to second range, including PPF and PPD, using weak paired or multiple stimuli to presynaptic afferents (minimal stimulation). Excitatory synaptic currents (EPSCs) in CA1 cells revealed a strength dependence, which was hard to explain as an isolated synaptic phenomenon, and so suggesting a role for unreliable activation of afferents. This idea was supported by CA3 cell recording, either to monitor axonal activity or used as a model for near threshold spike generation. Action potential firing thresholds in CA3 cells/axons were significantly lower for the second pulses of the paired-pulse stimulation than for the first pulses. This has consequences for interpreting measurements of synaptic parameters under unreliable presynaptic activation; e.g. release probability, paired pulse ratio and coefficient of variation.

The subsequent work involved longer lasting plasticity. Subunit-specific NMDA-R antagonists were used to target NR2A- or NR2B-containing receptors and were tested on LTP and two forms of LTD. It was found that NR2A-containing receptors dominate, both with respect to plasticity induction and their contribution to isolated NMDA-R responses. Experiments using a lowered Mg^{2+} concentration to amplify Ca^{2+} entry demonstrated that both subunit types contributed to induction of LTP and LTD. The data suggest that Ca^{2+} influx into the postsynaptic spine via different types of NMDA-Rs makes up a “final common pathway”, controlling synaptic plasticity by its magnitude and temporal pattern, regardless of the source. This issue was further interrogated by a protocol where NMDA-R activation was suddenly increased by switching from single-pulse stimulation (SPS) to paired-pulse stimulation (PPS). This led to an initial short-term potentiation of AMPA responses followed by a slowly developing LTD of both AMPA and NMDA. These results suggest that NMDA-dependent synaptic changes do not only depend on the instantaneous Ca^{2+} concentration in the postsynaptic spine but are also influenced by prior induction events. The results can be described by a modified BCM-model of metaplasticity with an activity-dependent sliding threshold. In addition to NMDA-R driven processes, passive relaxation contributes to the plasticity and in some cases can outbalance the active control.

Keywords: Glutamate, hippocampus, plasticity, synapse, LTP, LTD, AMPA, NMDA

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