Li, R. (2006) **Chemical and stimulus-induced NMDA-dependent plasticity and the possible involved mechanisms.** Department of Medical Biophysics, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Göteborg University, Medicinaregatan 11, Box 433, SE-405 30 Göteborg, Sweden

Abstract. Long-term potentiation (LTP) and long-term depression (LTD) are considered as the most important forms of synaptic plasticity involved in learning and memory. The traditional way to induce LTP and LTD is by electric stimulation leading to activation of NMDA-R. Later research also revealed a form of NMDA-dependent plasticity induced by direct application of NMDA. I have investigated the involvement of AMPA-R and NMDA-R in NMDA-induced LTD as well as their contribution to early and late phases of stimulus-induced LTP; examined the roles of different NMDA-R subunits in several forms of synaptic plasticity; and tried to elucidate the possible mechanisms underlying NMDA-induced plasticity.

The experiments were performed in hippocampal slices, 400 μm thick, from 12 to 20 days old Sprague-Dawley rats. Extracellular recording was used to study field excitatory postsynaptic potential (EPSPs) in the CA1 apical dendritic layer. Isolated AMPA EPSPs were obtained in standard solution or in low Mg^{2+} containing NMDA-R blocker AP5. Composite EPSPs were recorded in low Mg^{2+} whereas isolated NMDA EPSPs were expressed in low Mg^{2+} solution with AMPA-R blocker CNQX. LTP was elicited by HFS trains (100 impulses, 100 Hz) or in some cases theta-burst stimulation (10 times 4 impulses, 100 Hz, 200 ms interval). NMDA-induced LTD was achieved by brief (4 min) bath application of NMDA.

The results showed that 20-50 μM NMDA application persistently depressed both AMPA and NMDA responses to a nearly equal extent. In addition, a waveform prolongation of AMPA but not of NMDA EPSPs occurred 15-25 min after NMDA application. On the contrary, stimulus-induced LTP potentiated AMPA and NMDA responses to a different degree, with about two-fold larger increase of AMPA than NMDA component at both 1h and 4 h after induction. Different tests revealed noninvolvement of voltage dependent channels as well as GABAa-ergic inhibition in the NMDA-induced prolongation of AMPA EPSPs. However, EPSP prolongation was occluded by a similar change induced by AMPA-R modulator cyclothiazide (CTZ); and facilitated by AMPA-R modulator aniracetam.

The comparison of NMDA-induced effects in pathways with and without prior LTP demonstrated a larger depression and smaller waveform change in the LTP pathway. LTP and NMDA-induced LTD, as well as a form of stimulus-induced LTD, were all largely prevented by NVP-AAM077, a blocker of NMDA receptors that contain subunits of type NR2A. However, the blockade in these cases could be counteracted by general amplification of NMDA responses by lowering the perfused Mg^{2+} concentration. Blockers of NR2B- containing NMDA receptors by Ro25-6981 or Ifenprodil had no effect on the two forms of LTD whereas LTP was partially blocked. It was found that subunits NR2A and NR2B contributed to about 80% and 20%, respectively, of isolated NMDA EPSPs.

Our results demonstrate that NMDA applied on brain tissue induces multiple synaptic plasticity. Modifications underlying NMDA-induced LTD differ from those in LTP in several respects; however, these two forms of plasticity also interact, suggesting a possible relation. This is also supported by the fact that both LTP and NMDA-induced LTD require activation of NR2A containing NMDA receptors, and that both LTP and NMDA-induced waveform changes interact with AMPA receptor modulators. Notably, NR2A subunits play an essential role in all types of synaptic plasticity examined in this study whereas NR2B also contribute under certain circumstances. We therefore believe that the final magnitude and temporal pattern of Ca^{2+} influx in the spine is a key factor determining the induced synaptic plasticity.

Keywords: synaptic plasticity, hippocampus, LTP, LTD, AMPA, NMDA, NR2A, NR2B

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