André Leopold Ante Mihaljevic
Dr. med.

Analysis of recombinant glutamate receptors in the hippocampus of the mouse

Geboren am 19.07.1977 in Darmstadt, Hessen
Staatsexamen am 17.11.2005 an der Ruprecht-Karls Universität Heidelberg

Promotionsfach: klinische Neurobiologie (Neurologie)
Doktorvater: Frau Prof. Dr. med. Hannah Monyer

Synaptic plasticity, i.e. activity-dependent prolonged changes in the transmission of nerve cells, is the leading model to explain memory formation and learning. Long-term potentiation (LTP), the most widely analyzed form of synaptic plasticity, has been studied extensively at the synapses of the Schaffer collaterals to CA1 principal neurons in the hippocampus, a brain structure involved in explicit memory formation. Ionotropic glutamate receptors of the NMDA and AMPA subtype have been shown to be essential for LTP induction and maintenance, respectively. In this study, we demonstrate the influence of the NMDAR subunit NR2A on LTP induction. We show that in contrast to wild-type controls, in mice lacking the C-terminal domain of NR2A ($NR2A^{\Delta C/\Delta C}$) LTP at CA3-to-CA1 synapses in juvenile as well as in adult mice is solely dependent on NR2B containing complexes although NR2A subunits are incorporated into NMDA receptors and can be found at synaptic sites. This illustrates the importance of the C-terminal domain of NR2 subunits in mediating the induction of hippocampal LTP. Furthermore, we report the establishment of a transgenic system for the conditional expression of a green fluorescent protein (GFP) -tagged version of the AMPA receptor (AMPAR) subunit GluR-B (^{GFP}GluR-B). We show that the expression of ^{GFP}GluR-B in principal neurons of the forebrain can be regulated by doxycycline *in vivo*. In addition, we demonstrate that ^{GFP}GluR-B is incorporated into AMPAR complexes, exhibits the same subcellular localization as endogenous GluR-B and reverses Ca^{2+}-permeable AMPAR currents to Ca^{2+}-impermeable currents in GluR-B knockout mice. ^{GFP}GluR-B, however, does not co-assemble with other GluR-B subunits neither in total hippocampal extracts

nor in purified tetrameric AMPAR complexes. Moreover, quantification of endogenous AMPAR subunits in the hippocampus of wild-type mice shows a two- to threefold excess of GluR-A over GluR-B subunits. These results suggest the following new model of heteromeric AMPAR assembly in the hippocampus: AMPAR subunit dimers preferentially combine to form asymmetric tetramers containing a single GluR-B and three GluR-A or –C subunits.