Calcium dependent modulation of magnesium block in different NMDA-receptor subtypes

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N-methyl-D-aspartate (NMDA) receptors are among the major excitatory cation channels in the brain. Key properties of these channels are their high Ca^{2+} permeability and voltage-dependent block by Mg^{2+}. Postsynaptic Ca^{2+} influx through NMDA receptors is important for the activation of molecular cascades underlying both short-term and long-term plasticity. Furthermore, the voltage-dependent Mg^{2+} block suggests a role for the NMDA channel as a coincidence detector of pre- and postsynaptic activity. At hyperpolarized membrane potentials, a synaptic event releasing glutamate on NMDA receptors will not cause a Ca^{2+} influx through these channels, because they are blocked by Mg^{2+}. However, when this synaptic event coincides with a postsynaptic depolarization, Mg^{2+} block is releaved, and NMDA receptors can conduct Ca^{2+}.
Pilot experiments suggest that the voltage-dependent Mg^{2+} block of NMDA receptors containing the NR2C or NR2D subunit can be modulated by extracellular Ca^{2+} concentrations. Since the voltage dependence of the Mg^{2+} block determines the window of postsynaptic depolarization in which coincidence detection is highest, modulation of this voltage dependence could be very important for synaptic integration. Changes in extracellular Ca^{2+} concentration are likely to occur upon high network activity. But even local changes in Ca^{2+} concentrations, for instance in the synaptic cleft, could have a high impact on NMDA receptor functioning.
Hence, we hypothesize that functional expression of specific NMDA receptor subtypes, combined with physiological relevant changes in extracellular Ca^{2+} concentration, may give rise to a hitherto unknown mechanism underlying the induction of synaptic plasticity. Currently we are studying Ca^{2+} dependent modulation of different NMDA receptor subtypes by expression of these subtypes in HEK-293 cells. Furthermore, using the nucleated patch technique in addition to paired whole cell recordings, we will study this same mechanism on NMDA receptors of different cell types in slices of the mouse prefrontal cortex, to determine its physiological significance.

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Poster session of choice: Neuroscience 2 on Thursday 3 June