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Ambient glutamate as a tool to dissect synaptic and extrasynaptic NMDA receptor pools

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NMDA receptors (NMDARs) play a central role in synaptic plasticity in the majority of excitatory synapses in the central nervous system. An additional important aspect of NMDARs activity is their contribution to neuronal health. Depending on their subcellular localization they promote neuronal survival or death. Synaptic NMDARs are coupled to pro-survival signaling whereas extrasynaptic NMDARs (ES-NMDARs) activate pro-death pathways.

This thesis describes a novel method to quantify the number of ES-NMDARs in an acute slice preparation of hippocampal CA1 pyramidal neurons. It takes advantage of the tonic activity of ES-NMDARs mediated by ambient glutamate whose spatial distribution is tightly regulated by glutamate transporters. Ambient glutamate is kept out of synaptic cleft and preferentially interacts with ES-NMDARs. Incubation of the slice with MK-801, a quasi-irreversible NMDAR active channel inhibitor, favorably blocks ES-NMDARs, and thereby allows a segregation of the two NMDAR pools. The results suggest that at least one quarter of NMDARs in the apical dendrites are located extrasynaptically. No receptor trafficking between synaptic and extrasynaptic locations could be detected.

Interestingly, applying the same method in the basal dendrites fails to detect any ES-NMDARs. The difference between basal and apical dendrites requires further investigation.