Summary of the thesis

Glutamate is a main excitatory neurotransmitter in the brain of mammals, which activates both ionotropic and metabotropic glutamate receptors. Ionotropic receptors are responsible for fast synaptic transmission leading to membrane depolarization and Ca2+ influx into the cell. On the other hand mGlu receptors play an important role in regulation of the transmission via heterotrimeric G-proteins and activation of various signaling pathways. Postsynaptically localized group I mGlu receptors (mGluR1, 5) together with ionotropic NMDA and AMPA receptors share common large receptor signaling complexes, or signalosome facilitating glutamate signal transductions. Individual mGluR1 splice variants are differently associated with signalosome including scaffold proteins like PSD-95 which organize postsynaptic density (PSD).

Heterodimerization of different mGluR1 splice variants is a focal point of my thesis together with investigation of recently discovered protein IL1RAPL1 (interleukin-1 receptor accessory protein-like 1) and its role in organization of postsynaptic signalosome.

Using biochemical, immunocytochemical and functional assays we showed heterodimers of mGluR1a/1b were expressed on the plasma membrane and that heterodimers are fully functional in the recombinant system. Next we showed that the long splice variant mGluR1a had a chaperon effect on cell surface targeting of the short mGluR1b. C-termini that distinguish between the mGluR1a and mGluR1b do not prevent heterodimerization of functional receptors. Heterodimerization of mGlu receptors offers new possibilities for increasing functional variability of glutamate signaling that facilitate metabotropic receptors.

In the second part of the thesis we successfully identified several MAGUK (membrane associated guanylate kinase) proteins as proteins interacting with IL1RAPL1. MAGUK proteins play an important role in organizing of a three dimensional protein structure in PSD. Next we concentrated on the well-known PSD-95 protein. Using Y2H tests, biochemical and immunocytochemical methods we characterized individual domains of both IL1RAPL1 and PSD-95 that were responsible for detected interaction. We showed that IL1RAPL1 regulates PSD-95 localization in postsynaptic densities, thereby probably fundamentally influence strength of synaptic transmission, synaptic plasticity and number of glutamatergic synapses in hippocampus. Loss-of-function mutation in IL1RAPL1 gene can be responsible for mental retardation via dysregulation of PSD-95 in patients with mutated IL1RAPL1.