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Characterization of novel AMPA receptor interacting proteins

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AMPA receptors are ionotropic glutamate receptors that mediate the vast majority of fast excitatory neurotransmission in the mammalian brain and play a key role in short- and long-term synaptic plasticity. In addition to pore-forming subunits GluA1-GluA4, AMPA receptor complexes contain different auxiliary subunits, namely TARPs, CNIHs, SynDIG1, CKAMP44, GSG1-l, and most likely several other hitherto uncharacterized proteins. Each of these auxiliary subunits is differentially expressed across the mammalian CNS and influences AMPA receptor function in distinct ways.

In this study, three proteins closely related to CKAMP44 – named CKAMP39, CKAMP52, and CKAMP59 – are introduced as novel putative AMPA receptor auxiliary subunits. Co-immunoprecipitation assays revealed that all members of the CKAMP family interact with GluA1-containing AMPA receptors in a heterologous expression system. When overexpressed in hippocampal neurons, the new CKAMP family members were present – and in the case of CKAMP39 enriched – in dendritic spines, suggesting their potential association with AMPA receptors. In order to study the impact of CKAMPs on AMPA receptor function *in vivo*, AAV vectors have been generated to knock down the expression of CKAMP39, CKAMP52, and CKAMP59, respectively, in the mouse brain. To critically evaluate if the novel CKAMP family members can be defined as AMPA receptor auxiliary subunits, future studies would need to determine to what extent CKAMPs associate with AMPA receptors *in vivo* and what impact they have on AMPA receptor function.

In the hippocampus, CKAMP44 and TARP γ-8 are two of the most abundant AMPA receptor auxiliary subunits. Co-immunoprecipitation assays have shown that CKAMP44 and TARP γ-8 can be part of the same AMPA receptor complexes both *in vitro* and *in vivo*. Finally, AMPA receptors containing TARP γ-2/4 also seem to contain CKAMP44, suggesting that TARPs and CKAMPs use distinct binding sites for their interaction with AMPA receptor subunits.

Future challenges in the study of CKAMPs and other AMPA receptor interacting proteins will be to unravel the structural mechanism of their interaction with AMPA receptors, to test how their respective functions relate to one another, and to investigate the dynamics of their interaction. An in-depth investigation of the glutamatergic synapse is of major importance for the understanding of many neuropsychiatric disorders, and might eventually contribute to target-oriented treatments for these diseases.