SL02 Regulation of Neurotransmitter Receptors and Synaptic Plasticity in the Brain

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Neurotransmitter receptors mediate signal transduction at the postsynaptic membrane of synaptic connections between neurons in the nervous system. We have been studying the molecular mechanisms in the regulation of neurotransmitter receptor function. Recently we have focused on glutamate receptors, the major excitatory receptors in the brain. Glutamate receptors can be divided into two major classes: AMPA and NMDA receptors. AMPA receptors mediate rapid excitatory synaptic transmission while NMDA receptors play important roles in neuronal plasticity and development. Studies in our laboratory have found that both AMPA and NMDA receptors are multiply phosphorylated by a variety of protein kinases. Phosphorylation regulates several functional properties of these receptors including conductance and membrane targeting. Recent studies in our lab have demonstrated that the phosphorylation of AMPA receptors is regulated during cellular models of learning and memory such as long-term potentiation (LTP) and long-term depression (LTD). Moreover, phosphorylation of the AMPA receptor GluR1 subunit is required for the expression of these forms of plasticity, for the retention of spatial memory and also regulate emotional memory formation and erasure.

We have also been examining the mechanisms of the subcellular targeting and clustering of glutamate receptors at synapses. We have recently identified a variety of proteins that directly or indirectly interact with AMPA and NMDA receptors. We have found a novel family of proteins that we call GRIPs (Glutamate Receptor Interacting Proteins) that directly bind to the C-termini of the GluR2/3 subunits of AMPA receptors. GRIPs contain seven PDZ domains, protein-protein interaction motifs, which crosslink AMPA receptors to each other or link them to other proteins. In addition, we have found that the C-termini of GluR2 also interacts with the PDZ domain of PICK1, a protein kinase C-binding protein that is found at excitatory synapses. The GluR2 subunit also interacts with the NSF protein, a protein involved in the regulation of membrane fusion events. These AMPA receptor interacting proteins are critical in the proper membrane trafficking and synaptic targeting of these receptors. We have shown that the binding of PICK1 and GRIP is required for a specific form of LTD in the cerebellum that is a cellular model for motor learning. Moreover, we have found that this receptor complex is critical for hippocampal LTP and LTD and spatial learning.

Importantly, recent evidence has implicated the AMPA receptor complex in several neurological and psychiatric disorders including Alzheimer's disease, schizophrenia, autism, mental retardation as well as in chronic pain and drug addiction.

In summary, we have examined the molecular mechanisms underlying the regulation of neurotransmitter receptor function. Our studies have suggested that regulation of receptor function may be a major mechanism for the regulation of synaptic plasticity in the nervous system in health and disease and may be an important determinant of animal behavior.