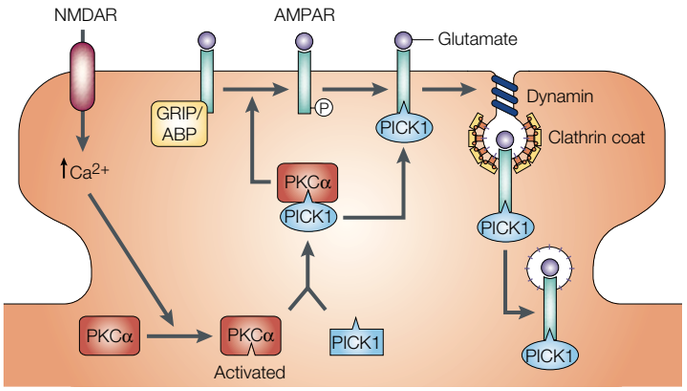

SYNAPTIC PLASTICITY

PICKing out the detail of LTD

The ability of neurons to change their responsiveness to synaptic input is a fundamental concept in neuroscience. But although many molecules have been implicated in long-term synaptic plasticity, we have only just begun to work out the ways in which these molecules interact to produce sustained changes in synaptic strength. In a paper published in *The Journal of Neuroscience*, Perez and colleagues contribute to this effort by showing how PICK1 (protein that interacts with C kinase) might participate in the long-term depression (LTD) of synapses.

There is increasing evidence to suggest that the transport of AMPA-type glutamate receptors in and out of the synaptic membrane is central to activity-dependent changes in synaptic strength. In particular, AMPA receptor endocytosis is thought to contribute to the expression of LTD. In neurons, PICK1 interacts with the AMPA receptor subunit GluR2 by its single PDZ domain. Perez *et al.* now show, in heterologous cells and in neurons, that PICK1 also interacts directly with protein kinase Cα (PKCα), again by its PDZ domain. But whereas the binding of GluR2 to PICK1 was found to be constitutive, the formation of PICK1–PKCα complexes was dependent on the activation of PKCα, which is thought to expose its PDZ-binding site.

In cultured hippocampal neurons, PICK1 protein expressed alone was distributed throughout the cell. Without 12-*O*-tetradecanoyl-13-phorbol acetate (TPA), which was used to activate PKC in these experiments, PKCα was also distributed diffusely in neurons. However, in TPA-treated cells, PICK1 strongly colocalized with PKCα in dendritic spines. Likewise, the expression of PICK1 with GluR2 caused these proteins to co-cluster in spines. Perez *et al.* considered the possibility that PICK1 might promote the PKC phosphorylation of GluR2 in these clusters. They found that phosphorylated GluR2 was abundant in the dendrites of TPA-treated cells compared with untreated controls, and strongly colocalized with PICK1 in spines. Finally, they showed that the PDZ-dependent association of PICK1 with GluR2 significantly reduced the plasma membrane levels of this receptor subunit.

On the basis of these findings, the authors propose that PICK1 targets activated PKCα to dendritic spines, where it phosphorylates GluR2, releasing AMPA receptors from the synaptic anchoring proteins GRIP (glutamate-receptor-interacting protein) and ABP, and allowing the PICK1-dependent removal of GluR2 from the synaptic membrane. These studies highlight the important role of PICK1 in the activity-dependent endocytosis of AMPA receptors.

The expression of LTD has been studied in the both the cerebellum and hippocampus; it will be interesting to learn whether similar mechanisms underlie AMPA receptor endocytosis in these areas.

Rebecca Craven

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CELL BIOLOGY OF THE NEURON

Transmitter receptors scratch the surface

Just as removal of receptors from the synapse is tightly controlled, their reinsertion obeys rules that we're only beginning to understand. Two recent papers in *Nature Neuroscience* illustrate this point with reference to GABA and AMPA receptors, and reveal new opportunities for the regulation of synaptic function.

Bedford *et al.* used a two-hybrid screen to isolate new proteins that bind $GABA_A$ receptors, and identified Plic-1 — a ubiquitin-like protein. Plic-1 was enriched at inhibitory synapses, particularly at subsynaptic membranes, and was able to modulate receptor function. So, if the interaction between GABA receptors and Plic-1 was blocked with an inhibitory peptide, GABA-elicited currents decreased in amplitude, an effect linked to a reduction in receptor number at the membrane. But if Plic-1 was co-expressed with GABA receptors, their surface expression was increased without affecting receptor internalization. So Plic-1 seems to stabilize $GABA_A$ receptors at the synapse, possibly by blocking their targeting to the proteasome, as suggested for other ubiquitin-like proteins.

Passafaro *et al.* explored the dynamics of AMPA receptor exocytosis using a thrombin cleavage assay in which tagged receptors are 'shaved' at the membrane by applying this protease, allowing the subsequent detection of newly inserted receptors. They found that the AMPA receptor subunit GluR1 was inserted more slowly than GluR2, a property conferred by the carboxy-terminal domain of the protein. If both subunits were co-expressed, then GluR1 dominated over GluR2 and surface insertion was slow. As the assay also allowed the authors to visualize the spatial pattern of insertion, they found that GluR2 was directly inserted into synaptic sites, whereas GluR1 insertion was initially extrasynaptic. Last, the insertion of GluR1, but not GluR2, was stimulated by NMDA receptor activation. Passafaro *et al.* concluded that GluR1 governs the dynamics of AMPA receptor exocytosis.

Receptor dynamics at the membrane has emerged as one of the most explosive topics in neuroscience. Although our insights are becoming deeper and deeper, it's easy to imagine that only the tip of the iceberg has appeared above the surface of the membrane.

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WEB SITE Model of AMPA receptor trafficking