Published in final edited form as:

Nature. 2009 April 2; 458(7238): 585–586. doi:10.1038/458585a.

AMPA receptors get 'pickled'

Alexander C. Jackson and Roger A. Nicoll

Department of Cellular and Molecular Pharmacology, University of California, San Francisco, San Francisco, California 94143, USA.

Abstract

In mediating fast synaptic communication in the brain, AMPA receptors require TARP auxiliary proteins. It seems that another distinct class of proteins also bind to AMPA receptors and regulate their function.

It is now well established that ion channels are not solitary creatures, but often have an entourage of auxiliary proteins. Indeed, voltage-gated potassium, sodium and calcium channels form stable complexes with an assortment of both cytoplasmic and transmembrane proteins that profoundly affect their localization and function¹. The ligand-gated cation channels referred to as AMPA receptors (AMPA receptors) — a subtype of receptors activated by the neurotransmitter glutamate — are also known to robustly and selectively interact with a family of proteins termed transmembrane AMPA-receptor regulatory proteins (TARPs). As the first known examples of auxiliary subunits for ligand-gated ion channels, TARPs regulate both the surface expression and biophysical properties of AMPARs^{2,3}. Writing in *Science*, Schwenk *et al.*⁴ describe the unexpected interaction between AMPARs and another family of transmembrane proteins, named after the French word for a type of pickle — the cornichons. They find that, like TARPs, cornichons seem to influence both the intracellular trafficking and gating activity of AMPARs (Fig. 1, overleaf).

The regulation of AMPARs at excitatory synapses between neurons are of particular interest, because plastic changes in the localization and function of these receptors are thought to underlie certain forms of learning and memory^{5,6}. Stargazin, the prototypical TARP, was originally identified as being essential for the surface expression of AMPARs and for targeting them to synapses in granule cells of the cerebellum. Apart from stargazin, which is also called γ -2, the TARP family is now known to include γ -3, γ -4, γ -5, γ -7 and γ -8. These transmembrane proteins are widely expressed in the central nervous system and are intimately involved with AMPARs throughout their lives — from synthesis to surface expression and synaptic targeting^{2,3}.

TARP proteins localize to synapses through motifs in their carboxy terminus that bind to the PDZ domain of scaffolding proteins, such as PSD-95, in postsynaptic neurons^{2,3}. TARPs are also powerful modulators of AMPAR gating and pharmacology: they slow channel deactivation and desensitization; enhance single-channel conductance; convert the partial agonist kainate into a full agonist; and cause the competitive antagonist CNQX to act as a partial agonist⁷.

Schwenk and colleagues' data⁴, however, indicate that TARPs are not the only intimates in AMPARs' inner circle. The authors used a proteomic approach to uncover the identity of

proteins in the rat brain that interact with AMPAR subunits. They detected two proteins that had not previously been linked with glutamate-receptor trafficking or synaptic transmission — CNIH-2 and CNIH-3.

These members of the mammalian CNIH family are homologous to the cornichon proteins, which have been characterized primarily in flies and yeast. In both the fruitfly *Drosophila* and mammals, cornichon is a cargo receptor necessary for the export of epidermal growth factor receptor (EGFR) ligands from the endoplasmic reticulum, a subcellular organelle^{8,9}. This common mechanism of action underscores the remarkable phylogenetic conservation of function among cornichon proteins¹⁰. In this context, a close association with AMPARs seems to be a decidedly extracurricular activity for the cornichons.

Schwenk *et al.* posit that a surprisingly small proportion (30%) of AMPARs associate with TARPs, with the remaining 70% forming complexes with CNIHs. The proportion of TARP-associated AMPARs proposed may be an underestimate, however, as the authors used an antibody directed against γ -2/3 as a proxy for all TARPs. In fact, the other TARPs, including γ -4, γ -5, γ -7 and γ -8, are also expressed in the brain and exhibit a robust association with AMPARs^{2,3,11,12}.

Nevertheless, the suggestion that native AMPARs can be parsed into mutually exclusive pools — one associated with TARPs and another with CNIHs — is intriguing. As TARPs have carboxy-terminus PDZ-binding motifs and CNIHs do not, it is tempting to speculate that there is a division of labour between these two sets of auxiliary proteins in their handling of AMPARs. Are there two trafficking pathways for AMPARs, one TARP-dependent and the other CNIH-dependent? Are TARPs and CNIHs interchanged during their transport from one subcellular compartment to another, or from extra synaptic sites to synaptic sites? Can TARPs, CNIHs and AMPARs form ternary complexes? And could it be that a portion of the CNIH-associated pool of AMPARs remains in the endoplasmic reticulum, reflecting the established role of CNIHs in trafficking EGFR ligands?

Apart from forming complexes with AMPAR subunits, CNIH-2 and CNIH-3 share other features with TARPs. Like TARPs, CNIHs are widely distributed in the brain and are expressed in principal neurons, interneurons and glial cells in the brain's hippocampus, cerebellum and neocortex. A clear exception is cerebellar granule cells, in which CNIHs are conspicuously absent and in which surface expression and synaptic targeting of AMPARs have been shown to rely on γ -2 (refs 2, 3). It is also interesting to note that two other members of the mammalian cornichon family, CNIH-1 and CNIH-4, are widely expressed in the mouse brain¹³, although to date they have no clear neuronal function. Whether the differential expression of TARPs and CNIHs is cell-type specific, and how their functions segregate or overlap in single cells, are questions that are likely to pique the curiosity of researchers in the field.

Another property that CNIHs share with TARPs is that they not only modulate AMPAR trafficking, but also dramatically slow the deactivation (Fig. 1b) and desensitization kinetics of these receptors, thus potentially enhancing the charge transfer associated with synaptic events^{2-4,7}. Intriguingly, the magnitude of CNIHs' effect on AMPAR kinetics greatly outstrips that of γ -2. It will be interesting to assess what other effects CNIHs have on the biophysical properties and pharmacology of AMPARs, especially when compared with the established effects of TARPs. For instance, what is the influence of CNIH association on the single-channel conductance of AMPARs? Do CNIHs dramatically influence kainate efficacy, like TARPs? Is glutamate affinity altered by CNIH-AMPAR interactions? And can CNIHs modify TARP-associated AMPARs, or vice versa?

These are exhilarating times for the study of glutamate-receptor regulation. Several other candidate auxiliary subunits for ionotropic glutamate receptors have also emerged in the past

few years: NETO1 and NETO2 for kainate receptors¹⁴, NETO1 for NMDA receptors¹⁵, and SOL-1 for GLR-1 receptors in the nematode worm *Caenorhabditis elegans*¹⁶. Along with cornichons, these discoveries add richness and diversity, as well as further complexity, to our view of glutamate-receptor regulation in the nervous system. Having identified these new players, it will be of great interest to investigate their potential roles in development, in synaptic-plasticity mechanisms associated with learning and memory, and in the mechanisms underlying disease.

References

1. Vacher H, et al. *Physiol. Rev* 2008;88:1407–1447. [PubMed: 18923186]
2. Nicoll RA, et al. *Science* 2006;311:1253–1256. [PubMed: 16513974]
3. Ziff EB. *Neuron* 2007;53:627–633. [PubMed: 17329203]
4. Schwenk J, et al. *Science* 2009;323:1313–1319. [PubMed: 19265014]
5. Malinow R, Malenka RC. *Annu. Rev. Neurosci* 2002;25:103–126. [PubMed: 12052905]
6. Brecht DS, Nicoll RA. *Neuron* 2003;40:361–379. [PubMed: 14556714]
7. Milstein AD, Nicoll RA. *Trends Pharmacol. Sci* 2008;29:333–339. [PubMed: 18514334]
8. Roth S, et al. *Cell* 1995;81:967–978. [PubMed: 7540118]
9. Bökel C, et al. *Development* 2006;133:459–470. [PubMed: 16396907]
10. Castro CP, et al. *J. Cell Sci* 2007;120:2454–2466. [PubMed: 17607000]
11. Kato AS, et al. *Neuron* 2008;59:986–996. [PubMed: 18817736]
12. Soto D, et al. *Nature Neurosci* 2009;12:277–285. [PubMed: 19234459]
13. Lein ES, et al. *Nature* 2007;445:168–176. [PubMed: 17151600]
14. Zhang W, et al. *Neuron* 2009;61:385–396. [PubMed: 19217376]
15. Ng D, et al. *PLoS Biol* 2009;7:e41. [PubMed: 19243221]
16. Zheng Y, et al. *Nature* 2004;427:451–457. [PubMed: 14749834]

Figure 1. AMPA receptors expand their circle of friends

a, Schwenk *et al.*⁴ show that, in addition to TARPs, the AMPA subtype of glutamate receptors (AMPARs) can bind to another group of transmembrane proteins — CNIHs. Like TARPs, CNIHs mediate trafficking of AMPARs to the cell surface. **b**, Moreover, CNIHs slow the deactivation (illustrated) and desensitization of AMPARs that have been activated by glutamate. (**b** adapted from ref. ⁴.)