SYNAPTIC PHYSIOLOGY

Guidance from the stars

The path that receptors, channels and other synaptic molecules must follow to reach their final destination is not as straightforward as one could imagine. A plethora of proteins that are responsible for the correct assembly of the synapse have been discovered over the past few years, and the identification of new molecules does not show signs of slowing down. The latest addition to the list is stargazin, a protein involved in AMPA-receptor targeting.

Stargazin is the protein defective in the so-called stargazer mutant mice, a strain characterized by the presence of seizures and ataxic gait. As stargazin is slightly homologous to a calcium channel subunit, it was suspected that the effect of the mutation involved changes in channel activity. However, as Chen *et al.* report now in *Nature*, stargazin can bind to PSD-95 and other synaptic proteins, as well as to several AMPA-receptor subunits in culture, interactions that seem necessary for targeting AMPA receptors to the membrane. Stargazin-deficient cells lack surface AMPA receptors and AMPA-receptor-mediated synaptic currents, phenotypes that can be rescued by stargazin transfection.

A notable result from this study is that when the interaction between stargazin and PSD-95 is disrupted, AMPA receptors can still reach the membrane but not the synapse. Does this imply that AMPA-receptor targeting by stargazin involves two separate steps, first to the membrane and then to the synapse? To answer this question it will be useful to find out whether the three proteins already form a complex in the Golgi apparatus or whether they assemble only after reaching the cell membrane. Similarly, it will be important to determine under what conditions stargazin binds to AMPA receptors in the intact brain, an interaction that Chen *et al.* were not able to document. Last, it is noteworthy that AMPA receptors can directly bind PDZ-domain-containing proteins such as PSD-95. Why, then, is stargazin needed at all? What is its specific role? The answer to these questions may require additional guidance from the stars.

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ENCYCLOPEDIA OF LIFE SCIENCES Glutamatergic synapses: molecular organization | AMPA receptors

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SIGNALLING

An X-orphan

Signalling through the retinoid receptor pathway is important for a wide variety of developmental processes in vertebrates, including the patterning of the nervous system. There are two families of receptor, the retinoic-acid receptors (RARs) and the retinoid-X receptors (RXRs), which combine to form heterodimers that function as ligand-activated transcription factors. Retinoids are likely to be endogenous ligands for at least some of these receptors but, in some cases, the ligands that activate them *in vitro* have proved difficult to find in the living organism. For example, RXRs are activated by 9-*cis* retinoic acid in a reporter assay, but this compound is barely detectable *in vivo*, leading to doubts about its role as endogenous RXR activator. Because of this uncertainty, RXRs have until recently been classified as 'orphan' receptors. Now, Mata de Urquiza *et al.* present compelling evidence to show that the polyunsaturated fatty acid docosahexaenoic acid (DHA) is an endogenous RXR ligand.

The authors used a cell-based reporter assay to identify brain extracts that were able to activate mouse RXR. They found that conditioned medium from adult brain could activate the receptors, and that the strongest activity resided in the striatum, hippocampus, motor cortex and cerebellum. Using a series of extraction techniques, they concluded that the ligand responsible was a negatively-charged lipophilic molecule. They purified the activating fraction by HPLC, then analysed the peak fractions using mass spectrometry. Using this technique, they identifed the active component as DHA, and this was further confirmed by testing the purified compound in the cell-based reporter assay.

Several lines of evidence make DHA a strong candidate to be an endogenous RXR ligand. First, unlike other ligands that have been previously implicated, it is highly abundant in the brain, making up 30–50% of the total fatty acid content. Second, the effects of DHA deficiency, which include defects in brain maturation and spatial learning, are remarkably similar to those of RXR knockouts. Last, the activating ability of DHA is affected by mutations that disrupt the ligand binding site of RXR. So, in addition to identifying an endogenous RXR ligand, these observations provide important new information regarding the mode of action of DHA in brain development and function.

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