Perspectives on Ion Channel Assembly

The purpose of the Perspectives in General Physiology is to provide a forum where scientific uncertainties or controversies can be discussed in an authoritative, yet open manner.

The Perspectives are solicited by the editors—often based on recommendations by the advisory editors or members of the editorial board, who may be asked to coordinate the process. To frame the issue, two or more experts are invited to present brief points of view on the problem, which are published back-to-back in *The Journal*. These Perspectives are accompanied by one or two editorial paragraphs that introduce the problem—and invite the submission of comments, in the form of letters-to-the-editor, that are published in a single, predetermined issue (usually four months after publication of the Perspectives). The letters may be no longer than two printed pages (approximately six double-spaced pages) and are subject to editorial review. They may contain no more than one figure, and may not contain significant references to unpublished work. After the letters-to-the-editor have been published, further responses are limited to full manuscripts.

In this issue of *The Journal*, William N. Green (University of Chicago) and Steven H. Keller and Palmer Taylor (University of California, San Diego) provide two different views on the folding and assembly of a membrane channel, the nicotinic acetylcholine receptor (nAChR). The nAChR is arguably the channel that is best understood biochemically. Nevertheless, significant uncertainties remain about the path(s) by which the channel subunits fold and assemble into the $\alpha_2\beta\gamma\delta$ pentamer, which forms the active channel in the plasma membrane. As emphasized in the Perspectives, the uncertainties do not pertain to the experimental results per se, but to their interpretation, which provides for a constructive dialogue. First, to what extent are subunit folding and assembly concurrent, as opposed to sequential, events—to what extent does folding precede oligomerization? Second, are stable intermediates kinetic dead-ends or important intermediates along the folding/assembly path? Third, how should one envisage the reorganization of the oligomeric intermediates in the path from nascent monomers to functioning channels? Fourth, to what extent, and how, are folding and assembly catalyzed by chaperones? Finally, to what extent do insights from studies on the nAChR help understand the folding and assembly of other membrane proteins?

The folding and assembly of integral membrane proteins and soluble, globular proteins are likely to share important similarities—and useful insights may be obtained from proteins for which high resolution structures are known. The subunit interactions in the bacterial reaction center (Deisenhofer et al. 1985. *Nature.* 318:618) and glutamine synthase (Almassy et al. 1986. *Nature.* 323:304), for example, involve single α-helices from one subunit that extend along the outer surface of, or penetrate into, another subunit. This organization suggests that concurrent folding and assembly could be a more general feature than is commonly appreciated. In fact, the folding and assembly of voltage-dependent and inward-rectifier channels become easier to envisage if the pore-lining residues are inserted relatively late in the process—after the tetramer has been assembled. If that were the case, it would obviate the energetic problem of having an extended peptide chain (Doyle et al. 1998. *Science.* 280:69) in direct contact with the bilayer acyl chains. These questions are not settled, but the present Perspectives serve to define the scope of the problems that need to be resolved.

Letters to the editor related to this topic will be published in the June 1999 issue of *The Journal of General Physiology*. Letters to the editor should be received no later than April 1, 1999 to allow for the editorial review. Letters can be submitted electronically, by sending a formatted text file as an attachment in an e-mail to the editorial office (jgp@rockvax.rockefeller.edu). Figures must be submitted in hard copy (they can be faxed so that they are received in the editorial office by the April 1 deadline).

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Editor
The Journal of General Physiology

J. Gen. Physiol. © The Rockefeller University Press • 0022-1295/99/02/161/1 $2.00
Volume 113 February 1999 161
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