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NEUROSCIENCE:

Excitatory view of a receptor

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Abstract

Ion channels opened by glutamate mediate fast cell-to-cell information transfer in the nervous system. The structure of a full-length tetrameric glutamate receptor is both confirmatory and revelatory.

Anyone who wears glasses knows the experience of putting them on. What was fuzzy, blurry and ill-defined suddenly snaps into focus. On page 745 of this issue, Sobolevsky *et al.*¹ offer those working on signalling in the nervous system, and on membrane proteins in general, a pair of glasses. The authors provide the first structure of a full-length glutamate receptor, giving a spectacular, panoramic view of a surprising landscape with at least a few unanticipated features.

Fast cell-to-cell signalling in the nervous system — the basis of our ability to perceive, think and respond — occurs at specialized structures called synapses, sites where encoded information is transferred from one cell to another by a chemical neurotransmitter. In the nervous system, glutamate is the major excitatory neurotransmitter, binding to and activating ionotropic glutamate receptors. These receptors are transmembrane proteins that have a glutamate-recognition site (ligand-binding domain) that, when bound by glutamate, opens an associated ion channel. They are therefore at the heart of nervous-system function. Regrettably, when unregulated, they can also contribute to an array of debilitating disorders, including schizophrenia, Alzheimer's disease and Parkinson's disease, and are involved in the neuronal damage that accompanies stroke and traumatic brain injury.

The structure presented by Sobolevsky *et al.*¹ is of one of the main glutamate-receptor subtypes, an AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor from the rat. It is made up of four GluA2 subunits (GluR2 in older nomenclature) that are identical in terms of amino-acid sequence, and it encompasses three structural/functional domains (Fig. 1a, overleaf). Two of these domains are located on the external side of the cell membrane, and we have seen them individually before — the modulatory amino-terminal domain (ATD)^{2–4} and the ligand-binding domain (LBD)⁵ with its clamshell-like arrangement. The third component is the transmembrane domain (TMD), which forms the ion channel, and this is our first view of it. In many ways the structure is comforting, because it consolidates and verifies much previous functional and structural work. But at the same time it is exhilarating, owing to the unexpected way in which these domains are intertwined and linked together.

The ATD and LBD in the new structure overlap remarkably well with earlier, isolated structures^{2–5} of these domains. They are arranged as dimers, a key structural/functional motif for receptor function; the agonist (glutamate) recognition site, in this instance occupied by a competitive antagonist, is located within the clam shell formed by the LBD. These domains also have a two-fold symmetry relative to the axis perpendicular to the cell membrane. Conversely, the TMD has four-fold symmetry, which is perhaps not surprising given its kinship to another kind of transmembrane ion channel, the potassium (K⁺) channel.

A completely unanticipated feature of the tetrameric GluA2 receptor is that domain swapping and crossover occurs between subunits. As a result, the homotetrameric GluA2 protein complex has two conformationally distinct pairs of subunits, referred to as A/C and B/D (Fig. 1b). Thus, at the level of the ATD, the dimer pairs are A–B and C–D, with considerable inter-pair interactions between the B and D subunits; at the level of the LBD, however, the dimer pairs are A–D and B–C, with inter-pair interactions occurring between A and C (Fig. 1b). This pairwise arrangement is abolished in the TMD, in which four independent but equivalent subunits have four-fold symmetry.

Sobolevsky and colleagues' work¹ also gives us our first glimpse of the glutamate receptor's transmembrane ion channel. Functional evidence has supported the once radical idea^{6,7} that the core of the glutamate-receptor ion channel — transmembrane helix M1, the M2 pore loop and transmembrane helix M3 — shares structural similarity and perhaps evolutionary homology with the permeation pore in K⁺ channels⁸, an idea overwhelmingly supported by the new structure. Moreover, glutamate receptors also reprise another feature of K⁺ channels: they have an additional peripheral transmembrane helix, the M4 segment, that associates with the ion-channel core of an adjacent subunit, as do peripheral transmembrane helices in voltage-gated K⁺ channels. The significance of this arrangement in glutamate receptors is unknown. It may, however, represent a common structural theme in transmembrane proteins and adds a further intriguing aspect to the evolutionary history of glutamate receptors.

In the new structure¹, the LBD is occupied by a competitive antagonist, so the status of the associated ion channel is not controversial — it is in a closed, non-conducting state. As predicted from previous experimental results^{9,10}, highly conserved residues at the apex of the transmembrane gating helix M3 (like the inner helices in a K⁺ channel) are positioned in close proximity and presumably form the gate that blocks ion permeation through the closed channel. A clear definition of the channel gate is an essential step forward in defining receptor function, and will stimulate experiments that further focus our view of channel activation.

Earlier images of glutamate-receptor fragments/domains were missing the two sets of linkers that couple the ATD to the LBD and the LBD to the TMD. Yet it is these linkers that accommodate both the domain swapping and symmetry mismatch, and ultimately transduce ATD modulatory effects to the LBD/TMD and the conformational change in the LBD to channel opening and closing. Indeed, visualization of the details reveals previously unknown linker arrangements — especially for those coupling the LBD to the ion channel, which, as Sobolevsky *et al.*¹ propose, may be essential for receptor function. For example, the linker preceding the M1 transmembrane helix (the pre-M1 region) makes a short helix parallel to the plane of the membrane and contacts the protruding carboxy- and amino-terminal ends of transmembrane helices M3 and M4, respectively. Closure of the LBD clamshell presumably moves this pre-M1 helix away from the M3 helix, permitting this main transmembrane gating element to rotate away from the central axis of the pore and opening the ion channel. Thus, the new structure hints at potential gating steps¹¹ that may be functionally distinct. It allows specific predictions to be made that could transform kinetic studies of glutamate

receptors from an impersonal mathematical exercise to one that also involves matchmaking between elementary kinetic steps and protein conformations.

The different conformations for identical subunits within a tetrameric protein were unanticipated. However, another glutamate receptor subtype, the NMDA (*N*-methyl-daspartate) receptor, requires two different types of subunit to function — typically two GluN1 and two GluN2 subunits, although their exact arrangement was unknown. Using a biochemical approach, and taking advantage of the two conformationally distinct sets of subunits, Sobolevsky *et al.*¹ provide evidence that the GluN1 subunits take the A–C role and the GluN2 subunits take the B–D role, and that the subunit arrangement is GluN1–GluN2–GluN1–GluN2. This is a provocative result and seems rational given the need for different subunits.

It is easy to be excited by these data, and Sobolevsky *et al.*¹ should indeed be commended for their groundbreaking work, which will shift studies of glutamate receptors in a fresh direction. But, of course, more work is needed. A deeper understanding of receptor function will require not only clever functional experiments inspired and guided by structure, but also structures of higher resolution, snapshots of alternative states, and structures of other members of the glutamate-receptor family. We should also retain a healthy dose of caution, lest we rush to transfer all the principles learned here prematurely to the entire glutamate-receptor family. However, for the moment, enjoy the newly afforded clearer view.

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Figure 1. Structure of a full-length tetrameric glutamate receptor

Sobolevsky *et al.*¹ report the first X-ray structure of a full-length glutamate receptor (minus the carboxy-terminal domain), specifically of the AMPA receptor subtype. **a**, Surface representation of the AMPA receptor with the four subunits of identical amino-acid sequence (A–D) coloured green (A), red (B), blue (C) and yellow (D). The amino-terminal domain (ATD) and ligand-binding domain (LBD) residing on the external side of the cell membrane, and the transmembrane domain (TMD) that forms the ion channel, are indicated. The circles indicate competitive antagonists (grey) occupying the agonist-recognition sites. **b**, Top-down view of the ATD, LBD and TMD, illustrating the domain swapping and symmetry mismatch (between LBD and TMD). The dashed line for the ATD and LBD indicates the dimer containing the A subunit, which in the ATD associates with the B subunit, but in the LBD associates with the D subunit. The TMD shows four-fold symmetry. Because the LBD is bound by an antagonist, the permeation pore, located in the centre of the TMD, is closed.