

Another strategy taken on membrane proteins is to produce soluble constructs of parts of the proteins. The resolution (quality) of structures usually are much higher of soluble proteins compared to membrane proteins and this allows detailed information on, e.g., ligand–receptor interactions and water networks in the binding site.

One example of important membrane proteins is the ionotropic glutamate receptors (iGluRs). These receptors mediate most fast excitatory synaptic transmission within the central nervous system. The glutamate receptors are involved in various aspects of normal brain function but are also implicated in a variety of brain disorders and diseases. For example, the drug memantine targeting the iGluRs is used in the treatment of Alzheimer’s disease and the drug perampanel (Fycompa) was approved by the European Commission in 2012 for treatment of epilepsy. Hence, iGluRs are potential targets for biostructure-based drug design (for further details on glutamate receptor structures, see Chapters 12 and 15).

In 1998, the first structure of a soluble ligand-binding domain construct of an iGluR was reported, and 10 years later the first structure of a full-length iGluR, confirming that the receptor is composed of four subunits, each containing an *N*-terminal domain, a ligand-binding domain where glutamate binds, a transmembrane region and a C-terminal region, the latter not seen in the structure (Figure 4.11). In 2014, new full-length iGluR structures appeared in the literature, both of different types of iGluRs and in different conformational states. Presently, more than 300 structures (mostly domain constructs) of iGluRs with bound glutamate, agonists, antagonists, or allosteric modulators have been reported.

The binding of ligands to the ligand-binding domain of iGluRs can be described as a “Venus flytrap” mechanism. In the resting state, the ligand-binding domain is present in an open form

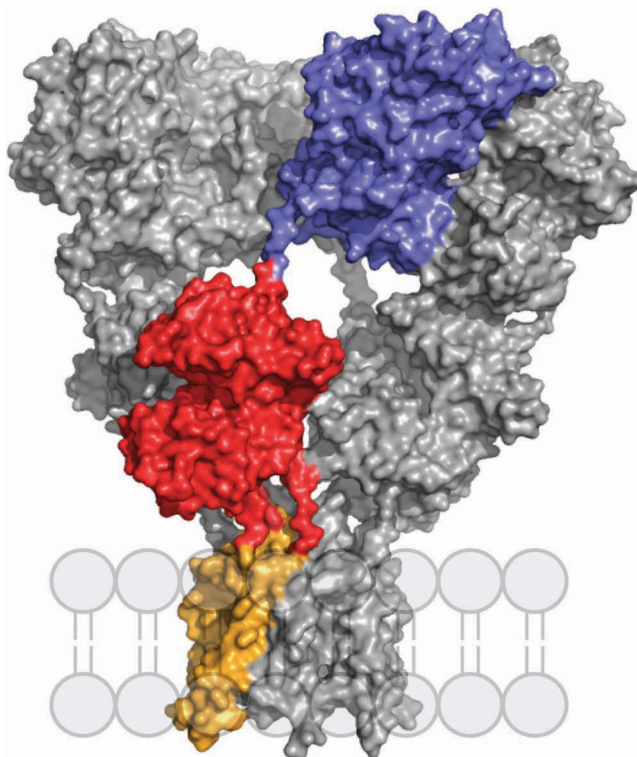


FIGURE 4.11 Structure of a full-length tetrameric iGluR (pdb-code 3KG2). The domains in one subunit are shown in different colors: The *N*-terminal domain in blue, the ligand-binding domain where glutamate binds in red, and the ion channel part in orange. The location of the cell membrane is indicated.