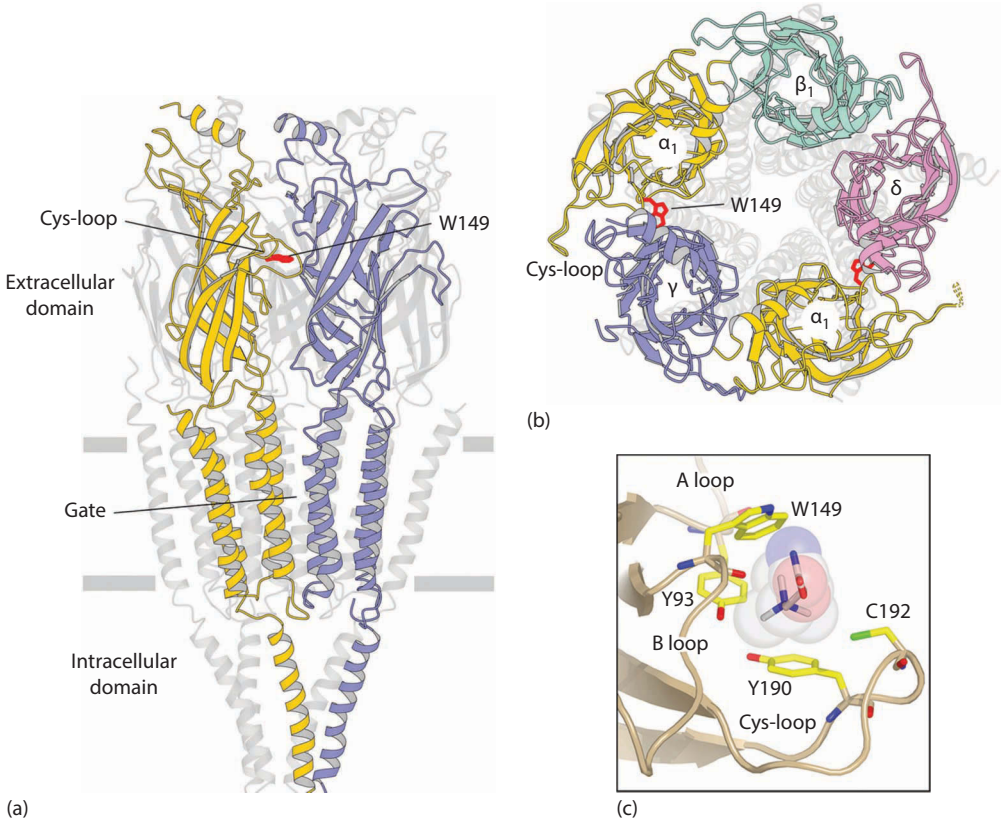

FIGURE 12.6 Structure of the family of Cys-loop ligand-gated ion channel receptors. (a) Side view and (b) top view of 3D structure of the neuromuscular nicotinic acetylcholine receptor which consist of five subunits (two α_1-, one β_1-, one γ-, and one δ-subunit) forming an ion channel in the center. The two agonist binding sites are located in the $\alpha_1\gamma$ and $\alpha_1\delta$ interfaces in the extracellular domain. Each subunit has four transmembrane α-helices of which the M2 helices of the five subunits line the pore. A gate, consisting of hydrophobic leucine and valine residues, is located in the most constricted part of the pore which tilts outward upon receptor activation leading to channel opening. (c) Close-up of the orthosteric binding site of the acetylcholine-binding protein (AChBP) with the agonist carbamylcholine bound highlighting the important cluster of aromatic residues and a cysteine forming key interactions with the agonist. (Adapted from Unwin, N., *Q. Rev. Biophys.*, 46, 283, 2013. With permission.)

α_1 subunits and three other subunits (β_1, γ and δ) which form a pentameric pore in the cell membrane. The agonist binding site is located in subunit interfaces in the extracellular domain. The pore itself is lined with five α-helices (termed M2), one from each of the five receptor subunits which contain hydrophobic leucine and valine residues at the most constricted part of the pore forming the gate for the hydrophilic ions. Agonist binding to the extracellular part of the α-subunits induces conformational changes, which are then relayed through the receptor subunits and ultimately leads to tilt of the pore-lining M2 helices, removal of the hydrophobic gate-lock, and channel opening.

Several high-resolution 3D structures of acetylcholine-binding protein (AChBP), a water-soluble homolog of the ligand-binding domain of nicotinic acetylcholine receptors from the snail *Lymnaea stagnalis*, have been solved in the presence of various ligands (Figure 12.6). These structures have shown that agonists bind in the interface between the subunits and provide detailed insight into the ligand–receptor interactions. For example, all endogenous agonists of the Cys-loop family contain an amine, which, according to the AChBP structures, is interacting with a cluster of aromatic residues via π-cation bonding.