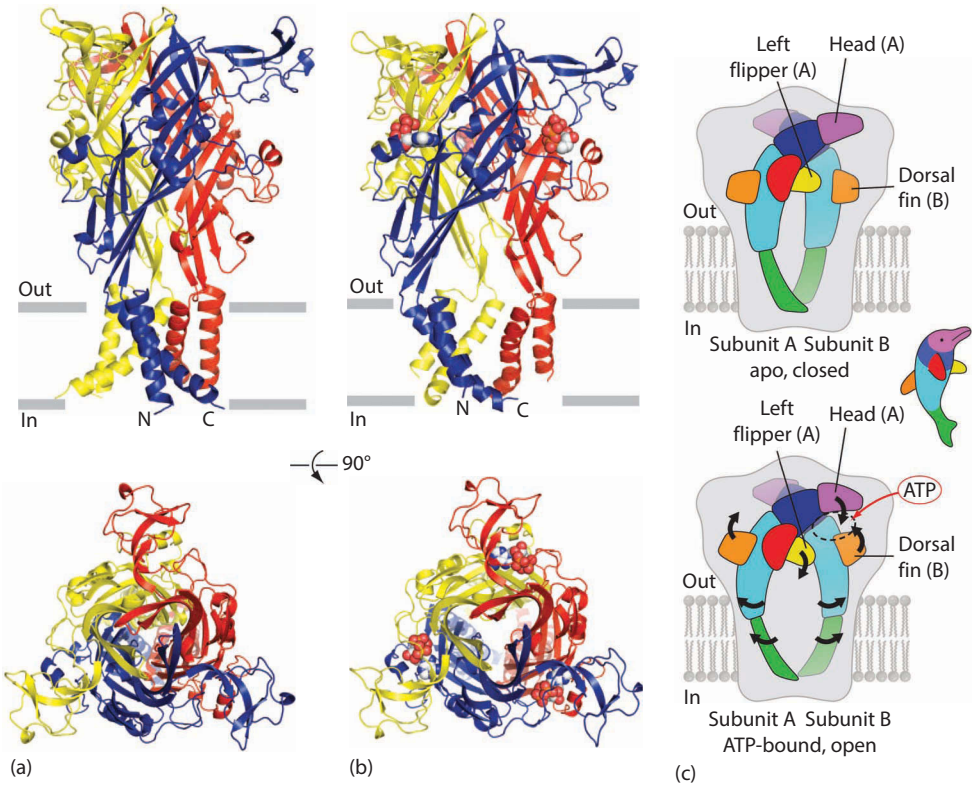

FIGURE 12.8 (a) 3D structure of a full-length purinergic $P2X_4$ receptor in its inactive apo (left) and (b) active ATP-bound (right) structure viewed from the side (top) and extracellular side (bottom). The receptor consists of three subunits shown in different colors with the orthosteric binding site located between the subunits. (c) Cartoon showing the movement when going from the inactive (top) to the active ATP bound (bottom) conformations (only two subunits shown for clarity). Each subunit adopts a dolphin-like structure. ATP binding in the inter-subunit cleft leads to downward movement of the "head" in one subunit and upward movement of the "dorsal fin" in the other subunit to encapsulate the agonist which simultaneously pushes the "left flipper" away. Through a lever motion, this leads to an outward movement of the transmembrane domains and opening of the nonselective cation channel. (Adapted with permission from Hattori, M. and Gouaux, E., *Nature*, 485, 207, Copyright 2012, Macmillan Publishers Ltd.)

autophosphorylation. One of the best understood examples in this regard is the EPO receptor of which the 3D structure of the extracellular agonist binding domain has been determined in the absence and presence of EPO (Figure 12.10). In the absence of EPO, the domain is a dimer in which the ends are too far apart for the JAKs to reach each other. EPO binds to the same amino acids on the receptor that forms the dimer interface and thereby tilts the two receptor subunits. This brings the JAKs close together and initiates the autophosphorylation (Figure 12.10).

12.2.4 Nuclear Receptors

Nuclear receptors are cellular proteins and are thus not embedded in the cell membrane like the previously described receptors. In contrast to the membrane bound receptors, they bind small lipophilic compounds and function as ligand-modulated transcription factors. The nuclear receptors have been classified into six subfamilies according to the type of hormone they bind and receptor sequence similarity. Ligands include steroid hormones (glucocorticoids, progestestins, mineralocorticoid androgens, and estrogens) and steroid derivatives (vitamin D_3 and bile acids), and nonsteroids (e.g., thyroid