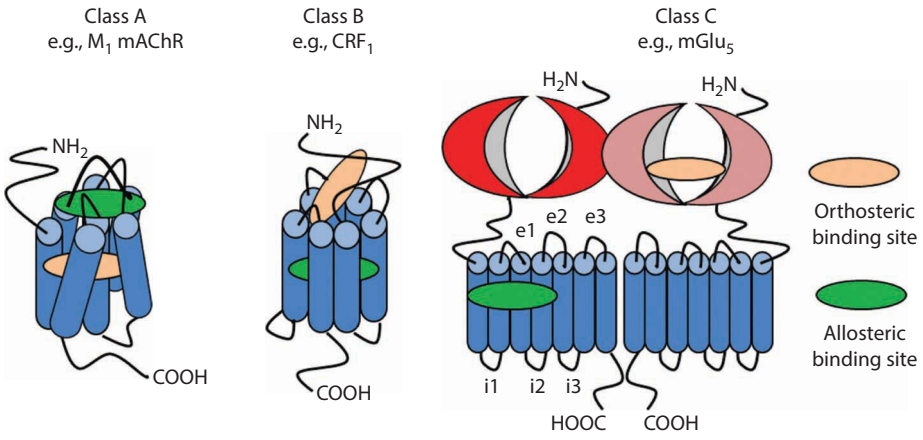

FIGURE 12.3 The superfamily of G protein-coupled receptors. All G protein-coupled receptors contain seven α-helical transmembrane segments and are thus also called seven-transmembrane (7TM) receptors. Cartoon of the three classes showing the typical orthosteric (endogenous agonist) and allosteric binding sites. (Reprinted with permission from Melancon, B.J., Hopkins, C.R., Wood, M.R. et al., *J. Med. Chem.*, 55, 1445–1464. Copyright 2012 American Chemical Society.)

amino-terminal domain of class B receptors (e.g., glucagon and GLP-1 GPCRs) and exclusively in the extracellular amino-terminal domain of class C receptors (e.g., glutamate and GABA GPCRs, see Chapter 15). Allosteric binding sites have also been located in all three receptor classes as outlined in Figure 12.3.

The intracellular loops of GPCRs interact with G proteins. As illustrated in Figure 12.4, the G protein is trimeric consisting of Gα, Gβ, and Gγ subunits. Receptor activation will cause an interaction of the receptor with the trimeric Gαβγ protein, catalyzing an exchange of GDP for GTP in the Gα subunit whereupon the G protein disassociates into activated Gα and Gβγ subunits. Both of these will then activate effector molecules such as adenylate cyclase or ion channels (Figure 12.4). 16 Gα, 5 Gβ, and 12 Gγ subunits have been identified in humans and like the receptors they form groups based on the amino acid homology and the effectors they interact with.

Most GPCRs desensitize quickly upon activation via phosphorylation of specific serine/threonine residues in the intracellular loops and/or C-terminal by kinases such as G protein-coupled receptor kinases (GRKs). Once phosphorylated, β-arrestin molecules will bind to the receptor and cause arrest of the G protein-mediated signaling and induce internalization. Recent evidence has shown that β-arrestins can activate the tyrosine kinase pathway directly leading to non-G protein-mediated cellular effects (Figure 12.5a). In some cases, it has even been possible to develop ligands that selectively activate or inhibit the β-arrestin pathway without activating the G proteins or vice versa. Such biased ligands will induce different cellular effects than ligands activating or inhibiting both signaling pathways with the potential to retain the desired clinical effect while diminishing unwanted side effects (Figure 12.5b and c). The molecular mechanisms of biased ligand action is a matter of debate but is likely either caused by ligand stabilization of different active or inactive receptor conformations, or by differences in ligand kinetics.

Recent evidence has shown that some if not all GPCRs exist as dimeric or even oligomeric complexes. As shown in Figure 12.3 class C receptors dimerize which leads to either homo- or heterodimers. The latter is, for example, the case for $GABA_B$ receptors, which are formed by heterodimerization of $GABA_{B1}$ and $GABA_{B2}$ receptor subunits whereas, e.g., metabotropic glutamate receptors (mGluRs) homodimerize. Whether class A and B receptors also homo- or heterodimerize have been heatedly debated in the literature and only a few examples have been convincingly shown