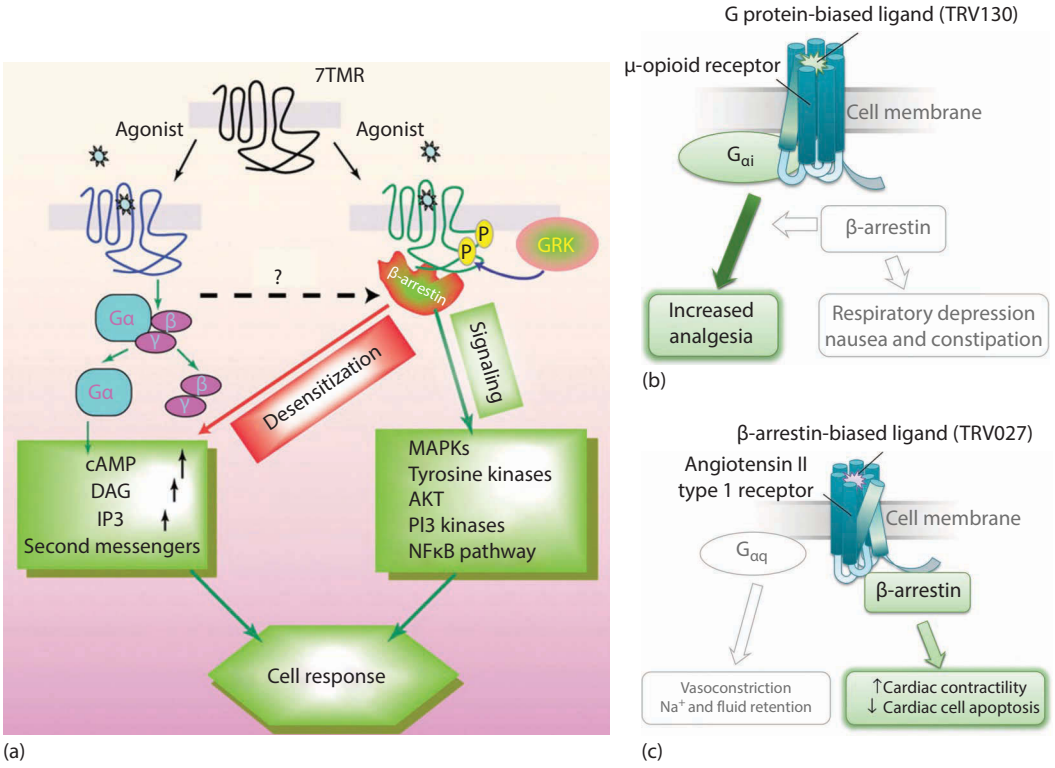

FIGURE 12.5 (a) The G protein and β-arrestin signaling pathway of 7TM receptors (7TMRs). Agonist activation of 7TMRs initiates the classical G protein cascade (see Figure 12.4 for further details) and rapid receptor phosphorylation by G protein-coupled receptor kinases (GRKs). The latter lead to recruitment of β-arrestins which cause desensitization and internalization of the receptor and activation of tyrosine kinase pathways. (b) Hypothesis that a G protein pathway biased agonist at the μ-opioid receptor would retain analgesic effect while lowering unwanted side effects mediated through the β-arrestin pathway. TRV130 ([(3-methoxythiophen-2-yl) methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine) is an example of such a G protein pathway biased agonist which has shown efficacy in pain in human trials. (c) Hypothesis that a β-arrestin pathway biased agonist at the angiotensin II type 1 receptor would retain desired cardiac effects while lowering unwanted side effects mediated through the G protein pathway. The octapeptide TRV027 (Sar-Arg-Val-Tyr-Ile-His-Pro-D-Ala-OH) has such a biased profile and have shown promising results in early human clinical trials of chronic heart failure. (a: From Lefkowitz, R.J. and Shenoy, S.K., *Science*, 308, 512, 2005. Reprinted with permission from AAAS; b and c: Reprinted from *Trends Pharmacol. Sci.*, 35, Violin, J.D., Crombie, A.L., Soergel, D.G. et al., Biased ligands at G protein-coupled receptors: Promise and progress, 308–316. Copyright 2014, with permission from Elsevier.)

12.2.2 Ligand-Gated Ion Channel Receptors

Ligand-gated ion channel receptors can be divided into three major groups termed the Cys-loop, ionotropic glutamate receptor, and purinergic P2X families, respectively. Whereas the two latter families are exclusively excitatory cation-permeable channels, the former are either excitatory (serotonin and nicotinic acetylcholine receptors) or inhibitory (glycine and GABA receptors) by influx of Na^+/Ca^{2+} or Cl^- ions which will hypo- or hyperpolarize the cell, respectively (see Chapter 13 for further details).

12.2.2.1 Cys-Loop Receptor Family

The nicotinic acetylcholine receptor, at the nerve-muscle synapse, is the best understood Cys-loop receptor which upon acetylcholine binding allows as many as 10,000 potassium and sodium ions per millisecond to pass through the channel. As shown in Figure 12.6, the receptor consists of two