

12.3.5 CONSTITUTIVELY ACTIVE RECEPTORS AND INVERSE AGONISM

Most receptors display no or only minor basal activity but some receptors display increased basal activity in the absence of agonist, which has been referred to as constitutive activity. Interestingly, it has been shown that inverse agonists can inhibit this elevated basal activity, which contrast antagonists that inhibit agonist-induced responses but not the constitutive activity (Figure 12.13a).

Examples of important constitutively active receptors include the human ghrelin receptor and several viral receptors that display constitutive activity when expressed in the host cell. This latter group includes the ORF-74 7TM receptor from human herpesvirus 8 (HHV-8), which show a marked increased basal response when expressed in recombinant cells (Figure 12.13b). ORF-74 is homologous to chemokine receptors and does indeed bind chemokine ligands. As shown in Figure 12.13b, chemokines display a wide range of activities on the receptor from full agonism (e.g., GRO α) to full inverse agonism (e.g., IP10), which correlates with the angiogenic/angiostatic effects of the chemokines.

Constitutive activity can also be caused by somatic mutations. Known examples include constitutively activating mutations in the thyrotropin receptor and the luteinizing hormone receptor which leads to adenomas, and the rhodopsin receptor which leads to night blindness.

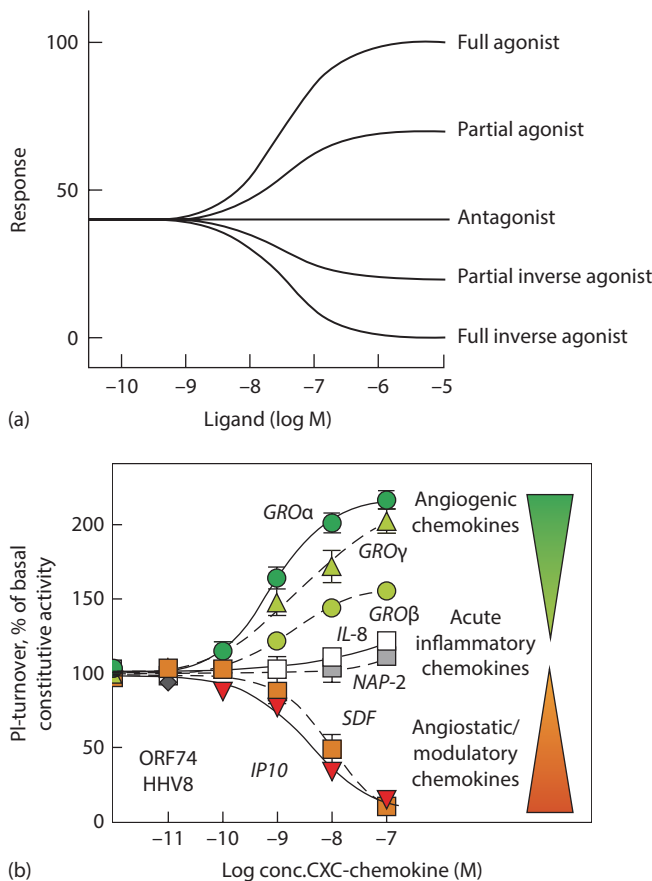


FIGURE 12.13 (a) The nomenclature of ligand efficacies and schematic illustration of their concentration-dependent effects on constitutive activity. (b) Ligand regulation of the constitutively active ORF-74 receptor from human herpesvirus 8 (HHV8). ORF-74 is a G protein-coupled receptor coupled to phosphatidylinositol (PI) turnover, which is regulated by a variety of human chemokines ranging from full agonism by GRO α to full inverse agonism by IP10. (Reprinted from *Neuropharmacology*, 48, Rosenkilde, M.M., Virus-encoded chemokine receptors—Putative novel antiviral drug targets, 1–13. Copyright 2005, with permission from Elsevier.)