by the neurotransmitter concerned may open up the prospect of highly selective pharmacological intervention. Nevertheless, indirect mechanisms of targeting receptors via regulation of the level of the endogenous agonist at the site-of-action remains an important pharmacological principle which has also been applied outside the synapse as exemplified by compounds increasing insulin release and preventing glucagon-like peptide-1 (GLP-1) breakdown.

Direct activation of receptors by full agonists may result in rapid receptor desensitization (insensitive to further activation). Partial agonists are less liable to induce receptor desensitization and may therefore be particularly interesting for neurotransmitter replacement therapies. Desensitization may be a more or less pronounced problem associated with therapeutic use of receptor agonists, whereas receptor antagonists which in other cases have proved useful therapeutic agents, may inherently cause receptor supersensitivity. The presence of allosteric binding sites at certain receptor complexes, which may function as physiological modulatory mechanisms, offer unique prospects of selective and flexible pharmacological manipulation of the receptor complex concerned. Whilst some receptors are associated with ion channels, others are coupled to second messenger systems. Key steps in such enzyme-regulated multistep intracellular systems (Figure 12.2), also including regulation of gene transcription by second messengers, represent novel targets for therapeutic interventions.

12.2 RECEPTOR STRUCTURE AND FUNCTION

Receptors have been divided into four major superfamilies: G protein-coupled receptors, ligand-gated ion channels, tyrosine kinase receptors, and nuclear receptors. The three first receptor superfamilies are located in the cell membrane and the latter family is located intracellularly.

Our understanding of ligand–receptor interactions and receptor structure has increased dramatically during the last decade, not least due to the rapidly growing number of 3D crystallographic structures that have been determined of either full receptors or isolated ligand binding domains. Thus, today, structures of partial or full receptors of all four receptor superfamilies have been determined. Clearly, the information obtained from 3D structures of ligand binding domains in the presence of ligands is very valuable for rational drug design (see Chapter 4). Likewise, knowledge about receptor mechanisms can be used to, e.g., design allosteric modulators interfering with receptor activation.

12.2.1 G Protein-Coupled Receptors

The G protein-coupled receptors (GPCRs) are the largest of the four superfamilies with some estimated 800 human receptor genes. Approximately, 50% of these are taste and odor-sensing receptors, which are not of immediate interest for the pharmaceutical industry, but are of interest for, e.g., tastant and fragrance manufactures. Nevertheless, it is estimated that 30% of all currently marketed drugs act on GPCRs and the superfamily thus remains a very important target for drug research. It is fascinating to note the very broad variety of signaling molecules or stimuli, which are able to act via this receptor superfamily, including tastes, odors, light (photons), ions, monoamines, nucleotides, lipids, amino acids, peptides, proteins, and pheromones.

The GPCRs are also referred to as seven-transmembrane (7TM) receptors due to the seven α-helical transmembrane segments found in all GPCRs (Figure 12.3) and the fact that the receptors can also signal via G protein independent pathways (see later). The GPCRs have been further subdivided into class A, B, and C based on their amino-acid sequence homology. Thus, receptors within class A are more closely related to each other than to receptors in class B and C, etc. This grouping also coincides with the way ligands bind to the receptors. Thus, as illustrated in Figure 12.3, the orthosteric binding sites (binding site of the endogenous agonist) are generally located in the transmembrane region of class A receptors (e.g., acetylcholine, histamine, dopamine, serotonin, opioid, and cannabinoid GPCRs, see Chapters 16 through 19), both in the extracellular loops and