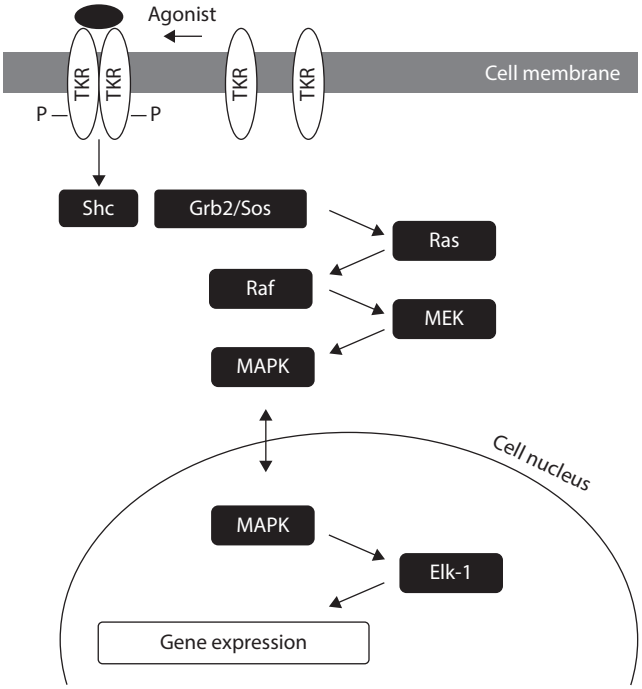

FIGURE 12.9 Cartoon of a protein cascade initiated by agonist binding to two tyrosine kinase receptors (TKR) causing autophosphorylation of the dimerized intracellular receptor domains. This causes activation of a cascade of intracellular proteins (abbreviated Shc, Grb2/SOS, Ras, Raf, MEK, and MAPK) which ultimately leads to activation of transcription factors (e.g., Elk-1) and thus regulation of gene expression.

hormone, retinoids, prostaglandins). The receptor family is relatively small (48 human subtypes), of which 50% still belongs to the group of orphan receptors with no known endogenous ligand.

The nuclear receptors consist of a ligand binding domain, a DNA binding domain, and a variety of other regulatory domains. Upon activation, two receptors dimerize, as homo- or heterodimers, and bind to specific recognition sites on the DNA. Co-activators will then associate with the dimeric receptor and initiate transcription of the target gene(s). Each receptor recognizes specific DNA sequences, also known as the hormone response elements which are located upstream of the genes that are regulated. Three-dimensional high-resolution structures of both ligand and DNA binding domains as well as full-length receptor bound to DNA have been determined. In drug research the main focus has been on the structures of the ligand binding domains which for several receptors have been determined in the absence and presence of ligands.

12.3 RECEPTOR PHARMACOLOGY

12.3.1 Recombinant versus In Situ Assays

The last decades have had a profound impact on how receptor pharmacology is performed. As mentioned in the introduction, receptor cloning was initiated in the mid-eighties and today the vast majority of receptors have been cloned. Thus, it is now possible to determine the effect of ligands on individual receptor subtypes expressed in recombinant systems rather than on a mixture of receptors in, e.g., an organ. This is very useful given that receptor selectivity is a major goal in terms of decreasing side effects of drugs and development of useful pharmacological tool compounds which can be used to elucidate the physiological function of individual receptor subtypes. Furthermore, recombinant assays allow one to assay cloned human receptors which would