

More than 100 years ago, the mystery of why only certain molecules produced a specific therapeutic response was rationalized by the ideas of Emil Fischer and further elaborated by John Langley and Paul Ehrlich that only certain cells contained receptor molecules that served as hosts for the drugs. The resulting combination of drug and receptor created a new super molecule that had properties producing a response of therapeutic value. One extension of this conception was that the drug fits the target specifically and productively like “a key into its corresponding lock.” When the fit was successful, a positive pharmacological action (agonistic) followed, analogous to opening the door. On the contrary, when the fit prevented the intrinsic key to be inserted an antagonist action resulted—i.e., the imaginative door could not be opened. Thus, if one had found adventitiously a ligand for a receptor, one could refine its fit by opportunistic or systematic modifications of the ligand’s chemical structure until the desired function was obtained.

This productive idea hardly changed for the next half century and assisted in the development of many useful drugs. However, a less fortunate corollary was that it led to some limitations of creativity in drug design. The drug and its receptor (whose molecular nature was unknown when the theory was formulated) were each believed to be rigid molecules precrafted to fit one another precisely. Today, we know that receptors are highly flexible transmembrane glycoproteins accessible from the cell surface that often comprise more than one drug compatible region. Further complexities have been uncovered continually. For example, a number of receptors have been shown to consist of clusters of proteins either preassembled or assembled as a consequence of ligand binding. The component macromolecules may be either homo- or heterocomplexes. The challenge of developing specific ligands for systems of this complexity may readily be imagined (Chapters 4 and 12).

The opposite extreme to “the lock and key model” is “the zipper model.” In this view, a docking interaction takes place (much as the end of a zipper joins the talon piece) and, if satisfactory complementarity is present, the two molecules progressively wrap around each other and adapt to the steric and electrostatic needs of each other. A consequence of accepting this mutual adaptation is that knowledge of the receptor ground state may not be particularly helpful as it adjusts its conformation to ligand binding. Thus, in many cases, one now tries to determine the 3D structure of the receptor–ligand complex. In those cases where X-ray analysis remains elusive, modeling of the interactions involved is appropriate. This is the subject of Chapters 2 through 4.

Earlier, it was also noted that enzymes could be modulated for therapeutic benefit. Enzymatic proteins share many characteristics with receptors, although enzymes catalyze biochemical reactions. Receptor ligands interact with the receptor glycoproteins or with the interfaces between the macromolecular subunits of di- or polycomponent receptor complexes and modify the conformation and dynamics of these complexes. Thus, neither receptor agonists nor antagonists directly interfere with chemical reactions and generally are dissociated from the receptor recognition sites structurally unchanged.

The reaction mechanisms underlying the function of the vast majority of enzymes have been elucidated in detail, and based on such mechanistic information, it has been possible to design a variety of mechanism-based enzyme inhibitors, notably k_{cat} inactivators and transition-state analogs, many of which are in therapeutic use (Chapter 11). Until very recently, it was usually only possible to inhibit enzyme action rather than facilitate it. Actually, diseases frequently result from excessive enzymatic action, making selective inhibition of these enzymes therapeutically useful.

Much later, further classes of receptors were disclosed, explored, and exploited as therapeutically relevant pharmacological targets. This heterogeneous group of receptors comprises nuclear receptors operated by steroid hormones and other lipophilic biochemical mediators, a broad range of membrane-ion channels (Chapter 13), DNA or RNA (Chapter 22), and a number of other biostructures of known or unknown functions. These aspects will be discussed in different chapters of this book.