

II

PART

TWO-STATE MODELS: COMPLEX AGONISM AND MODULATION

In Part II we are still at the receptor level. In Part IV on super-complex agonism and regulation, we will move beyond the confines of the ligand-receptor level.

The word ‘complex’ in the title to Part II is a reference to reaction schemes that involve two-state receptor models. Thus, in reality, the adjective ‘complex’ covers the concept of ‘two-state’ reaction schemes.

The two-state model, developed for ion-channels and enzymes during the 1950s, has recently undergone a dramatic re-emergence in and impact on pharmacology (Rang 2006). Paul Leff writes (1995) ‘Until recently pharmacological receptor theory developed along non-mechanistic lines and largely overlooked the two-state concept’.

II.1. Two-state Models?

What do we mean by ‘two-state’ reaction schemes? The intervention reaction scheme in Chapter 2 consisted of four symbols for a receptive unit, R, RS, IR, and IRS (Fig. 2.1). These symbols signify that the receptive unit exists in four different states. The same is true for the four receptor symbols of the ternary-complex model described for G protein-coupled receptors (GPCRs) (see Section 2.7.2). However, to make it very clear, the designation ‘two-state’ in the term ‘two-state model’ (TSM) is a reference to the number of states for the **un-liganded** receptive unit. Therefore, as we shall see, a model by Katz and Thesleff from 1957 is a TSM, since it explicitly operates with the un-liganded receptor in two conformations, R and R* (Figs. 5.1A and 5.4). Similarly, when we come to the allosteric and the homotropic TSMs, as well as the extended-ternary-complex and

the cubic-ternary-complex models in Chapter 7, these additional four models are also true ‘two-state’ reaction schemes even though they each cover a total of six to eight different conformations for the receptive unit. Their sole un-liganded receptive units are R and R*, i.e., they are genuine TSMs (cf. Chapters 7 and 14). Note, that the intervention reaction scheme analyzed in Chapter 2 (Fig. 2.1), and the ternary-complex model (TCM) described for GPCRs (front quadrant of Fig. 7.4A) are not genuine TSMs. In these two models, there is only one form of the un-liganded receptive unit.

Thus, the reader should realize that ‘complex’ and ‘TSMs’ need a context to be perceived correctly, and certainly within the frame of this book.

II.2. Agonism. Two-steps Versus Two-states

A simple **two-step** model, the del Castillo & Katz (dC&K) model (Figs. 5.1B, 5.2A and 5.3B), and a simple **two-state** model, such as the original by Katz & Thesleff (Figs. 5.1A and 5.2C), are developed in sub-chapters 5.6–5.9. ‘Two-step’ covers reaction schemes in which intermediate conformations of liganded but non-active receptive units are involved together with liganded conformations that are active (Fig. 5.3B). Meanwhile, a receptive unit in both an un-liganded and an active state, R*, is not necessarily part of the two-step reaction, as it has to be in TSMs (Fig. 5.4). The simple one-state reaction scheme, as formulated by del Castillo & Katz (1957) (Fig. 5.1B), supports the classic view of first-binding-then-activation (see sub-chapter 5.6). Three additional two-step models, described in Chapter 6, follow the first-binding-then-

activation scheme and are the so-called ordered, random, and ping-pong reaction schemes.

II.3. Intervention and Modulation

Chapter 2 in Part I outlined ant-agonism and inhibition by intervention. To recapitulate, ‘intervention’ means mutually inclusive, i.e., two different ligands can bind simultaneously to their respective binding sites, while the two ligands do not bind at either site. There is no co-lateral binding possible (Section 2.6.3 and Fig. 2.4). On the other hand, when such a two-sited receptive unit for both interventor and agonist is also capable of a ‘two-state’-switch, $R \rightleftharpoons R^*$, its full thermodynamic reaction scheme involves eight receptor conformations, and ligand interaction at the secondary binding site is now denoted ‘modulation’ rather than ‘intervention’. This type of reaction scheme is covered in Chapter 7 by the allosteric two-state model (ATSM).

II.4. Auto-intervention and Auto-modulation

Chapter 3 in Part I covered a simple auto-intervention reaction scheme, in which a single ligand could bind to either of two separate sites. Therefore, for such an auto-intervention reaction scheme, it was possible to have both mutually inclusive as well as co-lateral binding. A ligand, which can bind to either site and simultaneously to both sites, will affect the binding characteristics for the very same type of ligand at the opposite binding site. If we assume that this receptive unit with auto-intervention can also switch between ‘two-states’, then ligand interaction

at the secondary binding site is now denoted ‘auto-modulation’ rather than ‘auto-intervention’. The full thermodynamic reaction scheme for such an auto-modulatory receptive unit may be equated by the homotropic two-state model (HOTSM), surveyed in Chapter 7. In Chapter 5 on complex agonism, we shall first deal with a receptive unit in two-states, but only with a single binding site.

II.5. Dissociation Versus Association Constants

In developing the two-state concept in Part II, we will also switch freely between equilibrium dissociation and association constants. At equilibrium the parameters can be dissociation constants, such as K_s , K_d , K_{ss} , K_{si} , K_{is} , and K_{ii} , plus K_{sm} , K_{ms} , and K_{mm} , and association constants, such as A_s , A_m , A_{ss} , A_{is} , A_{si} , and A_{ii} , plus A_{ms} , A_{sm} , and A_{mm} ; thus far used for normalizing ligand concentrations. In these subscripts ‘i’ signifies an inhibitor/interventor or its binding site and ‘m’ stands for a modulator or its binding site (Fig. II.1). For rules on subscript nomenclature see Box 2.1 in Chapter 2.

The choice of either dissociation or association is selected *ad hoc* as it simplifies formulation and understanding in the theoretical analyses of models. Thus, in theoretical analysis of slightly complicated reaction schemes with ‘two-state’ isomerization, it is sometimes convenient and more straightforward to use ‘forward’ association constants, although ‘backward’ dissociation constants have the useful dimension of concentration. In principle, they are equally valid. Van Rossum (1966) has given arguments for selecting either association or dissociation constants.



Figure II.1. Modulator (M) against interventor (I).