12.3.6.1 Negative Allosteric Modulators (Noncompetitive Antagonists)

As noted in the previous section, the Schild analysis is very useful to discriminate between competitive and noncompetitive antagonists, and an example of the latter is shown in Figure 12.14. Fenobam is a selective antagonist at the mGluR5 receptor, and the Schild analysis clearly demonstrates that the antagonism is noncompetitive due to the depression of the maximal response (compare Figures 12.12 and 12.14). As noted previously, glutamate binds to the large extracellular amino-terminal domain whereas fenobam has been shown to bind to the extracellular part of the 7TM domain. Fenobam does not hinder binding of glutamate to the extracellular domain, but hinder the conformational change leading to receptor activation.

12.3.6.2 Positive Allosteric Modulators

Positive allosteric modulation can be achieved through several mechanisms. For example, benzodiazepines positively modulate the $GABA_A$ receptor by increasing the frequency of channel opening (see Chapter 15). Positive modulation can also be obtained by blocking receptor desensitization as exemplified by cyclothiazide (see Chapter 15).

12.4 CONCLUDING REMARKS

The last decade of receptor research has provided many breakthroughs in our understanding of receptor structure, function, and pharmacology. The many new 3D structures of either full receptors or important domains have provided detailed knowledge about ligand–receptor interactions and receptor activation mechanisms. It has been shown that most receptors can activate several different signaling pathways which may also be selectively activated/inhibited by biased ligands. Finally, inverse agonism and allosteric modulation have pointed to novel ways that receptors can be regulated in vivo. Collectively, these new developments have created the foundation for structure-based drug design and new concepts of pharmacological intervention.

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