12.3.6 Allosteric Modulators

Allosteric modulators can both be stimulatory or inhibitory (noncompetitive antagonists) and typically these compounds bind outside the orthosteric binding site (Figure 12.3). Allosteric modulators have a number of potential therapeutic benefits compared to agonists and competitive antagonists which has led to significant increased pharmaceutical interest in recent years. This increased interest has also been fueled by the development of functional high-throughput screening assays which has made it possible to screen for allosteric modulators (see Section 12.3.2).

The allosteric modulators mentioned below act through allosteric mechanisms as evident from the fact that they do not displace radiolabeled orthosteric ligands. Furthermore, their activity is dependent on the presence of agonists as they do not activate the receptors by themselves. The fact that they bind outside of the orthosteric ligand binding pocket often leads to increased receptor subtype selectivity. Evolutionary pressure has led to conservation of the orthosteric binding site at different subtypes, as radical mutations would severely impact the binding properties. Thus, it is often seen that the orthosteric binding site is much more conserved than the remaining part of the receptor and accordingly, ligands binding to an allosteric site have a higher chance of being selective. Likewise, the allosteric ligands will have a different pharmacophore than the endogenous ligand which might improve, e.g., bioavailability. For example, ligands acting at the orthosteric site of the $GABA_A$ receptor need a negatively charged acid function and a positively charged basic function which greatly impairs the transport through biomembranes, whereas allosteric ligands such as the benzodiazepine diazepam (see Chapter 15) does not have any charged groups and show excellent bioavailability. It is well known that many agonists, particularly full agonists, lead to desensitization and internalization of receptors (Figure 12.5). Unlike agonists, the positive modulators should prevent the development of tolerance (as seen for, e.g., morphine), because they merely potentiate the endogenous temporal receptor activation pattern and avoid prolonged receptor activation leading to desensitization and internalization. The fact that the receptors are stimulated in a more natural way by positive modulators rather than the prolonged receptor activation caused by agonists may also lead to a difference in physiological effects which may or may not be an advantage.

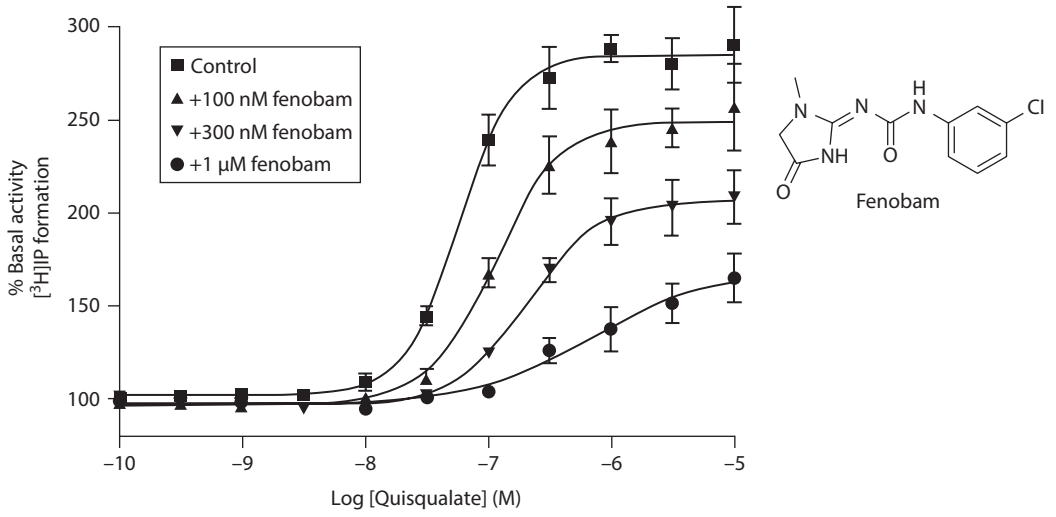

FIGURE 12.14 Schild analysis of the noncompetitive antagonist fenobam on cells expressing the metabotropic glutamate receptor subtype mGluR5. Concentration–response curves of the agonist quisqualate were generated in the presence of varying concentrations of fenobam. In contrast to the Schild analysis shown in Figure 12.12, a clear depression of the maximal response is seen with increasing antagonist concentrations. This shows that the antagonist is noncompetitive. The localization of the orthosteric and allosteric binding sites is depicted in Figure 12.3. (Adapted from Porter, R.H. et al., *J. Pharmacol. Exp. Ther.*, 315, 711, 2005.)