that seen for an SSRI. It later became clear that the 5-HT_{2C} receptor activity was less pronounced than originally thought, but vortioxetine had pronounced 5-HT_{1A} and 5-HT_3 receptor affinity. This was further investigated and a part of the lead optimization program was redirected toward compounds that combined SERT inhibition, 5-HT_{1A} receptor agonism, and 5-HT_{3A} receptor antagonism in a single molecule. Vortioxetine remained the overall best compound due to its superior combination of pharmacodynamic and DMPK properties Vortioxetine has later been shown to most likely mediate its pharmacological activities through SERT inhibition, 5-HT_{1A} receptor agonism, and 5-HT_3 receptor antagonism, as well as antagonism at 5-HT_7 and 5-HT_{1D} receptors and partial agonism at 5-HT_{1B} receptors.

Vortioxetine has shown efficacy in the treatment of patients with MDD in a comprehensive clinical program. Furthermore, preclinical studies had indicated that vortioxetine could have beneficial effects on cognitive dysfunction in MDD, a residual symptom not well treated by the established antidepressants. This hypothesis has been confirmed in clinical studies which showed that vortioxetine can improve cognitive dysfunction in patients with MDD across a broad range of cognitive domains. Thus, vortioxetine's multimodal mechanism of action indicates a different antidepressant profile compared to other antidepressants in clinical use, and vortioxetine is the first antidepressant to include in its label an effect on certain aspects of cognitive dysfunction in patients with MDD.

18.5 MODELING TRANSPORTER AND RECEPTOR LIGAND BINDING

For a general introduction to structure-based drug design, the reader is referred to Chapter 4. In the following, a specific discussion of the modeling of key transporters and receptors relevant for antidepressant drug research is discussed.

In the previous decade, computational chemists had to rely solely on ligand-based design methods to guide medicinal chemistry in the design of novel ligands for GPCRs and biogenic amine transporters (BATs). These proteins are challenging targets for structure determination due to their instability outside of their natural membrane environment. However, over the previous decade the field has been revolutionized, especially for GPCRs, with more than 35 unique structures determined and some co-crystallized with over 10 different ligands. Structure-based drug design for GPCRs is now possible, and fragment screening is also a viable option. Application of these techniques has the potential to accelerate the development of novel therapeutic compounds, including for challenging or previously undruggable GPCRs, for the treatment of a wide range of disorders and diseases. Structure determination of neurotransmitter transporters including BATs has also become a reality with high-resolution X-ray structures of bacterial homologs of Na^+/Cl^--dependent neurotransmitter transporters such as the leucine transporter (LeuT) and, most recently, DAT. Structural information about the BATs and their interactions with antidepressant drugs is important for the understanding of their mechanism of action and for future drug development.

18.5.1 Modeling 5-HT Receptor-Ligand Binding

Multimodal drugs like vortioxetine were developed in the late 1990s to early 2000 when the only available GPCR X-ray structure was the rhodopsin receptor. This receptor has only little sequence identity to any of the 5-HT receptors that vortioxetine modulates and modeling efforts to guide chemistry were, therefore, limited to ligand-based design methods such as fingerprint searches, shape matching, and pharmacophore modeling using known SERT and 5-HT ligands. In 2013, the X-ray structures of the inactive states of the 5-HT_{1B} and 5-HT_{2B} receptors in complex with the antagonist ergotamine were published. The amino acid sequence identity between 5-HT_{1A} and 5-HT_{1B} is high (~40%), and there is now a good prognosis for building a fairly accurate homology model of the 5-HT_{1A} receptor. It is, however, important that modeling efforts are supported by site-directed mutagenesis of residues suggested by the model to be situated in the binding site and that interact with the target ligands. Such studies will help validate the model and guide binding