

performed in the human SERT supports a similar binding pose for the other TCAs clomipramine, imipramine, and amitriptyline. A molecular docking model of imipramine in SERT found a binding pose almost completely overlapping that of nortriptyline in dDAT.

The binding site for SSRIs is less conclusive. Here, dDAT crystal structures have so far not been of any assistance. Instead, LeuT has been engineered to harbor SERT-like pharmacology by mutating all key residues within 10 Å of the substrate binding pocket. Although the mutated LeuT was unable to transport, it was possible to produce diffracting crystal structures of this in complex with several inhibitors including the SSRIs sertraline, paroxetine fluoxetine, and fluvoxamine. In subsite A, Asp24, which corresponds to Asp46 in dDAT, forms a salt bridge with the amine group in the SSRIs. A similar interaction has been proposed with the aligned Asp98 in SERT. Subsite B has the most interactions which can be partitioned into two types of interactions: First, nonpolar residues interact with hydrophobic ring structures in the SSRIs. These are mediated by residues Val104 (dDAT: Val120) and Phe259 (dDAT Phe325). Second, a groove accommodates the polar groups in the rings of the drugs: the dichloro of sertraline, trifluoromethyl of fluoxetine and fluvoxamine, and the benzodioxol group of paroxetine. The groove is aligned by the residues Pro101, Ala105, Gly359, and Ser356 and capped by Tyr108 (Tyr124 in dDAT). Subsite C interacts with the bulky drugs paroxetine and fluoxetine but only partly with the smaller sertraline. Also the methoxy group of fluvoxamine protrudes into the groove. A similar pattern of interaction between SERT and the SSRIs has been suggested based on mutagenesis of selected residues within the three subsites. No structures have been solved in complex with citalopram. Mutagenesis studies suggests that it occupies all three subsites, but current docking models do not show a significant portion of S-citalopram protruding into subsite C. Rather it seems to have a pronounced subsite B component with its fluorophenyl protruding all the way in between TM3 and TM8. Also the cyano group appears to come in close proximity to the unwound part of TM6.

14.3.4 OTHER ATYPICAL BIOGENIC AMINE TRANSPORTER INHIBITORS

Of other inhibitors that do not belong to the classes of psychostimulants or antidepressants, we find modafinil and ibogaine. Modafinil is a selective and low potency DAT inhibitor dominated by its diphenylmethyl moiety connected by a sulfinyl to an organic amide. Modafinil is used in the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy. It also has an off-label use for fatigue as well as a memory-enhancing drug (study drug) even though no clinical studies have reported positive effects of the latter. Experimental data suggest that modafinil have binding properties competitive to dopamine but its actual binding site has not been elucidated. However, it seems like the DAT binding conformation resembles that of the benzotropines which might explain why it does not appear to possess stimulant properties. Ibogaine is a substance found in plants of the Apocynaceae family such as *Tabernanthe iboga*. It has a powerful psychedelic action and does also seem to interfere with the serotonergic system as reported for MDMA. Indeed, Ibogaine is an inhibitor of SERT, but in a noncompetitive manner. Compared to the other inhibitors of the biogenic amine transporters, the location of the binding site for ibogaine is probably the least characterized but could be completely unrelated to other known drugs. Apart from its psychedelic effects, ibogaine has been proposed to have anti-addictive properties and is used in medical subcultures as part of the treatment for cocaine addiction.

14.4 INHIBITORS OF GLYCINE AND GABA TRANSPORTERS: SPECIFICITY, USE, AND MOLECULAR MECHANISM OF ACTION

Other SLC6 family transporters than the biogenic amine transporters are targets for drugs or for drug discovery. GAT-1 is, for example, the target for the antiepileptic drug tiagabine; however, the molecular basis for its interaction with GAT-1 is not known. The *N*-dithienyl-butenyl derivative of *N*-methyl-*exo*-THPO (4-methylamino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol) (EF1502) has been