uptake via DAT but also by promoting reversal of transport resulting in efflux of dopamine via the transporter. This efflux dramatically increases levels of extracellular dopamine and is believed to be of major importance for the psychostimulatory properties of amphetamines. Increasing evidence supports that this efflux is not just the result of "facilitated exchange," but also might involve a channel mode of the transporter. Furthermore, studies suggest that the efflux is dependent on binding to the DAT C-terminus of Ca^{2+}/calmodulin-dependent protein kinase α (CaMKIIα) that in turn facilitates phosphorylation of one or more serines situated in the distal N-terminus of the transporter.

As for the inhibitors, dDAT has been crystallized in complex with D-amphetamine and (+)-methamphetamine. Relative to dopamine, the binding site for amphetamine is still overlapping, but moved more into subsite A by almost 3 Å and interacts directly with Asp46 and the main chain carbonyl of Phe319. In the crystal structure, the two amphetamines also appear to bind to an outward facing conformation. Experimental analysis and molecular docking models on hDAT suggested a more closed-to-outside conformation. Equal for both models is the intact hydrogen bond between Asp46 and Tyr124.

Of other types of stimulant drugs, we find the emerging group of bath salts. The name derives from instances in which the drugs have been sold disguised as true bath salts. The synthesis forms white granules or crystals which resemble the structure of true bath salts, but the content is entirely different. These drugs are designer drugs, derivatives of methamphetamine, and usually contain a benzoylethanamine also called a cathinone. Methylenedioxypyrovalerone (MDPV) is one of the more frequently used "bath salts." It is a potent inhibitor of both DAT and NET, but not a very potent inhibitor of SERT. The robust stimulation of dopamine transmission by MDPV predicts serious potential for abuse and may provide a mechanism to explain the adverse effects observed in humans taking high doses of "bath salts" preparations. However, the abuse potential of MDPV and similar fast evolving group of designer drugs is still not clarified.

14.3.3 Antidepressants

The biogenic amine transporters are also targets for medicines used against depression and anxiety, as also discussed in Chapter 18. The SSRIs (selective serotonin reuptake inhibitors), such as citalopram, fluoxetine, paroxetine, and sertraline are, as implicated by their name, potent and selective inhibitors of SERT (Figure 14.3). Another class of antidepressants includes the so-called SNRIs (serotonin norepinephrine reuptake inhibitors) or "dual action" antidepressants such as venlafaxine and duloxetine that are active at both SERT and NET (Figure 14.3). Finally, the classical and still often used tricyclic antidepressants (TCAs) are potent inhibitors of NET and/or SERT with imipramine and amitriptyline being approximately 10-folds more potent on SERT, while desipramine is a relative selective inhibitor of the NET. Interestingly, the anti-obesity drug sibutramine exerts its action via combined inhibition also of NET and SERT. However, a DAT component cannot be completely ruled out. Conceivably, this effect is achieved through a combination of an anorectic effect due to increased extracellular serotonin levels and increased thermogenesis due to increased norepinephrine levels. Sibutramine has now been withdrawn from the market in several countries including the EU and the United States due to cardiovascular side effects.

The binding sites for antidepressants at their main targets, NET and SERT, are poorly described. Also here, dDAT has been solved in complex with the TCA nortriptyline which might provide suggestions about the binding poses in its mammalian cousins (Figure 14.3). For the human transporters, nortriptyline seems only to bind to NET and SERT. However, dDAT seems to possess a binding pharmacology more similar to the human NET than human DAT. The structure is solved in the outward open conformation with the inhibitor bound to a site overlapping with the binding site for substrate and in close proximity to the Na^+ and Cl^-. The dibenzocycloheptene ring is binding in subsite B saddling around TM3. Parts of the tricyclic ring protrude into subsite C and interact with Ala479. The N-methylpropylamine group extends across the width of the drug binding site and forms a hydrogen bond with the main-chain carbonyl of Phe43 in subsite A. Mutagenesis studies