transport DA, 5-HT, and/or NE from the synapse and into the cell using the sodium gradient across the membrane. They are not specific for their substrates, and NET is, for example, important for the transport/clearance of DA in the cortex. This also fits with the fact that the highest homology among the cloned human transporters is found between DAT and NET. Recently, X-ray crystal structures of transporters have provided very important information about the molecular basis for antidepressant action and have expanded the understanding of the mechanism and regulation of neurotransmitter uptake at chemical synapses. Also, X-ray structures of D_3, $5\text{-}HT_{1B}$, $5\text{-}HT_{2B}$, and $5\text{-}HT_3$ receptors are now available. Application of the new structures in drug design using computational methods will be discussed (Section 18.5). Several ligands have been described for many of these receptors and transporters. Antipsychotic drugs that are used in the treatment of schizophrenia will be discussed as examples of ligands binding to DA and 5-HT receptors (Section 18.2), whereas antidepressant drugs that are used for the treatment of depression and anxiety will be discussed as examples of ligands for transporters (Section 18.3 and Chapter 14). The multimodal antidepressant drugs will be discussed as examples of ligands that act via both transporters and receptors (Section 18.4).

18.2 RECEPTOR LIGANDS

18.2.1 Antipsychotic Drugs

Antipsychotic drugs are primarily used to treat schizophrenia. Schizophrenia is distinguished from other psychotic disorders based on a characteristic cluster of symptoms, where the positive symptoms appear to reflect an excess or distortion of normal function (i.e., delusion, hallucinations, disorganized thinking, disorganized behavior, and catatonia), whereas the negative symptoms appear to reflect a diminution or loss of normal functions (i.e., affective flattening, poverty of speech, and an inability to initiate and persist in goal-directed activities). The cognitive symptoms (i.e., impairment of memory, executive function, and attention) have attracted more and more attention and much research is directed toward understanding the role of these symptoms in order to discover a treatment.

The antipsychotic drugs are typically divided into the classical and the atypical antipsychotic drugs. The classical antipsychotic drugs were discovered in the 1950s with chlorpromazine (**18.1**, Figure 18.1) as the first prominent example, whereas the atypical antipsychotic drugs were introduced into the treatment of schizophrenia during the 1990s. It is believed that the antipsychotic drugs exert their effect on positive symptoms by reducing DA hyperactivity in limbic areas of the brain.

The term classical antipsychotic drug is linked to compounds that show effect in the treatment of positive symptoms at similar doses that induce extrapyramidal symptoms (EPS, i.e., Parkinsonian symptoms, dystonia, akathisia, and tardive dyskinesia). It is believed that EPS is caused by the blockade of DA activity in striatal areas of the brain. The classical antipsychotic drugs are without effect on negative and cognitive symptoms, and these drugs may even worsen these symptoms. It has been argued that the deterioration of negative and cognitive symptoms by classical antipsychotic drugs may be a consequence of their EPS, and the separation of the antipsychotic effect and EPS is the foremost important property of the atypical antipsychotic drugs.

Thus, the term atypical antipsychotic drug is linked to a diverse group of drugs having antipsychotic effect at doses not giving EPS. However, all drugs from this group have their own compound-specific limitations, such as a strong tendency to increase weight for some of the compounds, whereas others have a tendency to prolong the QT interval (total duration of cardiac ventricular electrical activity) in the surface electrocardiogram. In the following, the classical as well as atypical antipsychotic drugs will be discussed with focus on their discovery, including structural considerations and pharmacological profiles of key compounds.