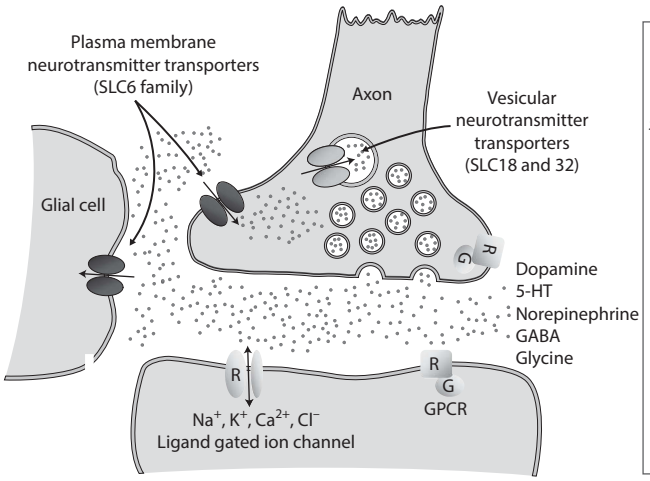

SLC6 gene family members:

- Dopamine transporter (DAT)
- Serotonin transporter (SERT)
- Norepinephrine transporter (NET)
- GABA transporters (GAT-1, GAT-2, GAT-3)
- Glycine transporters (GLYT-1, GLYT-2)
- Betaine transporter (BGT1)
- Taurine transporter (TAUT)
- Creatine transporters (CT1, CT2)
- Proline transporter (PROT)
- Cationic amino acid transporter (ATB[0+])
- Large neutral amino acid transporter (SBAT1)
- Neutral amino acid transporter (B^0AT1, B^0AT2, B^0AT3)
- Imino acid transporter (SIT1)
- Two orphan transporters (NTT4, NTT5)
- Prokarytotic homologs in bacteria and archaea (>200 different, e.g., LeuT from *Aquifex aeolicus*)

FIGURE 14.1 The role of neurotransmitter transporters in synaptic signaling. Neurotransmitters are sequestered into synaptic vesicles through the vesicular monoamine transporters (VMAT1-2) belonging to the SLC18 gene family or through the vesicular inhibitory amino acid transporter (VIAAT) belonging to the SLC32 gene family. Upon arrival of an axon potential, the synaptic vesicles release its content of neurotransmitter into the synaptic cleft by fusion of the vesicle with the plasma membrane. The neurotransmitter exerts its effects by activating ionotropic receptors (ligand-gated ion channels), such as $GABA_A$, glycine receptors and for $5\text{-}HT_3$ receptors or via G-protein-coupled receptors (GPCRs) such as dopamine, adrenergic, 5-HT, and for metabotropic $GABA_B$ receptors. The fast removal of neurotransmitter from the synaptic cleft is governed by neurotransmitter transporters belonging to the SLC6 family located on the presynaptic neuron (DAT, SERT, NET, GlyT2, GAT-1, and GAT-2) or on glia cells (GlyT-1, GAT-1, GAT-2, and GAT-3). Neurotransmitters taken up by the presynaptic neuron allow recycling with presumed savings in synthetic cost.

14.2.1 Structures and Mechanisms of SLC6 Transporters

It is generally believed that SLC6 transporters function according to an alternating access model first proposed by Peter Mitchell in 1957 and refined by Oleg Jardetzky in 1966. The model suggests a transport mechanism in which at any given time the substrate binding site only is accessible to either the intracellular or the extracellular side of the membrane. Thus, at all times, an impermeable barrier exists between the binding site and one side of the membrane, but the barrier can change from one side of the binding site to the other, giving the site alternate access to the two aqueous compartments that the membrane separates. A prerequisite for this model is the existence of both external and internal "gates," i.e., protein domains that are capable of completing the barrier by occluding access to the binding site of substrate from the external and internal domain, respectively (Figure 14.2). In order for a transport process to occur, the two gates must function in a coordinated manner so one is open when the other is closed. The coordination is likely triggered by the binding and unbinding of either substrate or ions or both in concert.

In the absence of any direct structural information on SLC6 transporters, the identification of substrate binding sites and gating domains is highly limited. Thus, structural information from homolog proteins is an important tool to obtain insight into the structure and function of this class of proteins. For the monoamine transporters, the structures of three homolog transporters have been solved: the previously mentioned bacterial NSS proteins, LeuT and MhsT as well as the dopamine transporter from *Drosophila melanogaster* (dDAT). LeuT which displays 20%–25% sequence identity to its mammalian counterparts was the first protein of this class to be successfully crystallized. Its structure was solved at high resolution (1.65 Å). Later the dDAT structure which bears more than 50% homology to its mammalian counterparts, was solved. It turned out to possess an overall structure very similar to LeuT (the LeuT-fold). The fact that the structural fold is conserved from