shown to inhibit not only GAT-1 but also the betaine carrier (BGT-1) and to act as a very efficient anticonvulsant whose action is synergistic with that of tiagabine. Thus, BGT-1 is likely to be an important antiepileptic drug target. The explanation for the observations might be related to a differential distribution of BGT-1 and GAT-1. While GAT-1 is localized to synaptic sites, BGT-1 is localized to astrocytes and possibly extrasynaptic loci in the neurons; hence the efficacy of EF1502 owing to its interaction with BGT-1 could be explained by modulation of extracellular GABA concentrations at extrasynaptic sites.

The high-affinity glycine transporters (GlyT-1 and GlyT-2) might also represent interesting drug targets. Physiologically, GlyT-1 appears to play a role in astroglial control of glycine availability at NMDA receptors whereas GlyT-2 is likely to play a fundamental role in glycinergic inhibition as reflected in a lethal neuromotor deficiency in GlyT-2 knock-out mice. The putative role of GlyT-1 in regulating glycine availability at NMDA receptors has warranted attempts to develop high-affinity inhibitors of GlyT-1 as a novel class of antipsychotic drugs, i.e., blockade of the GlyT1 is envisioned to increase synaptic levels of glycine ensuring saturation of the glycine-B (GlyB) site at the NMDA receptor at which glycine acts as an obligatory co-agonist. Importantly, a derivative of sarcosine (3-(4-fluorophenyl)-3-(4′-phenylpheroxy))propylsarcosine (NFPS) has been shown to potentiate NMDA receptor-sensitive activity and produce an antipsychotic-like behavioral profile in rats. Several GlyT-1 and GlyT-2 inhibitors have now been described; however, details about their mode of interaction, e.g., from X-ray crystal structures, are still needed for these classes of transporters.

14.5 CONCLUDING REMARKS

The SLC6 neurotransmitter transporters represent a prototypical class of ion-coupled membrane transporters capable of utilizing the transmembrane Na^+ gradient to couple "downhill" transport of Na^+ with "uphill" transport (against a concentration gradient) of their substrate from the extracellular to the intracellular environment. The transporters play key roles in regulating synaptic transmission in the brain by rapidly sequestering transmitters such as dopamine, norepinephrine, serotonin, GABA, and glycine away from the extracellular space. Moreover, they are targets for a wide variety of drugs, including antidepressants, antiepileptics, and psychostimulants, as well as they are subject to current drug discovery efforts. High-resolution structural information has become available for this class of transporters through crystallization of the dopamine transporter from *Drosophila melanogaster* as well as from the bacterial homolog, LeuT. These structures serve as an important framework for future studies aimed at deciphering the precise molecular details and dynamics of the transport process for mammalian neurotransmitter transporters. The binding mode for a wide class of transporter inhibitors has been solved based on crystal structures of dDAT and LeuT in complex with substrates and inhibitors. The described structures serve as an important template for delineating the molecular determinants for drug binding to SLC6 neurotransmitter transporters.

FURTHER READING

Beuming, T., Kniazeff, J., Bergmann, M. et al. 2008. The binding sites for cocaine and dopamine in the dopamine transporter overlap. *Nat. Neurosci.* 11:780–789.

Kristensen, A.S., Andersen, J., Jørgensen, T.N. et al. 2011. SLC6 neurotransmitter transporters: Structure, function, and regulation. *Pharmacol. Rev.* 63:585–640.

Loland, C.J. 2015. The use of LeuT as a model in elucidating binding sites for substrates and inhibitors in neurotransmitter transporters. *Biochim. Biophys. Acta* 1850:500–510.

Shi, L., Quick, M., Zhao, Y., Weinstein, H., and Javitch, J.A. 2008. The mechanism of a neurotransmitter:sodium symporter—Inward release of Na^+ and substrate is triggered by substrate in a second binding site. *Mol. Cell* 30:667–677.

Wang, H., Goehring, A., Wang, K.H., Penmatsa, A., Ressler, R., and Gouaux, E. 2013. Structural basis for action by diverse antidepressants on biogenic amine transporters. *Nature* 503:141–145.