Pharmacology of Neurotransmitter Transport into Secretory Vesicles

Farrukh A. Chaudhry, Jean-Luc Boulland, Monica Jenstad, May K. L. Bredahl, and Robert H. Edwards

Abstract Many neuropsychiatric disorders appear to involve a disturbance of chemical neurotransmission, and the mechanism of available therapeutic agents supports this impression. Postsynaptic receptors have received considerable attention as drug targets, but some of the most successful agents influence presynaptic processes, in particular neurotransmitter reuptake. The pharmacological potential of many other presynaptic elements, and in particular the machinery responsible for loading transmitter into vesicles, has received only limited attention. The similarity of vesicular transporters to bacterial drug resistance proteins and the increasing evidence for regulation of vesicle filling and recycling suggest that the pharmacological potential of vesicular transporters has been underestimated. In this review, we discuss the pharmacological effects of psychostimulants and therapeutic agents on transmitter release.
1 Introduction: Neurotransmitter Recycling

Synaptic transmission involves the exocytotic release of neurotransmitter from a presynaptic site and the activation of specific receptors on the membrane of postsynaptic or surrounding cells. Given the high rates of firing observed for many neuronal populations, sustained signaling also requires replenishment of the released transmitter. Indeed, the nerve terminal expresses a series of transport activities designed to recycle transmitter. Among these activities, one class confers the reuptake of dopamine and other classical transmitters across the presynaptic plasma membrane, regulating their levels in the synaptic cleft, and recycling them for subsequent release (Figure 1) (Raiteri et al., 2002; Torres et al., 2003). Although the amino acid transmitters glutamate and particularly GABA recycle in part by reuptake into the nerve terminal, most of the released glutamate and a substantial proportion of the released GABA undergo transport into surrounding glial cells, where they are converted into glutamine (Danbolt, 2001; Bak et al., 2006). Transported back to the nerve terminal, glutamine serves to regenerate both glutamate and GABA (through conversion from glutamate by glutamic acid decarboxylase) (Figures 1C, 1D) (Chaudhry et al., 2002). Essentially all of the plasma membrane neurotransmitter transporters rely on a Na$^+$ gradient produced by the Na$^+$ pump, cotransporting Na$^+$ with transmitter, but vary in the stoichiometry of ionic coupling and in coupling to other ions such as chloride.

The exocytotic release of classical transmitters requires their transport into synaptic vesicles. In contrast to the plasma membrane transporters, the vesicular transport activities depend on a H$^+$ gradient created by the vacuolar-type H$^+$-ATPase rather than a Na$^+$ gradient, and function as H$^+$ exchangers. Biochemical studies have also revealed multiple, distinct vesicular transport activities. The monoamines dopamine, norepinephrine, and serotonin enter secretory vesicles through a common carrier. Distinct activities have been identified for the vesicular transport of acetylcholine (ACh), GABA, and glutamate (Schuldiner et al., 1995; Liu and Edwards, 1997). Well-characterized drugs acting on plasma membrane transporters do not affect the vesicular activities, but a variety of other drugs inhibiting vesicular transport have dramatic effects on brain function, and psychostimulants also interact with vesicular transport mechanisms.

Molecular identification of the proteins mediating vesicular neurotransmitter transport has revealed similarity to bacterial proteins, rather than to plasma membrane transporters (Figure 2). In contrast to concentrative uptake by plasma membrane transporters, the direction of vesicular transport resembles the efflux of many drugs from bacteria. Indeed, the first vesicular transmitter transporter was identified by expression cloning using selection in the neurotoxin N-methyl-4-phenylpyridinium (MPP$^+$) (Liu et al., 1992). The vesicular monoamine transporters protect against MPP$^+$ by sequestering the toxin inside vesicles, away from its primary site of action in mitochondria. The vesicular transporters thus represent important drug targets with a diversity of potential applications.