Glycinergic Neurotransmission and Neurologic Disease

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Introduction

It was first proposed in 1965 that glycine acts as a neurotransmitter in mammalian spinal cord (Aprison & Werman, 1965; Davidoff, et al., 1967), and since then it has been demonstrated that glycine meets all of the criteria for that designation. Glycine is widely recognized as a major inhibitory neurotransmitter in the vertebrate CNS, especially the spinal cord and brainstem, where it is crucial for the regulation of motor neuron activity (Lynch, 2009). In addition, glycinergic interneurons are found in the hippocampus, retina, auditory system and other areas involved in the processing of sensory information. γ-Aminobutyric acid (GABA) and glycine are the two major inhibitory transmitters in the CNS and both are fast acting on ligand-gated chloride ion channels. Like GABA, glycine inhibits neuronal firing by gating Cl^- channels but with a characteristically different pharmacology (see Ch.18) (Dresbach et al., 2008).

Biochemistry and Transport of Glycine

The immediate precursor of glycine is serine

Serine is converted to glycine by the activity of the enzyme serine hydroxymethyltransferase (SHMT) (see Fig. 42-3). Glycine is degraded intracellularly by the glycine cleavage system (see Fig. 42-3), a multienzyme complex composed of four different proteins, which, in the CNS, appears to be primarily localized in astrocytes. Mutations in the glycine cleavage system cause nonketotic hyperglycinemia, a disease characterized by severe mental retardation (‘glycine encephalopathy’) (details discussed in Ch. 42).

Glycine is concentrated from the cytoplasm into synaptic vesicles by the H1-dependent vesicular transporter (VIAAT or vGAT)

VIAAT is the vesicular inhibitory amino acid antiporter that also concentrates GABA into vesicles (see Chap. 3). As is the case for GABA, Ca^2-dependent release of glycine and specific postsynaptic glycine receptors have both been rigorously demonstrated. The postsynaptic action of glycine is terminated by its reuptake via high-affinity plasmalemmal transporter systems located in glycinergic nerve terminals and glial cells. Molecular cloning has identified two glycine transporter genes, glyT1 and glyT2, which are members of the Na,Cl-dependent transporter superfamily [see in Chap. 3]. GlyT1 is abundantly expressed in astrocytes throughout the CNS, whereas GlyT2 is highly localized in glycine-releasing nerve terminals of spinal cord and brain stem. Both glycine transporters differ in their transport stoichiometries and substrate affinities and appear to have different roles at glycinergic synapses [Eulenburg & Gomeza, 2010]. GlyT1 catalyzes the removal of glycine from postsynaptic glycine receptors, whereas GlyT2 is essential for replenishing the presynaptic pool of glycine from which synaptic vesicles are reloaded with neurotransmitter. GlyT1 may, in addition, regulate glycine levels at excitatory NMDA receptors (see below), and selective GlyT1 inhibitors may therefore prove useful in the treatment of diseases associated with impaired glutamatergic transmission, such as schizophrenia [see Chs. 17 and 58].