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The role of glycine transporters (GlyT1 and GlyT2) in synaptic transmission: physiology and pathophysiology (Eckhard Friauf)

Neurotransmission via chemical synapses is mediated primarily by two groups of neurotransmitters, excitatory and inhibitory. The latter group comprises mainly GABA and glycine, the two major inhibitory neurotransmitters in the mammalian central nervous system. The physiology and pharmacology of inhibitory transmission, which is mediated via about 1/3 of all synapses, is much less understood than excitatory transmission. Our planned project embarks on this issue by analyzing glycinergic synapses in the auditory brainstem, which contains microcircuits that are ideally suited for experimental approaches. The project is incorporated into the main research interest of our group, which focuses on the structural and functional development of auditory brainstem microcircuits that are involved in sound localization. Neurons in these microcircuits need to perform ultrafast signaling in the sub-millisecond range and at exquisitely high temporal precision. An important question is the role of the two neurotransmitter transporters (GLYT2, GLYT1) that are involved in the re-uptake and recycling of glycine. These two transporters are located in glial cells and axon terminals of presynaptic neurons, respectively, and their function is only poorly understood. Auditory brainstem neurons in general, and inhibitory projection neurons in particular, fire action potentials at very high and unprecedented rates (up to 800 Hz) and thus perform high-fidelity synaptic transmission under very strict constraints. Therefore, we postulate that efficient re-uptake and replenishing systems are established and maintained which participate in transmitter homeostasis and differ from those in other neural systems in which time precision is less crucially important. We will particularly analyze the projection from the medial nucleus of the trapezoid body (MNTB) to the lateral superior olive (LSO), which is very well suited for analyzing glycinergic transmission and GlyT function. Complex depletion and recovery protocols will be applied which provide evidence regarding their role in homeostasis in the short as well as intermediate time range (subsecond - 30 mins). Analyses will employ knockout mice for both transporters. Both systemic and conditional strains will be used; the latter are currently being generated by us and will be established as a new model. The investigations in knockout animals are further flanked with pharmacological approaches via the use of specific transporter antagonists.