4. H. Betz,[1] C.-M. Becker,[1] G. Grenningloh,[1] W. Hoch,[1] P. Knaus,[1] D. Langosch,[1] M. L. Malosio, B. Schmitt,[1] L. Thomas.[1] **Homology and Analogy in Transmembrane Channel Design: Lessons from Synaptic Membrane Proteins.** ([1]ZMBH, D-6300 Heidelberg, FRG)

The work of our laboratory focuses on synaptic channel proteins which are important for neurotransmission at central synapses.

The postsynaptic glycine receptor (GlyR) is a ligand-gated chloride channel protein which mediates inhibition in spinal cord and other regions of the vertebrate central nervous system (Betz and Becker, 1988). Using biochemical and cDNA cloning techniques we have recently shown that thus receptor is a typical member of the ligand-gated ion channel family whose subunits share amino acid sequence homology and predicted transmembrane topology with nicotinic acetylcholine and $GABA_A$ receptor proteins (Grenningloh *et al.*, 1987). Expression of the cloned ligand-binding subunit of the GlyR in *Xenopus* oocytes (Schmieden *et al.*, 1989)or mammalian cell lines (Sontheimer *et al.*, 1989) leads to formation of glycine-gated strychnine-sensitive chloride channels which resemble the receptors detected in primary spinal cord neurons. During development, different isoforms of the GlyR are detected which differ in antagonist affinity, immunological properties, and molecular weight of the ligand-binding subunit (Becker *et al.*, 1988). Evidence will be presented that the motor deficiency of the mouse mutant *spastic* results from inefficient expression of the adult GlyR isoform.

Synaptophysin is an integral membrane protein of small synaptic vesicles localized in peripheral and central nerve terminals (Wiedenmann and Franke, 1985; Rehm *et al.*, 1986). Determination of its primary structure by cDNA cloning revealed 4 putative transmembrane spanning regions with both N- and C-terminal domains located on the cytoplasmic side of the synaptic vesicle membrane (Leube *et al.*, 1987; Südhoff *et al.*, 1987). This transmembrane topology is very similar to that of the recently cloned gap junction protein from liver. Using biochemical and reconstitution techniques, we have been able to show that synaptophysin indeed is a structural and functional analogue of the gap junction hemi-channel which can form large-conductance channels upon reconstitution in lipid bilayers (Thomas *et al.*, 1988). Also, it shares a hexameric quarternary structure with gap junction proteins, although the polypeptides are not significantly related in amino acid sequence.

These data suggest that both divergent and convergent evolution of amino acid sequences have contributed to current designs of neuronal transmembrane channels. Speculations about elementary building blocks of such channel proteins will be discussed.

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