SYNAPSE FORMATION AND SYNAPTIC TRANSMISSION IN THE MOUSE LACKING NEUROLIGINS 1, 2 AND 3

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Neuroligins are cell adhesion proteins that are thought to instruct the formation and alignment of synaptic specializations. Overexpression of neuroligin 1 and 2 in non-neuronal cells has been reported to be sufficient for triggering presynaptic differentiation. The three known rodent neuroligin isoforms share homologous extracellular acetylcholinesterase-like domains that bridge the synaptic cleft and bind β-neurexins. All neuroligins have identical intracellular C-terminal motifs that bind to PDZ domains of various target proteins (e.g., neuroligin1 is able to bind major components of the postsynaptic density (PSD-95, S-SCAM, and others: See Meyer et al., 04, Neuropharmacology 47(5)). We show a widespread distribution of these three isoforms in the mouse brain. However, while neuroligin 1 is specifically localized to glutamatergic postsynaptic specializations, neuroligin 2 is exclusively localized to inhibitory synapses. The distribution of neuroligin 3 is currently being investigated.

Mutant mice lacking neuroligin 1, 2 or 3 were generated. All single and double mutant mice are viable and fertile, whereas triple mutant mice die within a few hours after birth, due to a dramatic impairment of respiratory function.

Analysis of synapse structure and function by combined biochemical, electrophysiological and morphological approaches demonstrate that synapses form and are functional in the absence of neuroligins, suggesting that neuroligins are not absolutely required for synaptogenesis. More subtle aspects of synaptic morphology and transmission are presented. In particular, patch-clamp recordings of neurons in the respiratory rhythm generating network (preBötzinger complex) reveals a complex impairment of sIPSCs and sEPSCs in the triple deletion mutant mouse.
(A) Quantification of neuroligins mRNA levels during development. (B, C) In Situ hybridization for neuroligins in newborn (B, frontal sections) and adult (C, sagittal sections) rat brain: All neuroligins are expressed at birth, and increasingly into adulthood, and are at all stages widely distributed.

Synapses are made in normal numbers in the brainstem of the newborn neuroligin triple-mutant mouse (n=3 Ctrl, 3 TKO).

(Left) Synaptic transmission was measured in acute brainstem slices, prepared from littermate neuroligin single (SKO), double (DKO) and triple KO (TKO) mice. (Middle) Respiration was monitored by whole-body plethysmography. (Right) The additive deleterious effect of neuroligins deletion onto newborn breathing is visible from sample traces of the ventilation in the triple mutant vs. littermates, and quantification of the ventilation frequency.