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Characterization of a binding partner of CHL1 and analysis of morphology and behavior of CHL1-deficient, NrCAM-deficient, and CHL1/NrCAM-double-deficient mice

Neural cell recognition molecules mediate cellular contacts during development and in the adult nervous system. The L1 family of cell recognition molecules is a subfamily of the immunoglobulin-superfamily and comprises four transmembrane proteins in mammals: L1, CHL1, NrCAM and Neurofascin. These molecules modulate cellular processes such as migration, axonal pathfinding and synaptic plasticity and thereby mediate learning and memory. Mutations of the L1 genes are associated with severe neuropsychiatric disorders. This study focuses on the functions of CHL1 and NrCAM at different levels. Ligand binding of CHL1, the latest identified transmembrane member of the L1 family, has not been investigated well. Therefore, the only identified binding partner of CHL1 was further characterized here. As important features like the complete structure of the gene and the complete cDNA sequence of this binding partner could not be established, further experiments will be necessary in the future.

To investigate specific functions of CHL1 and NrCAM *in vivo*, a direct comparison of CHL1-deficient, NrCAM-deficient, and CHL1/NrCAM-double-deficient mice was conducted. Projections of hippocampal mossy fibers and olfactory sensory axons were investigated in conjunction with the protein expression of these molecules. Additionally, size characteristics of the ventricular system and the cerebellar vermis were investigated. At the behavioural level, single and double-mutant mice were compared with respect to their motor coordination abilities and the gating of auditory information.

In contrast to CHL1-deficient mice, NrCAM-deficient mice do not show misguided hippocampal mossy fibers, but reveal misguided olfactory axons similar to CHL1-deficient mice. The misguided axonal projections of the double-mutant mice reflect the aberrations of the single mutants. The expression pattern of the proteins indicates that CHL1 mediates pathfinding as a receptor on ingrowing olfactory axons, whereas NrCAM optimizes the pathfinding of these axons possibly by repulsive effects. CHL1-deficient mice show an enlargement of the lateral and the third ventricles, whereas NrCAM-deficient mice reveal a reduction in size of these ventricles but enlargement of the fourth ventricle. The sizes of the lateral and the third ventricles in the double-mutants were comparable to wild-type mice. The enlargement of the fourth ventricle was preserved in double-mutant mice and correlated with a size reduction of the cerebellar vermis in NrCAM-deficient and double-mutant mice. Additionally, all mutants display specific alterations in the size of particular cerebellar lobules with partially opposing effects of the mutations of CHL1 and NrCAM in the double mutants. Performance on the rota-rod measuring motor coordination, and prepuls-inhibition measuring gating of auditory information did not reveal alterations in the single or double-mutants.

In summary, the investigation of the mutant mice reveals both, overlapping and specific functions, of CHL1 and NrCAM with respect to axonal pathfinding and size characteristics of morphological structures without an enhancement of phenotypes in the double mutants. Size alterations of the ventricular system and the cerebellar vermis indicate partially opposing functions of these molecules. Motor coordination abilities and gating of information were not altered in the mutant mice.