SCAP in glia-neuron interactions

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7. ENGLISH SUMMARY

The work presented in this thesis aims to obtain more insight into the role of glial lipid metabolism in functioning of the nervous system, and more specifically in neuron-glial interactions involving myelination and synaptic function. In particular, it focuses on sterol regulatory element binding protein (SREBPs) transcription factors as molecular regulators of lipid synthesis in glial cells.

Lipids are building blocks of cell membranes and influence membrane fluidity. In the nervous system, appropriate lipid composition determines the formation and function of highly specialized membranes, such as myelin and the synaptic membrane. Moreover, lipids serve as (precursors for) hormones, pro-inflammatory factors and neurotrophic factors that play an important role in brain development and synaptic transmission. Importantly, the nervous system is shielded from the circulation by the blood-brain and the blood-nerve barriers, and is therefore considered to be largely autonomous in lipid synthesis. As such, defects in brain lipid metabolism lead to developmental impairments (*e. g.,* Smith-Lemli-Opitz syndrome, Niemann Pick disease type C) and are associated with neurodegenerative diseases (*e. g.,* Hungtington's, Alzheimer's and Parkinson's diseases, and multiple sclerosis). Whereas neurons are poor in lipid production, glial cells are known for their high activity in production and secretion of lipids, at least *in vitro*. Whether glial cells are lipid suppliers for neurons *in vivo* and thereby regulate neuronal function remained to be determined.

In chapter 1, I reviewed the current literature on glial cells as lipid providers to the brain and propose a prominent role for SCAP activation of SREBPs, as the main pathway for lipid production in glial cells, analogous for liver cells where SCAP/SREBPs regulate the expression of lipogenic enzymes involved in synthesis of cholesterol and fatty acids.

Cholesterol and monounsaturated fatty acids are prominent components of myelin, a multilayer glial membrane that is wrapped around axons to increase nerve conduction velocity. In chapter 2, I experimentally assessed the role of SCAP/SREBPs in myelination by Schwann cells in the PNS. For this, I genetically deleted SCAP specifically from Schwann cells using cre/lox technology. This led to congenital hypomyelination of the peripheral nerve, showing that the SCAP/SREBP pathway is required for myelin lipid synthesis by Schwann cells. Moreover, we found that myelination improved during aging of the mice due to uptake of extracellular lipids. We concluded that SCAP function in Schwann cells is

necessary for timely regulated myelin formation and that extracellular lipids may rescue myelination when endogenous lipid synthesis is compromised. The source of extracellular lipids that may contribute to myelin membrane synthesis in the PNS remains to be determined but may involve lipids derived from the circulation or from other endodermal cells, *e. g.,* fibroblasts, non-myelinating Schwann cells. Interestingly, by generation of GFAP-SCAP mice in which SCAP is deleted from astrocytes (chapter 3), I showed that myelination, by oligodendrocytes, is even dependent on extracellular lipids (chapter 4). In chapter 3, I found that SCAP deletion in astrocytes leads to premature death and motor impairments, including paroxysmal dyskinesia, a type of motor disorder characterized by sudden uncontrollable choreatic attacks. Anatomical analysis of the brain of these mice revealed microcephaly. In chapter 4, I showed that the microcephaly is most pronounced in the white matter of GFAP-SCAP mutants, caused by hypomyelination. Importantly, a high-fat diet, enriched in cholesterol and monounsaturated fatty acids, was successful in rescuing hypomyelination as well as much of the premature death and motor impairments. I therefore conclude that CNS myelination by oligodendrocytes is dependent on the uptake of extracellular lipids derived from astrocyte and/or the circulation.

Astrocyte-derived lipids may also play a role in synapse formation and function. Synaptic membranes have abundant cholesterol and unsaturated fatty acids, which in literature are hypothesized, based on *in vitro* studies to be (partly) derived from astrocytes. In chapter 5, I aimed to determine the role of lipid deprivation on hippocampal function *in vivo*. For GFAP-SCAP mutant mice, in which SCAP is deleted in both hippocampal astrocytes and some granular neurons, we found strongly reduced LTP induction and impaired contextual fear conditioning, showing that hippocampal synaptic function requires controlled endogenous lipid synthesis.

Importantly, GFAP-SCAP mutant mice are relevant for human patients with perturbed lipid metabolism, *e.g.,* Smith-Lemli-Opitz syndrome, Niemann-Pick C, and Huntington's diseases, and multiple sclerosis. The work described in this thesis highlights the importance of this animal model in understanding the consequences of lipid deficiency in the brain and in particular, the use of lipid supplementation as a therapeutic strategy to treat these diseases.