Summary

Sphingolipids are essential components of cellular membranes where they are involved in a range of processes through their ability to regulate membrane organization. They constitute an intricate metabolic network centered around ceramide, which consists of sphingoid long-chain base attached to a fatty acid. Ceramide constitutes a building block from which more complex sphingolipids can be synthesized. Deciphering the roles of sphingolipids in cellular processes is not straightforward. Numerous sphingolipid species exist, and it is becoming evident that function of each species relies on its specific structure as well as its cellular localization. Sphingolipids are particularly abundant in the nervous system, and aberrations in the sphingolipid homeostasis have been associated with a vast number of neurological diseases. This PhD thesis is based on a review, a research paper, and unpublished results, which all revolve around understanding how perturbation of the sphingolipid network contributes to the development of neurological disorders, particularly epilepsy.

Sphingolipids have proven to be important for the development of the human brain as well as maintaining neurological functions, which is reviewed in *Supplement I*. Moreover, *Supplement I* discusses how sphingolipids, through their ability to compartmentalize the plasma membrane, are involved in many neurological processes, including neuronal differentiation, polarization, synapse formation, synaptic transmission, glial-neural interactions, and myelin stability. Lastly, *Supplement I* discusses how disturbances of the sphingolipid metabolism can lead to plasma membrane rearrangements, which has been linked to the development of several neurological diseases.

Deficiency of several enzymes in the sphingolipid network has been associated with the development of epilepsy. Here we have for the first time described a patient diagnosed with progressive myoclonic epilepsy linked to a heterozygous deletion of the gene encoding ceramide synthase 2 (*Supplement II*). Characterization of patient skin fibroblasts shows that the patient indeed has only one functional *CERS2* allele, which leads to alterations in the membrane lipid composition, particular in regards to sphingolipids and glycerophospholipids (*Supplement II* and *III*). These changes may disturb processes relying on plasma membrane compartmentalization and the dynamics hereof, as indicated by preliminary data suggesting that patient fibroblasts are more insulin sensitive. Thus, deregulation of plasma membrane composition and organization may contribute to the development of progressive myoclonic epilepsy.

The unpublished results addresses the role of sphingolipids in regulating proteins residing in the plasma membrane by investigating how perturbation of the sphingolipid metabolism affects properties of the late-rectifier potassium ion channel Kv2.1. Kv2.1 is, by its dynamic modulation of phosphorylation and localization in clusters in the plasma membrane, involved in regulating the intrinsic excitability of neurons. We find that sphingolipid metabolism is important for Kv2.1 cluster size, but not constitutive phosphorylation, in human embryonic kidney cells during a “resting” state. Future research is needed to determine if similar regulation is present during an “active” state and if Kv2.1 kinetics rely on intact sphingolipid homeostasis. This is pivotal for determining if disruption of the sphingolipid network affects the intrinsic excitability of neurons regulated by Kv2.1.

Collectively, this thesis emphasizes the importance of investigating sphingolipid metabolism in relation to neurobiology. By understanding the role of sphingolipids in the normal functioning brain, we are more able to deduce how dysfunctions in the sphingolipid network can lead to the development of neurological diseases, and ultimately develop efficient therapeutic treatments for these disorders.