Abstract

Solute carriers (SLCs) constitute the largest family of membrane-bound transporter proteins in humans, and they convey transport of nutrients, ions, drugs and waste over cellular membranes via facilitative diffusion, co-transport or exchange. Several SLCs are associated with diseases and their location in membranes and specific substrate transport makes them excellent as drug targets. However, as 30% of the 430 identified SLCs are still orphans, there are still numerous opportunities to explain diseases and discover potential drug targets. Among the novel proteins are 29 atypical SLCs of major facilitator superfamily (MFS) type. These share evolutionary history with the remaining SLCs, but are orphans regarding expression, structure and/or function. They are not classified into any of the existing 52 SLC families. The overall aim in this thesis was to study atypical SLCs with a focus on their phylogenetic clustering, evolutionary conservation, structure, protein expression in mouse brains and if and how their gene expressions were affected upon changed food intake. In Papers I-III, the focus was on specific proteins, MFSD5 and MFSD11 (Paper I), MFSD1 and MFSD3 (Paper II), and MFSD4A and MFSD9 (Paper III). They all shared neuronal expression, and their transcription levels were altered in several brain areas after subjecting mice to food deprivation or a high-fat diet. In Paper IV, the 29 atypical SLCs of MFS type were examined. They were divided into 15 families to facilitate functional studies, and their sequence relationships with other SLCs were established. Some of the proteins were found to be well conserved with orthologues down to nematodes and insects, whereas others emerged at first in vertebrates. The atypical SLCs of MFS type were predicted to have the common MFS structure, composed of 12 transmembrane segments. With single-cell RNA sequencing and in situ proximity ligation assay, co-expression of atypical SLCs was analysed to get a comprehensive understanding of how membrane-bound transporters interact.

In conclusion, the atypical SLCs of MFS type are suggested to be novel SLC transporters, involved in maintaining nutrient homeostasis through substrate transport.