Impacts of Adipose Triglyceride Lipase (ATGL) and Hormone Sensitive Lipase (HSL) on Brain Lipid Homeostasis

[1]Karoline Etschmaier, [1]Cornelia Schweinzer, [1]Monika Scholler, [2]Tatjana Becker, [3]Gerald Rechberger, [3]Ingo Streith, [3]Robert Zimmermann and [1]Ute Panzenböck

[1]Institute of Pathophysiology and Immunology, Medical University of Graz, Austria

[2]Institute of Experimental and Clinical Pharmacology, Medical University Graz, Austria

[3]Institute of Molecular Biosciences, Karl Franzens University Graz, Austria

The mammalian brain has the second greatest concentration of lipids, exceeded just by adipose tissue. The maintenance of lipid homeostasis is crucial for proper functioning of numerous physiological systems including transport, perception and signaling processes as well as for the structural properties of membranes. Lipases are jointly responsible for the catabolic degradation of neutral lipids and the provision of lipid intermediates which can serve as precursors for the formation of phospholipids (PL) and lipid mediators such as eicosanoids. In peripheral tissues, adipose triglyceride lipase (ATGL) was recently identified to be the rate limiting enzyme for triglyceride hydrolysis, whereas diglycerides are the preferential substrate for hormone sensitive lipase (HSL). Given that both enzymes are also expressed in the brain, we were interested in studying brain lipid homeostasis in the absence of ATGL or HSL, using knock-out mouse models. Profiles of neutral lipids, phospholipids, and free fatty acids (FFA) in lipid subclasses in mouse brains were analysed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC) and gas chromatography mass spectrometry (GC-MS), respectively. Hydrolytic activities, protein and relative mRNA expression levels of ATGL and HSL were determined in brain homogenates. To understand the impact of ATGL or HSL absence on monoglyceride (MG) metabolism, we also investigated monoglyceride lipase (MGL) and two poorly characterized MG hydrolyzing enzymes, α/β-hydrolase domain-containing protein 6 and 12 (ABHD 6 and ABHD 12). Interestingly, we detected increased levels of glycerol, ethanolamine and choline phospholipids in brains of HSL-deficient animals when compared to wildtype mice. In contrast, PL subclasses in ATGL knock-out mouse brains were unaltered amongst both genotypes. However, brains of fed when compared to fasted ATGL deficient animals showed significantly elevated ethanolamine, inositol, and choline phospholipid levels. Alterations of the relative FFA composition of distinct neutral lipid and phospholipid classes were observed in both, ATGL and HSL genotype brains. Real-time PCR analysis revealed significantly reduced MGL levels in brains of ATGL deficient mice and reduced levels of ABHD12 in HSL knock-out mouse brains. These findings indicate that the absence of ATGL or HSL influences brain lipid homeostasis in various ways. Whether these alterations result from peripheral or from cerebral modifications due to the absence of ATGL or HSL, remains to be elucidated.