Altered fatty acid distribution in lysosome-associated membrane protein-2 deficient mice

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（リソソーム関連膜タンパク質-2欠損マウスにおける脂肪酸分布の変化）

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論　文　内　容　の　要　旨

Lysosome-associated membrane protein-2 (LAMP2) deficiency causes the human Danon disease and represents a lysosomal dysfunction because of its pivotal role in regulating autophagy and lysosome biogenesis. LAMP2-deficient mice exhibit a spectrum of phenotypes, including cardioskeletal myopathy, mental retardation, and retinopathy, similar to those observed in patients with Danon disease. Its pathology is thought to involve altered energy metabolism and lipid dysregulation; however, the lipidomic profiles of LAMP2-deficient animals have not been investigated. In this study, we investigated lipid alterations in LAMP2 KO mice tissues, including those of the liver, plasma, and retina, using liquid chromatography-mass spectrometry. Our results revealed significantly increased free fatty acid (FFA) levels and decreased in triglyceride (TG) levels in LAMP2 KO liver tissues at three and six months. Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) species significantly decreased in LAMP2 KO mice livers at six months. Similarly, plasma TG and PC/PE levels decreased in LAMP2 KO mice. In contrast, plasma FFA levels were significantly lower in LAMP2 KO mice. Retina FFA levels were elevated in LAMP2 KO mice, accompanied by a partial decrease in PC/PE at six months. In summary, FFA levels increased in several tissues but not in the LAMP2 KO mice plasma, suggesting the potential consumption of FFA as an energy source in the peripheral tissues. The depletion of TG and PC/PE accelerated with age, suggesting an underlying age-dependent energy crisis condition. Our findings underscore the dysregulated distribution of fatty acids in LAMP2-deficient animals and provide new mechanistic insights into the pathology of Danon disease.