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学位論文内容の要旨

博士の専攻分野の名称：博士（保健科学）

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学位論文題名

Investigation of mechanisms underlying alteration in lysophosphatidylethanolamine and its protective effects on lifestyle-related diseases

(生活習慣病におけるリゾホスファチジルエタノールアミン変動メカニズムと
その保護効果に関する研究)

Lysophosphatidylethanolamine (LPE) is a deacylated product of phosphatidylethanolamine (PE) and a component of the plasma membrane and organelles in mammalian cells. LPE exhibits several bioactivities, including stimulation of intracellular Ca^{2+} levels, neurite outgrowth stimulation, and anti-inflammatory effects. Moreover, LPE ameliorated mitochondrial injury by restoring the mitochondrial PE levels. Several studies have reported alterations in LPE in patients with lifestyle-related diseases. Plasma LPE levels were decreased in patients with type 2 diabetes mellitus (T2DM) accompanied by cardiovascular disease, but increased in those with diabetic nephropathy. LPE levels decrease in patients with metabolic dysfunction-associated steatohepatitis (MASH), often accompanied by T2DM. Lifestyle-related diseases, particularly T2DM and MASH, have common features including obesity, insulin resistance, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction. Given the protective effects of LPE, its dysregulation may contribute to the development or progression of these diseases. However, the mechanisms underlying LPE dysregulation in T2DM and MASH remain unclear. Herein, we investigated the profiling of LPE and its metabolites using targeted and non-targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) and the expression of genes and proteins related to LPE metabolism using experimental models of T2DM and MASH to explore the relationship between LPE and the pathology of these diseases. Furthermore, we investigated the effects of oral LPE administration in a murine model of MASH.

Initially, to address the challenges in analyzing LPEs using LC-MS/MS, we improved a quantitative method for determining seven major LPEs (LPE 16:0, 18:0, 18:1, 18:2, 20:4, 20:5, and 22:6). We established an extraction method optimized for hydrophilic LPEs to overcome several issues regarding endogenous interference and time-consuming processes.

We applied this method to non-fasting plasma samples from healthy preadolescent children aged 9–12 years ($n = 342$ volunteers, boys = 181, girls = 161) living in Sapporo. Interestingly, decreased LPE 16:0 and increased LPE 22:6 levels were observed in overweight

children compared with the normal range (fold change: 0.909 and 1.174, respectively). Our findings suggest a possible relationship between LPE and overweight status.

We investigated the relationship between LPE and T2DM using an experimental animal model. Six-week-old male C57BL/6N mice were fed a regular diet (control, $n = 8$), high-fat diet (HFD, $n = 8$), or HFD with streptozotocin (HFD/STZ, $n = 6$) to induce the features of T2DM, including renal damage. In the plasma of HFD/STZ mice, the levels of combined major LPE species were increased, whereas most LPE species were decreased in the kidneys of HFD/STZ mice. Interestingly, the levels of glycerophosphorylethanolamine (GPE), a deacylated product of LPE, were increased in both the plasma and kidneys of HFD/STZ mice. We found that this dysregulation of PE metabolism was induced by the upregulation of Pnpla6, a lysophospholipase, in the kidney.

We investigated the dysregulation of LPE metabolism in the context of MASH. Seven-week-old male C57BL/6J mice were fed a high-fat (60%), high-cholesterol (1.25%), and high-cholic acid (0.5%) diet with 2% hydroxypropyl- β -cyclodextrin in drinking water (HFCC/CDX) for three weeks to mimic MASH features. HFCC/CDX mice showed fat accumulation, with increased liver weight, inflammation, and fibrosis. Except for LPE 18:1, most LPE species were decreased in both the plasma and liver of HFCC/CDX mice. We found that the deacylation of LPE to GPE was enhanced by the upregulation of Pnpla6 and Pnpla7 in the livers of HFCC/CDX mice.

Finally, we investigated the effects of oral administration of LPE 16:0 in the murine MASH model (HFCC/CDX mice). LPE 16:0 dissolved in methyl cellulose was orally administered to HFCC/CDX mice for three weeks (low dose: 0.1 mg/kg; medium dose: 1 mg/kg; high dose: 10 mg/kg). Oral LPE 16:0 administration tended to recover immune cell infiltration and partially reduce oxidized lipids in the livers of HFCC/CDX mice. However, LPE 16:0 did not attenuate hepatic fat accumulation or fibrosis. The limited efficacy of LPE 16:0 oral administration in attenuating the features of MASH could be explained by the degradation of LPE caused by Pnpla6 and Pnpla7 in the stomach, intestine, and colon. Despite LPE 16:0 administration, increased LPE 16:0 levels were suppressed in the plasma and liver. In contrast, plasma GPE levels were higher in the LPE group than in HFCC/CDX mice without LPE supplementation. Our findings suggest that LPE 16:0 is not effectively absorbed into the body after oral administration.

In conclusion, we successfully overcame the challenges in analyzing LPEs and identified novel factors of LPE dysregulation in T2DM and MASH. Our findings suggest that dysregulation of LPE metabolism is mainly caused by the upregulation of Pnpla6 in both T2DM and MASH model mice. Moreover, Pnpla7 is involved in the degradation of LPE to GPE in the livers of MASH mice. In this study, we could not prove the protective effects of the oral administration of LPE 16:0. Nonetheless, this study provides a new perspective for understanding the relationship between LPE and lifestyle-related diseases.