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学　位　論　文　名	Molecular Mechanisms of Ezetimibe-Induced Attenuation of Postprandial Hypertriglyceridemia （Ezetimibeによる食後高脂血症改善効果の分子メカニズムの検討）
論　文　審　査　委　員	（主査） 教　授　小室　一成 （副査） 教　授　下村伊一郎　　教　授　楽木　宏実

論　文　内　容　の　要　旨

〔　目　　的　〕

Postprandial hypertriglyceridemia (PHTG) has been shown to be associated with metabolic syndrome and atherosclerotic cardiovascular diseases. Our group recently reported that ezetimibe inhibits PHTG in patients with type IIb hyperlipidemia. Ezetimibe was also reported to attenuate PHTG in combination with low-dose statins in patients with obesity or metabolic syndrome. We reported CD36-deficient (CD36KO) mice as a new model for PHTG, in which the synthesis of chylomicron (CM) in the small intestines is enhanced. In the present study we investigated the effect of ezetimibe on PHTG in wild-type (WT) mice fed a western diet, and CD36KO mice fed a normal chow diet, respectively.

〔　方法ならびに成績　〕

Male, C57BL6/J WT and CD36KO mice 8-10 weeks of age were used for this experiment. Each strain of mice was separated into two groups in the following manner: CD36KO mice were fed a chow diet either with or without supplementation of 10 mg/kg ezetimibe, and WT mice were fed a western diet either with or without supplementation of ezetimibe. After 3 weeks of treatment, mice of each group were divided into 2 subgroups. One subgroup was euthanized after fasting for 12 h and the other was fasted for 12 h followed by an acute ingestion of 17 μl/g body weight of olive oil by intragastric gavage, and then euthanized 3 h after initiating oral fat loading. Plasma, intestinal lymph and tissues were collected from both subgroups at the time of euthanization. Additionally, WT mice fed a standard chow diet were used as controls for the TG determination study. The plasma and lymph lipoprotein profiles were analyzed by an online dual enzymatic method using high performance liquid chromatography (HPLC). Moreover mice from each group were fasted for 12 h and gavaged with 3μCi of [9,10-^{3}H(N)] triolein mixed into 17μl/g body weight of olive oil. Three hours after fat loading, the mice were euthanized and blood samples were collected from the inferior vena cava. The activity of radio-labeled tritium in 250 μl of plasma was determined by scintillation counting. The expression of the genes related to chylomicron production was evaluated by qRT-PCR. Ezetimibe dramatically reduced PHTG in both WT and CD36KO mice. HPLC of plasma showed that the decrease in TG content in CM and CM remnants-sized particles contributed to this suppression, suggesting that CM production in the small intestines might be reduced after treatment. Intestinal lymph was collected after oral fat loading in ezetimibe-treated and non-treated mice. Both TG content and apolipoprotein (Apo) B-48 mass were decreased in treated mice. The qRT-PCR of intestinal mucosa showed inhibition of the mRNA expression of FATP4 and ApoB in both groups along with FABP2, DGAT1, DGAT2 and SCD1 in WT mice at postprandial state after treatment.

〔　総　　括　〕

Ezetimibe alone reduces PHTG by blocking both the absorption of cholesterol and the intracellular trafficking and metabolism of long-chain fatty acids in enterocytes, resulting in the reduction of the formation of ApoB48 which is necessary for the ApoB48-containing lipoprotein production in the small intestines.

論文審査の結果の要旨

動脈硬化性疾患の発症抑制において脂質代謝異常の改善は重要でありそのメカニズムの解明は急務である。小腸コレステロール吸収阻害薬であるエゼチミブは高LDLコレステロール血症および食後高脂血症に伴う高TG血症を改善させる。今回筆者らはエゼチミブによる食後高脂血症改善効果の分子メカニズムについて検討した。食後高脂血症モデルであるCD36ノックアウトマウスにエゼチミブ投与下で脂肪負荷試験を行い、小腸でのカイロミクロン産生が抑制されていることを確認したが、これはコレステロール吸収抑制に伴う小腸内含有量の低下、脂肪酸の吸収低下に伴う小腸内TG形成の低下およびアポ蛋白であるapoB-48の産生低下によることが判明した。以上の発見は、今後の動脈硬化性疾患の強い発症リスクである食後高脂血症のメカニズム解析において示唆に富むものであり、治療介入の可能性も示したきわめて有意義なものと考えられ、学位の授与に値する。