Lipid metabolism changes in polyunsaturated fatty acid deficiency and their physiological significance

Yuri Hayashi

Introduction

Mammals are unable to synthesis polyunsaturated fatty acids (PUFAs) de novo, so linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) are called essential fatty acids. These carbon-18 (C18) PUFAs can be converted to ≥C20PUFAs such as arachidonic acid (20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3) via fatty acid desaturases (FADS) and elongation enzymes (ELOVLs). ≥C20PUFAs play important roles in determining the structure and integrity of biological membranes and generating bioactive lipids that mediate numerous physiological functions. In essential fatty acid (EFA) deficiency state, Mead acid (20:3n-9) is endogenously synthesized from oleic acid (18:1n-9) and is used as a diagnostic indicator of EFA deficiency. FADS2 is responsible enzyme for synthesis of ≥C20PUFAs such as arachidonic acid, DHA, and Mead acid. In this study, it was investigated that the effect of exogenous and endogenous ≥C20PUFAs deficiency on hepatic lipid accumulation using FADS2$^{-/-}$ mice fed a PUFA-deficient diet.

Methods

Male FADS2$^{-/-}$ mice (11 weeks old) were fed a PUFA-deficient diet for 4 weeks (KO-DEF). In addition, 11-week-old wild-type (WT) mice were fed a control diet (WT-CONT) or PUFA-deficient diet (WT-DEF) for 4 weeks. The control diet was AIN-93G containing 7% soybean oil as the lipid source, and the PUFA-deficient diet was AIN-93G with 7% tripalmitate (16:0-TAG).

Results and discussion

1. Hepatic lipid accumulation in PUFA-deficient FADS2$^{-/-}$ mice.

In WT and KO mice fed a DEF diet, the level of hepatic C18 PUFAs were decreased to 30% compared to WT mice fed a CONT diet. The level of ≥C20 PUFAs in the KO-DEF group was decreased to under one-fifth of that in the WT-CONT mice, whereas the reduction of ≥C20 PUFAs in the WT-DEF group was about 30%. Hepatic triacylglycerol (TAG) and cholesterol levels of FADS2$^{-/-}$ mice were significantly higher than those of two groups of WT mice. These results showed that severe deficiency of ≥C20 PUFAs caused accumulation of cholesterol as well as TAG

in the liver.

The expression of *Fasn*, *Acc*, *Scd* which are genes responsible for fatty acid synthesis was markedly increased in the KO-DEF group compared to the other two groups. Furthermore, the activation of SREBP-1, a master regulator transcription factor of lipogenesis was observed in the KO-DEF group. In addition, the TAG level in VLDL fraction and ApoB100 protein level in the plasma were declined in the KO-DEF group. Although the expression of the genes involved in cholesterogenesis such as *Hmgcr*, *Fdps* and *Lss* was also elevated in FADS2$^{-/-}$ mice, the activation of SREBP-2, transcription factor of cholesterogenetic genes was not observed. Moreover, there were no differences in the expression of genes involved in bile acid synthesis and bile excretion between WT and FADS2$^{-/-}$ mice. From these results, it was suggested that the induction of lipid synthesis and impaired lipid secretion appears to be involved in neutral lipid accumulation in the liver of FADS2$^{-/-}$ mice with severe deficiency of ≥C20 PUFAs.

2. The characteristic change of phospholipid composition in PUFA-deficient FADS2$^{-/-}$ mice

PUFAs exist as acyl chains of membrane phospholipids and provide mobility to the membrane, therefore, PUFA-containing phospholipids are essential for the maintenance of biological function. When PUFAs are deficient in vivo, changes in fatty acid metabolism may occur to compensate for the deficiency and maintain homeostasis. Thus, we performed a comprehensive analysis of the fatty acid chains of phospholipids in the liver of FADS2$^{-/-}$ mice fed the PUFA-deficient diet. The presence of non-methylene interrupted fatty acid (NMIFA) called sciadonic acid (20:3^{5,11,14}) was confirmed in phospholipids such as phosphatidylethanolamine (PE) and phosphatidylinositol (PI) of KO-DEF group. Sciadonic acid lacks the double bond at the Δ8 position in arachidonic acid and is thought to be produced from linoleic acid (18:2n-6) in FADS2-deficient mice by elongation of the carbon chain via ELOVL and desaturation via FADS1.

When the changes in PUFAs of each phospholipid in FADS2$^{-/-}$ mice were compared, the decrease in arachidonic acid (20:4n-6) of PE was less than that of other phospholipids. Moreover, there was no difference in DHA of PE among the three groups, and n-3 PUFAs such as 20:5n-3 and 22:5n-3 were markedly increased in PE of FADS2$^{-/-}$ mice. Thus, even though FADS2-deficient mice lacked PUFAs, the ≥C20 PUFAs amount in PE was retained, suggesting that the importance of ≥C20 PUFAs in PE.