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学位論文審査の要旨

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学位論文題名

Prevention of fatty liver by dietary intervention via regulation of 12 α -hydroxylated bile acid metabolism: Studies on oligosaccharide and dairy products in rats

（食餌による 12 α 水酸化胆汁酸代謝の調節を介する脂肪肝の予防：

オリゴ糖および乳製品を用いたラットにおける研究）

This thesis comprises 94 pages, 16 figures, 12 tables , 84 references, and 2 chapters with 2 reference thesis.

There is a growing concern about fatty liver worldwide. Excessive energy consumption increases biosynthesis of fatty acid or sterols in the liver. In this condition, biosynthesis of 12 α -hydroxylated bile acids (12 α OH-BAs) is also enhanced in the liver. Such alteration of BA metabolism is successfully mimicked in rats by a supplementation of cholic acid (CA) to diet, without any change in the proportion of lipids or carbohydrate contents in the diet. Moreover, the CA diet induces some symptoms that observed in fatty liver, such as liver steatosis or leaky gut. It is suggested that an increase in 12 α OH-BAs is one of the risk factors that induce fatty liver. Some studies have already shown that oligosaccharides or dairy products mitigate fatty liver, but such preventive effects seem diverse depending on those types and almost no information is available not only in BA metabolism but also the mechanisms underlying. The purpose of the study is to investigate relationship between hepatic steatosis and 12 α OH-BA metabolism in those dietary interventions.

1. Ingestion of difructose anhydride III partially suppresses the deconjugation and 7 α -dehydroxylation of BAs in rats fed with a CA-supplemented diet

Difructose anhydride III (DFAIII) is an indigestible oligosaccharide and prebiotic involved in the reduction of secondary BAs. After acclimation, the rats were fed with a control diet or a diet supplemented with DFAIII. Each group of the rats was further divided into two groups and fed diet with or without CA supplementation. As a result, DFAIII ingestion reduced the fecal deoxycholic acid (DCA) concentration via partial suppression of BA deconjugation and 7 α -dehydroxylation. However, no amelioration was observed of the CA-induced hepatic steatosis in the rats fed DFAIII.

2. Ingestion of dairy products partially recovers the CA-induced disorders accompanied by modulation of BA metabolism

There are some reports showing that consumption of ripened cheese or fermented milk reduces hepatic lipid contents. In the following experiments, the involvement of 12 α OH-BA was investigated in the reduction of liver lipids by consumption of dairy products in the CA-induced fatty liver model.

2-1. Cheese

A skimmed milk cheese was prepared and the ground sample was added to diet as protein source. The cheese diet partially ameliorated the CA-induced symptoms such as hepatic lipid accumulation and leaky gut. Also, the cheese diet improved plasma level of adiponectin. A negative correlation was observed between the gut permeability and the plasma adiponectin concentration. In BA metabolism, a significant decrease of CA was observed in feces. There was a massive reduction in unconjugated 12 α OH-BA excretion in aortic plasma and feces of the rats fed the cheese diet. A positive correlation was found between the expression of liver *Srebp1c*, a transcription factor that regulate fatty acid synthesis, and fecal DCA concentration. 12 α OH-BA in aorta and feces are able to be a predictive biomarker for fatty liver development.

2-2. Fermented milk powder (FMP)

The ingestion of FMP mitigated liver steatosis and leaky gut, accompanied by a partial reduction of serum aminotransferase activities. A decrease in food intake by FMP resulted in decrease of relative liver weight and there was a positive correlation between portal DCA concentration and serum aminotransferase activities. A reduction of fecal DCA concentration by FMP might contribute to alleviate leaky gut. Although 12 α OH-BAs remain at high level in the enterohepatic circulation there is an improvement in hepatic steatosis and leaky gut by the FMP ingestion.

Taken together, significant relationships were observed between the symptoms in fatty liver and 12 α OH-BA metabolism. Dietary intervention that regulates 12 α OH-BA metabolism especially in the organs related with enterohepatic circulation is possible to ameliorate fatty liver and related symptoms.

Therefore, we acknowledge that the author is qualified to be granted the Degree of Doctor of Philosophy in Agriculture from Hokkaido University.