学 位 論 文 の 要 旨

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学 位 論 文 名　A Diet High in Glucose and Deficient in Dietary Fibre Causes Fat Accumulation in the Liver without Weight Gain

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論 文 内 容 の 要 旨

INTRODUCTION

There is a strong association between obesity and diabetes and hepatic steatosis. The hepatic steatosis that complicates these metabolic syndromes has been proposed to be defined as Metabolic Dysfunction Associated with Fatty Liver Disease (MAFLD) since 2020. The etiology of MAFLD is affected by western diets and modern processed foods, which are typically high in fat and sugar and low in dietary fibre. The impact of high-fat diets on hepatic steatosis is well documented in both human and animal studies. Similarly, a diet high in sugar and low in fibre has the potential to induce liver steatosis, although there is currently limited information available on this topic.

In our previous study, we demonstrated that feeding a fiber-deficient diet leads to the exacerbation of colitis in mice within about one week. During the investigation, we happened to notice that the livers of the mice appeared slightly pale after they were fed the diet, that could be a sign of fat accumulation. Since our fiber-deficient diet was replaced dietary fibre with glucose to match the caloric content of a standard diet, we hypothesized that a standard calorie diet with high in glucose and deficient in dietary fibre induces hepatic fat accumulation in a week. Therefore, we examined the impact of the diet on the hepatic fat accumulation in mice to examine our hypothesis. In addition, metabolic disorders beyond the liver, including body weight gain and blood parameters, were evaluated. Furthermore, we screened the molecules which were potentially involved in fat accumulation in the liver.

MATERIALS AND METHODS

C57BL/6J male mice were fed a normal chow diet (ND) or the diet which is high in glucose and deficient in dietary fibre (HGD) from day 0 to day 7, and were sacrificed on day 7 to evaluated various parameters, that were described below in detail. We also examined a 14-day feeding period to evaluate the progression of hepatic steatosis and metabolic disorder. To evaluate hepatic fat accumulation, liver weights, levels of hepatic triglyceride, total cholesterol, and free fatty acids (NEFA) were compared between the groups. In addition, histopathological sections of the livers were stained with Oil Red O to visualize the fat accumulation. To evaluate the liver damage, plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were compared. Besides, body weight changes, blood parameters including glucose, triglyceride, cholesterol, and free fatty acids levels in the blood were compared to evaluate the metabolic disorders beyond liver. We also examined the absorption of glucose and glucose tolerance by oral glucose tolerance test (OGTT). Furthermore, the molecules responsible for hepatic fat accumulation were screened by microarray analysis and verified the results by qRT-PCR. Based on the results of qRT-PCR, the protein expression of the most responsible molecules was evaluated by ELISA. All experiments with animals in this study were approved by the Animal Care and Use Committee of Shimane University.

RESULTS AND DISCUSSION

The hepatic triglyceride levels of HGD group were higher than those of the ND group on both day 7 and day 14. The areas of oil droplets in the liver sections showed a similar tendency. In addition, the variation of individual triglyceride value in HGD group was smaller than that of the ND group on day 14 compared to day 7, although the triglyceride levels themselves were comparable between the groups. On the other hand, the liver weights and the hepatic NEFA levels were comparable in both groups on day 7 and day 14. The hepatic cholesterol levels in the HGD group were temporarily lower than those in the ND group on day 7 but were comparable between the groups on day 14. Besides, plasma AST and ALT levels of both groups were comparable through the experiment with an exception of the higher AST levels in HGD group on day 14. However, the degrees of the elevation were slight. These results indicate that the HGD induced hepatic fat accumulation within a week without severe damage to the organ.

In the comparison of systemic phenotypes associated with metabolic syndrome beyond liver, body weight changes were comparable in both groups throughout the experiment. Epididymal fat mass and the plasma lipids levels were not affected by HGD-intervention both on day 7 and day 14 with an exception of transient higher cholesterol levels in HGD groups on day 7. Besides, fasting blood glucose levels were lower in the HGD group than those of the ND

group on day 14, implying occurrence of glucose metabolism abnormalities. However, OGTT showed that the peak concentration of glucose and the AUC were comparable between both groups on day 7 and day 14, suggesting that both glucose absorption and glucose tolerance were not affected by HGD-intervention. These results indicate that a 14-day HGD consumption did not provoke the symptoms which are typically observed in metabolic syndrome beyond the liver.

Given the onset of fat accumulation on day 7, comprehensive gene profiles of HFD group and ND group were analyzed by microarray on day 7 and compared. Among the genes that were upregulated or downregulated by HGD consumption, the largest number of genes were related to the lipid metabolic process. Especially, the multiple lipogenesis-related genes were upregulated, including fatty acid synthase (FAS), Acetyl-CoA carboxylase α (ACCα), stearoyl-CoA desaturase 1 (SCD1), ATP citrate lyase (ACLY), and malic enzyme 1 (ME1). Among them, FAS, SCD1, and ACCα are closely involved in the synthesis of triglycerides. Therefore, we validated the expressions of these genes and protein. Consistent with the results of the microarray, the HGD group displayed a higher expression of these genes and proteins in comparison to the ND group. These findings indicate that HGD induces fat accumulation in the liver associated with upregulation of FAS, SCD1 and ACCα.

CONCLUSION

A diet high in glucose and deficient in dietary fibre increases hepatic fat deposition in a relatively short term. This is associated with an increased expression of the molecules related to de novo lipogenesis. The present study suggests that the adoption of a high-glucose, low-fibre, diet is breeding ground for fatty liver disease.