学 位 論 文 の 要 旨

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学 位 論 文 名	Effects of Quercetin Derivatives From Mulberry Leaves: Improved Gene Expression Related Hepatic Lipid and Glucose Metabolism in Short-term High-fat Fed Mice
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論 文 内 容 の 要 旨

INTRODUCTION

The prevalence of obesity and metabolic abnormalities are closely associated with lifestyle and becomes an urgent worldwide public health problem. Obesity was related with both metabolic abnormalities of glucose and lipids and productions of oxidative stresses, such as reactive oxygen species (ROS). Polyphenol compounds that are ubiquitous in edible plants (fruits, vegetables, and herbs) and plant-derived beverages have recently received attentions due to their biologic activities. Mulberry leaves contain rich quercetin derivatives. Previous studies have reported that quercetin derivatives inhibit hepatic enzyme for ROS production and prevent metabolic abnormalities by enhancing ß-oxidation in obese conditions. However, they included the interaction between obesity and metabolic abnormalities. There are few reports describing the effects of quercetin derivatives to metabolic abnormalities in non-obese. The aim of the current study was to evaluate the direct effects of

quercetin derivatives on metabolic abnormalities among non-obese conditions in short-term duration.

MATERIALS AND METHODS

C57BL/6N mice were fed a high-fat diet (HFD), supplemented with either 0% (control), 1%, or 3% mulberry leaf powder (Mul) or 1% catechin powder for five days. The dried Mul contained 763 mg quercetin 3-(6)-malonylglucoside, 96 mg quercetin 3-glucoside, and 226 mg quercetin 3-rutinoside in 100 g dry weight, respectively. Quercetin derivatives of the leaves were extracted by suspending the dried powder in an ethanol aqueous solution and analyzed by quantitative HPLC (LaChrom, Hitachi). Catechin powder was made from polyphenon (Mitsui Norin Co., Ltd.) and contained 432 mg epigallocatechin gallate, 88 mg epicatechin gallate, 176 mg epigallocatechin, and 80 mg epicatechin in 100 g dry weight, respectively. Anthropometric parameters and blood biochemistry were determined, and hepatic gene expression associated with lipid and glucose metabolism was analyzed. Comparisons of the four diet groups (HFD, HFD+1%Mul, HFD+3%Mul, HFD+1%catechin) were performed by one-way analysis of variance (*ANOVA*), and *post hoc* analyses were used by Tukey-HSD tests. All experiments with animals in this study were approved by the Ethics Committee for Animal Experimentation of Shimane University and they were handled according to our institutional guidelines.

RESULTS AND DISCUSSION

The weights in mice did not differ among the four groups after 5 days feeding. Plasma glucose and 8-isoprostane levels were significantly reduced in the 1%, 3% Mul and catechin groups, although plasma triglycerides, total cholesterol, and free

fatty acids did not have statistical significances between their groups. In some of liver gene expressions on the oxidation, *gp91phox,* which was a main component of NADPH oxidase, was significantly down-regulated, and peroxisome proliferator-activated receptor *α*, which was related with β-oxidation, was significantly up-regulated in the Mul groups compared with the control group. In some of glucose-metabolism related genes, glucokinase was significantly up-regulated, and glucose 6-phosphatase was significantly down-regulated in the Mul groups compared with the control group. In lipid metabolism, fatty acid synthase and glycerol-3-phosphate acyltransferase were significantly down-regulated, and enoyl-CoA hydratase / 3-hydroxyacyl-CoA dehydrogenase was significantly up-regulated in the Mul groups compared with the control group.

In this study, we found the potentiality that quercetin derivatives directly improved metabolic abnormalities of glucose and lipid by both stimulating β-oxidation and suppressing ROS production. Moreover, the 1% Mul and 1% catechin groups had identical levels of polyphenol compound intake (0.4×10^{-5} mol/ 5 days) and exhibited similar effects.

CONCLUSIONS

Our results suggest that quercetin derivatives from mulberry leaves directly prevent metabolic abnormalities among non-obese mice feeding high-fat diet. These effects may be related to decrease oxidative stresses and enhanced β–oxidations in their livers in short-time feeding without obesity influences.