論文審査の要旨

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Rosmarinic acid ameliorates hyperglycemia and insulin sensitivity in diabetic rats, potentially by modulating the expression of PEPCK and GLUT4
(ロスマリン酸は PEPCK および GLUT4 の発現を調節することによって、糖尿病モデルラットにおける高血糖およびインスリン感受性を改善する)

Background and Aims
Rosmarinic acid (RA) is a potent antioxidant that is present in many common culinary herbs. Studies of RA in diabetes treatment have suggested that RA may reduce diabetes-induced disorders and complications. RA may control plasma glucose by modulating sodium-glucose cotransporter 1 (SGLT1) trafficking to the intestinal brush-border membrane (BBM) to ameliorate postprandial hyperglycemia (HG) by a control over carbohydrate digestion and absorption. However, the mechanism(s) potentially underlying the RA-induced amelioration of diabetes mellitus (DM) remain unclear. In this study, the applicant tried to investigate the effects of RA on glucose homeostasis and insulin regulation in rats with streptozocin (STZ)-induced type 1 diabetes and high-fat diet (HFD)-induced type 2 diabetes.

Results
The applicant found that RA exerted a marked hypoglycemic effect on postprandial glucose test (PGT) in STZ-induced diabetic rats and on oral glucose tolerance test (OGTT) in normal and STZ rats. RA reversed insulin resistance on insulin tolerance test (ITT) and homeostasis model assessment of insulin resistance (HOMA-IR) in HFD-induced diabetic rats. These effects of RA were observed at all three different doses (120, 160, and 200 mg/kg) in a dose-dependent manner in both DM type 1 and 2 groups. Meanwhile, RA administration reversed the STZ- and HFD-induced increase in phosphoenolpyruvate carboxykinase (PEPCK) expression in the liver and the STZ- and HFD-induced decrease in glucose transporter type 4 (GLUT4) expression in skeletal muscle. Additionally, the administration of RA for 28 days caused a significant decrease in body weight in the HFD group.

Discussions
RA could improve glucose homeostasis administration in STZ-induced diabetic rats (DM type 1) and enhance glucose utilization and insulin sensitivity in HFD-fed diabetic rats (DM type 2), in a dose-dependent manner. Furthermore, RA could decrease PEPCK expression in the liver and increase GLUT4 expression in skeletal muscle that is suggested to contribute to a reduction in hyperglycemia and reverse the development of insulin resistance.

Conclusions
Taken together, their results demonstrated the role of RA on the amelioration of HG and insulin resistance by decreasing PEPCK expression in the liver and increasing GLUT4 expression in muscles in a dose dependent manner. This study supports the potential use of RA as a new therapeutic agent for treating DM and provides a novel finding on RA's anti-diabetic mechanisms by modulating the expression of PEPCK and GLUT4.

本研究は、ロスマリン酸 が PEPCK の発現を減少させ、GLUT4 の発現を増加させることによって血糖を低下させ、糖尿病を改善することを明らかにした。糖尿病の新規治療法の開発にもつながる知見を報告している点で興味深い。よって、本研究は学位論文として十分な価値を有するものと判定した。