論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

A high intake fructose may mediate insulin resistance. In the liver, AMPD2, an isoform of AMPD, has important glucose metabolic homeostasis functions including maintenance of AMP-activated protein kinase (AMPK). We speculated that AMPD2 induces impaired glucose tolerance after high fructose diet consumption. In this study, we compared wild-type (WT) mice and *Ampd2*-deficient mice that were fed with either normal-chow or high-fructose diet (HFrD) for 40 days.

As a result, glucose tolerance test (GTT) and pyruvate tolerance test (PTT) showed improvement of glucose tolerance in *Ampd2*-deficient mice as compared to wild-type mice after HFrD, which were independent of changes in body weight. Also, the levels of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, which are involved in hepatic gluconeogenesis, were significantly reduced in *Ampd2*-deficient mice. In addition, mRNA expression and protein expression of glucokinase, phosphofructokinase, and pyruvate kinase, which are involved in glycolysis, showed no differences between *Ampd2*-deficient mice and WT mice under HFrD. Furthermore, hepatic AMPK phosphorylation displayed no changes in the *Ampd2*-deficient mice under both conditions. Our results indicated that *Ampd2*-deficient mice are protected from high fructose diet-induced glycemic dysregulation through gluconeogenesis inhibition.

It is a paper that reported a role of AMPD2 in impaired glucose tolerance after high fructose diet and it seems to deserve a degree.

論 文 内 容 の 要 旨
Synopsis of Thesis

氏 名 Name	Athanasius Wrin Hudoyo
論文題名 Title	Role of AMPD2 in impaired glucose tolerance induced by high fructose diet (フルクトース負荷により生ずる糖代謝異常に関するAMPD2の役割)

論文内容の要旨

〔目 的(Purpose)〕

A high intake of products containing fructose is known to mediate insulin resistance. In the liver, AMPD2, an isoform of AMPD, has important glucose metabolic homeostasis functions including maintenance of AMP-activated protein kinase (AMPK). We speculated that AMPD2 induces impaired glucose tolerance in individuals who consume a high-fructose diet.

〔方法ならびに成績(Methods/Results)〕

We gave either a normal chow (NCD) or high-fructose (HFrD) diet for 40 days to 8-week-old male wild type (WT) and *Ampd2-/-* homozygote(A2-/-) C57BL/6 mice. A glucose tolerance test (GTT) and pyruvate tolerance test (PTT) were used to evaluate glucose metabolism. In addition, gluconeogenesis and glycolysis enzymes, and AMPK phosphorylation in the liver were investigated.

With consumption of the HFrD, A2-/- mice showed enhanced glucose tolerance in GTT and PTT results as compared to the WT mice, which were independent of changes in body weight. Also, the levels of phosphoenolpyruvate carboxy kinase and glucose-6-phosphatase (hepatic gluconeogenic enzyme) were significantly reduced in A2-/- as compared to WT mice. The hepatic glycolytic enzymes glucokinase, phosphofructokinase, and pyruvate kinase were also examined, though there were no significant differences between genotypes in regard to both mRNA expression and protein expression under HFrD. Surprisingly, hepatic AMPK phosphorylation resulted in no changes in the A2-/- as compared to WT mice under these condition.

〔総 括(Conclusion)〕

Our result indicated that Ampd2-deficient mice are protected from high fructose diet-induced glycemic dysregulation, mainly because of gluconeogenesis inhibition, and indicate a novel therapeutic target for type 2 diabetes mellitus.