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Fructose induces glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1 and insulin secretion: Role of adenosine triphosphate-sensitive K⁺ channels

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INTRODUCTION
Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are incretin hormones secreted from enteroendocrine K-cells and L-cells by nutrients such as carbohydrate1,2.

Adenosine triphosphate-sensitive K⁺ (KATP) channels play an important role in glucose-induced insulin secretion from pancreatic β-cells3. It was recently reported that the KATP channel is also found in the enteroendocrine K-cells and L-cells that secrete glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), respectively. In the present study, we investigated the involvement of the KATP channel in fructose-induced GIP, GLP-1 and insulin secretion in mice. Fructose stimulated GIP secretion, but pretreatment with diazoxide, a KATP channel activator, did not affect fructose-induced GIP secretion under streptozotocin-induced hyperglycemic conditions. Fructose significantly stimulated insulin secretion in Kir6.2+/+ mice, but not in mice lacking KATP channels (Kir6.2−/−), and fructose stimulated GLP-1 secretion in both Kir6.2+/+ mice and Kir6.2−/− mice under the normoglycemic condition. In addition, diazoxide completely blocked fructose-induced insulin secretion in Kir6.2+/+ mice and in MIN6-K8 β-cells. These results show that fructose-induced GIP and GLP-1 secretion is KATP channel-independent and that fructose-induced insulin secretion is KATP channel-dependent.

MATERIALS AND METHODS
Mice
C57BL/6J mice (Kir6.2+/+ mice) and mice lacking the KATP channel (Kir6.2−/− mice)4 were used. We carried out all animal experiments according to the protocol approved by the Nagoya University Institutional Animal Care and Use Committee.

Plasma Biochemical Analyses
Blood glucose levels were measured with ANTSENSE II (Bayer Medical, Leverkusen, Germany). Plasma total GIP and GLP-1 levels were measured using the GIP (TOTAL) ELISA kit (Merck)
Millipore, Billerica, MA, USA) and an electrochemiluminescent sandwich immunoassay (Meso Scale Discovery, Gaithersburg, MD, USA) as previously described. Plasma insulin levels were determined by an ELISA kit (Morinaga, Tokyo, Japan).

**Induction of Diabetes**

As described previously, streptozotocin (STZ; 150 mg/kg body-weight) was given intraperitoneally to Kir6.2+/+ mice after a 16-h fast.

**Diazoxide and Fructose Administration**

After 16 h of food deprivation, 240 mg/kg bodyweight of diazoxide (Wako, Osaka, Japan) was given orally. 90 min after diazoxide administration, 6 g/kg bodyweight of fructose was given orally.

**MIN6 Experiment**

MIN6-K8 β-cells were cultured and stimulated for 30 min by various materials after pre-incubation for 30 min in HEPES-Krebs buffer with 2.8 mmol/L glucose, and released insulin was evaluated by insulin assay kit as previously reported.

**Statistical Analysis**

Statistical analysis was carried out by unpaired, two-tailed Student’s t-test or two-way ANOVA.

**RESULTS**

**Fructose Induces GIP Secretion in the Diabetic State**

We first examined whether fructose stimulates GIP secretion. In Kir6.2+/+ mice, fructose tended to, but not significantly, stimulate GIP secretion in a normal state, but significantly enhanced the GIP secretion in the STZ-induced diabetic state (Figure 1a). To investigate the involvement of the KATP channel in fructose-induced GIP secretion in the diabetic state, we examined the effect of the KATP channel activator, diazoxide, on fructose-induced GIP secretion. Pretreatment of diazoxide did not affect fructose-induced GIP secretion in the diabetic state (Figure 1b). Fructose-induced GLP-1 levels at 15 min were not different under the normoglycemic condition and hyperglycemic condition (Figure 1c).

**KATP Channels Are Not Involved in Fructose-Induced GLP-1 Secretion In Vivo**

We next investigated whether the KATP channel participates in fructose-induced GLP-1 secretion in vivo, by utilizing Kir6.2−/− mice. Both in Kir6.2−/− and Kir6.2−/− mice, fructose significantly stimulated GLP-1 secretion more than twofold at 15 min of fructose administration (Figure 2b). In contrast, fructose did not stimulate GIP secretion in Kir6.2−/− mice at all (Figure 2a).

**KATP Channels Are Involved in Fructose-Induced Insulin Secretion In Vivo and In Vitro**

To assess whether fructose-induced insulin secretion requires the KATP channel pathway, we investigated blood glucose levels and serum insulin levels during oral fructose tolerance test in both Kir6.2+/+ and Kir6.2−/− mice. The blood glucose levels were significantly higher in Kir6.2+/+ mice than in Kir6.2−/− mice (Figure 2c). Fructose significantly stimulated insulin secretion in Kir6.2+/+ mice at 15 min, but not in Kir6.2−/− mice at
DISCUSSION

The mechanism by which fructose stimulates gut hormone secretion is not well known. In the present study, we investigated the role of the KATP channels in fructose-induced GIP, GLP-1 and insulin secretion in vivo.

We previously reported that the KATP channels in K-cells are in a closed state under the normoglycemic condition in vivo, and are in an open state under the hyperglycemic condition. The increase of ATP produced by metabolism of glucose closes the KATP channels in the K-cells under the hyperglycemic condition and enhances glucose-induced GIP secretion, suggesting that KATP channels in K-cells contribute to glucose-induced GIP secretion under the hyperglycemic condition. However, the present results show that this mechanism is not involved in fructose-induced GIP secretion in the diabetic state and that the KATP channels in K-cells do not contribute to fructose-induced GIP secretion under the hyperglycemic condition. In previous reports, 3 g/kg fructose did not stimulate GIP secretion in C57BL/6J mice, but did stimulate GIP secretion in obese type 2 diabetic model ob/ob mice. The mechanism of such fructose-induced GIP secretion in various diabetic models remains to be elucidated.

In the present study, fructose was found to significantly induce GLP-1 secretion in Kir6.2+/+ mice, and pretreatment of diazoxide did not block fructose-induced GLP-1 secretion at 15 min and fructose-induced GLP-1 secretion was not enhanced under the hyperglycemic condition. These results show that the KATP channel is not required for fructose-induced GLP-1 secretion in vivo. However, a previous in vitro study using GLUTag cells found that fructose-induced GLP-1 secretion was entirely KATP channel-dependent. This discrepancy could be due to the nature of the GLUTag cell line and/or...
It is reported that activation of sweet taste receptors in pancreatic β-cells stimulates insulin secretion through the phospholipase C pathway. Kyriazis et al. also reported that insulin secretion was not induced by glucose catalyzed from fructose, but by activation of the sweet taste receptor in a glucose-dependent manner through transient receptor potential cation channel, subfamily M, member 5. In the present study, the fructose-induced insulin secretion seen in Kir6.2+/− mice was not observed at all in Kir6.2−/− mice, and diazoxide completely blocked fructose-induced insulin secretion in vivo and in vitro. These results show that the K_{ATP} channel in β-cells plays an essential role in the fructose-induced insulin secretion. In contrast, we previously showed that insulin secretion mediated by the vagal nerve in vivo was K_{ATP} channel-independent, and it was reported previously that insulin secretion through activation of the phospholipase C pathway differed from that induced by carbachol, the activator of the muscarinic receptor. These findings suggest that the K_{ATP} channel-dependent phospholipase C-transient receptor potential cation channel, subfamily M, member 5 pathway is involved in fructose-induced insulin secretion in vivo.

In conclusion, fructose stimulates GLP-1 secretion under normoglycemia, but enhances GIP secretion under the hyperglycemic condition, both of which modifications are in a K_{ATP} channel-independent manner. K_{ATP} channels play an essential role in the insulin secretion induced by fructose in vivo.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES


