Effects of miglitol, an α-glucosidase inhibitor, on glycaemic status and histopathological changes in islets in non-obese, non-insulin-dependent diabetic Goto-Kakizaki rats

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Miglitol, a 1-deoxynojirimycin derivative, is an α-glucosidase inhibitor. In the present study, the effects of acute (single-dose) and chronic (8-week) oral administration of miglitol in Goto-Kakizaki (GK) rats, an animal model of type 2 diabetes, were investigated. Dose-dependent decreases in incremental blood glucose concentrations integrated over a period of 2 h (ΔAUC0–2h) for values of blood glucose after sucrose-loading in miglitol-treated GK rats were observed following an acute oral administration of miglitol (1, 3 or 10 mg/kg body weight). At 10 mg/kg, the ΔAUC0–2h of blood glucose was decreased by 45% compared with the control group. Following the oral administration of miglitol in a dietary mixture (10 mg, 20 mg or 40 mg miglitol/100 g control diet) for 8 weeks, the ratio of HbA1c at 8 weeks compared with 0 weeks in GK rats treated with 40 mg miglitol/100 g control diet miglitol was significantly decreased compared with control GK rats without changes in body weight. In oral glucose tolerance testing, miglitol caused a slight decrease in the ΔAUC0–2h of plasma glucose concentration. In addition, miglitol treatment slightly inhibited the reduction in β-cell mass, and lessened the irregular contours and fibrosis of the islets in GK rats. These results indicate that miglitol ameliorates the hyperglycaemic state of GK rats and the impaired function of the pancreatic islets, as well as preventing the degeneration of islets in GK rats.

Miglitol: α-Glucosidase inhibitor: β-Cell mass: GK rats

α-Glucosidase inhibitors, which are oral antidiabetic agents, delay carbohydrate absorption from the small intestine by inhibiting intestinal α-glucosidase activity. These drugs (e.g. acarbose, voglibose, miglitol) improve postprandial hyperglycaemia in diabetic patients1,2. Acarbose, a pseudotetrasaccharide, has been reported to be a competitive inhibitor of sucrase, glucoamylase and isomaltase3–6. Voglibose, an N-substituted valiolamine derivative, has been reported to have stronger α-glucosidase inhibitory activity against maltase and sucrase7.

Miglitol, a 1-deoxynojirimycin derivative, is another drug selected for development as an antihyperglycaemic drug8. Miglitol is a strong inhibitor of glucoamylase, sucrase and isomaltase9, and has been used clinically in Europe and the USA10,11. On the other hand, voglibose is not approved in Europe or the USA but has been widely used in the treatment of patients with diabetes in Asia. Miglitol causes less diarrhoea than acarbose and voglibose because it is almost completely absorbed in the upper region of the small intestine in rats, whereas acarbose and voglibose are not absorbed8,12.

Miglitol has recently been reported to reduce the plasma glucose concentration in a dose-dependent manner in normal rats13 and in several animal models of diabetes14–16. The question of whether or not a reduction in hyperglycaemia is achieved by acute or chronic oral administration of miglitol has not been investigated in Goto-Kakizaki (GK) rats, an animal model of non-obese, non-insulin-dependent diabetes characterised by low insulin secretion17,18. The effects of acarbose and voglibose have, however, already been investigated19–23. It has been reported that β-cells in GK rats are defective in their glucose-stimulated insulin secretion, whereas insulin synthesis is not affected24–26. This animal model exhibits functional and structural features of diabetic complications and is therefore considered suitable for studying type 2 diabetes27,28. It has also been reported that total β-cell mass was decreased in type 2 diabetic patients compared with control subjects29 and that β-cell loss was enhanced by sucrose-feeding via an increase in the rate of apoptosis in GK rats30. Furthermore, a reduction in β-cell volume was found to be inhibited by a reduction of hyperglycaemia in GK rats treated with...
voglibose\textsuperscript{19}. However, the effects of oral administration of miglitol for β-cell reduction as well as glycaemic control in GK rats are still unknown.

In the present study, we examined the acute effects of a single dose of miglitol on blood glucose concentrations and insulin secretion after sucrose-loading, as well as the chronic effects of long-term miglitol treatment in a dietary mixture on glycaemic control and β-cell reduction in GK rats.

Materials and methods

Animals

Diabetic GK male rats were obtained from CLEA Japan Inc., Japan. Non-diabetic Wistar male rats were purchased from Japan SLC (Hamamatsu, Japan). The rats had free access to standard laboratory chow (MF; Oriental Yeast, Tokyo, Japan) and water, and were housed in a room controlled for temperature (22 ± 3°C), humidity (55 ± 15 %) and light (hours of time 07:00–19:00 hours).

Effects of a single dose of miglitol in Goto-Kakizaki rats

GK rats were randomly assigned to a group based on body weight and the results of oral glucose tolerance testing (2 g/kg body weight). Rats whose blood plasma glucose concentration was less than 300 mg/dl were excluded. Eight rats (10 weeks old) were used in each group and were fasted for 18–20 h before the experiments. The experimental procedures were approved by the Ethical Committee for Animal Research of Mitsubishi Chemical Safety Institute Ltd.

Sucrose-loading test

The rats were administered with a single oral dose of miglitol or voglibose (miglitol 1, 3, 10 mg/kg body weight; voglibose 0.0125, 0.0375, 0.125 mg/kg body weight) dissolved in saline. Miglitol and voglibose provided by Bayer Yakuhin Ltd. (Osaka, Japan) were used in the present study. GK rats administered with only saline served as controls. The drug solutions were administered using a gastric tube in a volume of 5 ml/kg body weight. Blood glucose, body weight and food intake were measured immediately before sucrose-loading (2 g/kg body weight). Mbirds whose blood plasma glucose concentration was less than 300 mg/dl were excluded. Eight rats (10 weeks old) were used in each group and were fasted for 18–20 h before the experiments. The experimental procedures were approved by the Ethical Committee for Animal Research of Mitsubishi Chemical Safety Institute Ltd.

Effects of 8-week miglitol administration on Goto-Kakizaki rats

All animals received the high-sucrose and high-fat control diet (Table 1) for 2 weeks before assignment to a study group. Seven week-old male GK rats were assigned to one of six groups based on body weight and the results of the oral glucose tolerance test. Each group consisted of 5–7 animals.

Table 1. Composition of the high sucrose and high fat control diet

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<th>Parameter</th>
<th>g/kg</th>
<th>kcal/kg</th>
<th>energy %</th>
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<td>714.8</td>
<td>19.9</td>
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<tr>
<td>α-Methionine</td>
<td>2.6</td>
<td>10.2</td>
<td>0.3</td>
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<tr>
<td>α-Cornstarch</td>
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<td>85.2</td>
<td>2.4</td>
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<td>Sucrose</td>
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<td>47.5</td>
</tr>
<tr>
<td>Corn oil</td>
<td>66.0</td>
<td>594.0</td>
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</tr>
<tr>
<td>Lard</td>
<td>53.2</td>
<td>478.8</td>
<td>13.4</td>
</tr>
<tr>
<td>AIN\textsuperscript{76} Mineral mix</td>
<td>29.8</td>
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<tr>
<td>AIN\textsuperscript{76} Vitamine mix</td>
<td>8.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Choline bitartrate</td>
<td>1.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2% Agar</td>
<td>212.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>3585</td>
<td>100</td>
</tr>
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</table>

Each experiment consisted of one control Wistar rat group and six GK rat groups as follows: (1) control Wistar rats fed the control diet; (2) control GK rats fed the control diet; (3) miglitol-treated GK rats fed a diet containing 10 mg miglitol/100 g control diet; (4) miglitol-treated GK rats fed a diet containing 20 mg miglitol/100 g control diet; (5) miglitol-treated GK rats fed a diet containing 40 mg miglitol/100 g control diet; (6) voglibose-treated GK rats fed a diet containing 0.1 mg voglibose/100 g control diet; (7) voglibose-treated GK rats fed a diet containing 0.2 mg voglibose/100 g control diet. The rats were fed the control diet with either miglitol or voglibose ad libitum for 8 weeks. Feed mixtures containing miglitol or voglibose were prepared once a week.

The experimental procedures used in the present study conformed to the guidelines of the Animal Usage Committee of the University of Shizuoka.

Parameters

Blood glucose, body weight and food intake were measured after 0, 2, 4, 6 or 8 weeks of feeding. Physical signs were observed on an occasional basis.

HbA\textsubscript{1c} was assayed by HPLC (Waters, Tokyo, Japan) using a TSKgel Boronate-SPW column system (Tosoh Corporation, Tokyo, Japan). Blood samples were collected for determination of plasma glucose after the rats were fasted overnight. Plasma glucose was measured by the glucose oxidase method using a commercial kit (Wako Pure Chemical Industries, Osaka, Japan).

After treatment for 8 weeks, all animals underwent an oral glucose tolerance test. The rats were orally administered a glucose solution (2 g/kg body weight, 10 ml/kg body weight) after an overnight fast, and their plasma glucose and plasma insulin concentrations were determined using blood samples from the tail vein 0, 15, 30, 60 and 120 min later. The data for GK rats given 0.2 mg voglibose/100 g control diet were excluded from the assessment because it appeared that energy restriction occurred as a result of diarrhoea in these rats.

After the oral glucose tolerance test, the animals were again given the control diet with miglitol or voglibose ad libitum by 23.00 hours. They were then fasted overnight and killed by decapitation. The whole pancreas was excised, weighed following the removal of connective tissue and extraneous fat, and then fixed in 3:7% (v/v) formaldehyde and processed for paraffin embedding.
Islet pathology and morphometry of β-cells

Serial 4 μm thick paraffin sections were stained with haematoxylin & eosin or azan for islet pathology and immunostained for morphometric analysis of islet β-cells. To identify the areas of β-cells in the islets, immunoperoxidase staining was performed using a Vectastain ABC kit (Vector Laboratories, Burlingame, CA, USA). Briefly, deparaffinised sections were first incubated with guinea-pig anti-insulin antibody (Dako, Carpinteria, CA, USA). The slides were then incubated with biotinylated anti-guinea-pig immunoglobulin antibody. The secondary reaction products were visualised with diaminobenzidine. Nuclei were lightly counterstained with haematoxylin.

Calculation of the volume density of β-cells was performed using an image processor for analytical pathology (IPAP-WIN; Sumika Technoservice Corporation, Osaka, Japan). Areas of blood vessels, fat and connective tissue were excluded from the measurements. The identity of the sample was masked to the examiners during the process of morphometric analysis.

Statistical analysis

All experimental values are expressed as means with their standard errors for each group. Statistical analysis was performed using Dunnett’s test, analysis of linear regression and the Jonckheere-Terpstra test using SAS Proprietary Software (SAS Institute, Tokyo, Japan). The levels of body weight, food intake, blood glucose, plasma insulin and HbA1c were compared between control GK rats and rats treated with several concentrations of miglitol or voglibose. The level of volume density of β-cells was compared between control Wister rats and GK rats with/without miglitol or voglibose treatment. A level of $P < 0.05$ was considered to indicate statistical significance.

Results

Effects of a single dose of miglitol in Goto-Kakizaki rats

Blood glucose concentration. α-Glucosidase inhibitors inhibit the digestion of sucrose in the lumen of the small intestine. To estimate the effect of miglitol on postprandial hyperglycaemia as a result of inhibiting sucrose digestion in the lumen, the blood glucose concentrations after sucrose loading were measured. Blood glucose reached the highest concentration (382 mg/dl) 1 h after sucrose-loading in GK rats in the control group, following which values recovered to the pretreatment level at 4 h (Fig. 1(A)). Blood glucose concentrations were not significantly different between control GK rats and 1 or 3 mg/kg miglitol-treated GK rats. Blood
glucose concentrations in the 10 mg/kg miglitol-treated GK rats decreased significantly compared with the control group at 1 h after sucrose-loading (P < 0.05). In voglibose-treated GK rats, blood glucose concentrations were not significantly different from those of the control group at any dose.

The incremental blood glucose concentration integrated over a period of 2 h (ΔAUC0–2h values) after the administration of sucrose in the control group was 275 mg/dl per h (Table 2). At doses of 1 and 3 mg/kg, miglitol did not affect the ΔAUC0–2h of blood glucose. At 10 mg/kg, the ΔAUC0–2h of blood glucose fell by 45% compared with the control group (P < 0.05). None of the doses of voglibose affected the ΔAUC0–2h of blood glucose.

**Plasma insulin concentration.** Plasma insulin concentrations were increased at 0.25 h after sucrose-loading in control GK rats and returned to pretreatment levels 0.5 h after sucrose-loading (Fig. 1(B)). Thereafter, plasma insulin concentrations in control GK rats increased again 1 h after sucrose-loading and reached their highest values (1.58 ng/ml) 2 h after sucrose-loading.

In GK rats treated with 1 mg/kg miglitol, there was no effect on plasma insulin concentration compared with the control group. The plasma insulin concentration at 0.25 h after sucrose-loading in the 3 and 10 mg/kg miglitol groups decreased by 44% and 22%, respectively, compared with the control group, but the differences were not significant. Voglibose at doses of 0.0125 and 0.0375 mg/kg did not affect the plasma insulin concentration.

Plasma insulin concentration 1 h after sucrose-loading in the 0.125 mg/kg voglibose-treated groups decreased by 35% compared with the control group, but was not significantly different from that of the control group.

**Effects of 8-week miglitol administration in Goto-Kakizaki rats**

**Body weight and food intake.** No differences in body weight were seen between the miglitol-treated and control GK rats (Table 3). Food intake in the miglitol-treated GK rats was decreased for 1 week after treatment but then returned to values similar to those of control Wistar and control GK rats (Table 4). Physical signs in the miglitol-treated GK rats were normal throughout the treatment period.

In GK rats fed the diet containing 0.1 mg voglibose/100 g control diet, no difference in body weight was seen compared with control GK rats, even though food intake was decreased 1 week after the treatment before returning to values similar to those of control GK rats. On the other hand, diarrhoea was observed 1 day after treatment in GK rats administered the diet containing 0.2 mg voglibose/100 g control diet. The body weight of these latter rats was significantly decreased compared with control GK rats throughout the experimental period (P < 0.01, P < 0.01, P < 0.01 and P < 0.01 for weeks 2, 4, 6 and 8 respectively), whereas food intake was significantly reduced at each time point until 4 weeks (P < 0.01, P < 0.01 and P < 0.01, respectively).

**HbA1c.** HbA1c concentrations were not significantly different between the control GK rats and the miglitol-treated GK rats (control, 6.90% (SE 0.24); 10 mg miglitol/100 g control diet, 6.49% (SE 0.11); 20 mg miglitol/100 g control diet, 6.30% (SE 0.18), 40 mg miglitol/100 g control diet, 6.45% (SE 0.19)). The HbA1c ratio of 8 weeks to 0 week (ΔHbA1c value) in miglitol-treated GK rats decreased in a dose-dependent manner (Fig. 2). In GK rats treated with 40 mg miglitol/100 g control diet, HbA1c was significantly decreased compared with control GK rats (P < 0.01), although the value in GK rats fed the diet containing 0.1 mg voglibose/100 g control diet was similar to that in control GK rats (HbA1c value, 6.68% (SE 0.11)).

An analysis of linear regression between the dosage of miglitol and the ΔHbA1c value showed clearly that treatment of the GK rats with miglitol reduced the ΔHbA1c value in a dose-dependent manner (P = 0.0007, R² = 0.386). Statistical treatment by Jonckheere-Terpstra analysis, which is well known for showing drug effects in a dose-dependent manner, indicated a significant tendency of HbA1c to decrease with an increase in miglitol concentration (P = 0.0007).

**Oral glucose tolerance test.** In the oral glucose tolerance test, blood glucose concentrations after glucose-loading were markedly elevated in GK rats, including control GK rats. In miglitol-treated GK rats, the reduction in the blood glucose concentration tended to occur earlier than that in control GK rats (Fig. 3(A)). The ΔAUC0–2h of plasma glucose in miglitol-treated GK rats was not significantly different from that of control GK rats (Fig. 3(C)). In GK rats treated with 0.1 mg voglibose/100 g control diet, the plasma glucose concentration and ΔAUC0–2h value of blood glucose were similar to those of control GK rats (Fig. 3(B), (C)).

**Islet structure and morphometry.** The weight of the pancreas in the control GK rats was greater than that of control Wistar rats by 42%. With the exception of GK rats treated with 0.2 mg voglibose/100 g control diet, pancreas weight in GK rats treated with miglitol or voglibose was similar to that of control GK rats (Table 5).

Although the differences in β-cell volume density between control GK rats and miglitol-treated GK rats or voglibose-treated GK rats were not statistically significant, the reduction in β-cell volume density was slightly inhibited in GK rats treated with 40 mg miglitol/100 g control diet compared with...
For voglibose at a dose of 0·125 mg/kg body weight, the sucrose-loading were decreased by a single dose of miglitol. Clearly showed that blood glucose concentrations after loading decreased by 45% (et al. was not significant. Odaka by 25% compared with control GK rats, but the difference was not significant from those of control GK rats (Dunnett’s test): *).

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Dose (mg/100 g control diet)</th>
<th>Number of animals</th>
<th>0 Weeks</th>
<th>2 Weeks</th>
<th>4 Weeks</th>
<th>6 Weeks</th>
<th>8 Weeks</th>
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<td>222 ± 7</td>
<td>278 ± 9</td>
<td>323 ± 10</td>
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<td>280 ± 5</td>
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<td>146 ± 3</td>
<td>176 ± 2</td>
<td>198 ± 5</td>
<td>234 ± 12*</td>
<td>258 ± 15***</td>
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</table>

Mean values were significantly different from those of control GK rats (Dunnett’s test): **P<0·01, ***P<0·001.

control GK rats (Table 5). The volume density of β-cells in control GK rats tended to be reduced by 69% compared with that in control Wistar rats, but this was not significant (P=0·0556). On the other hand, the β-cell volume density of rats treated with 40 mg miglitol/100 g control diet was almost equal to that of control Wistar rats (P=0·9949).

The islets of 15-week-old control GK rats showed irregular contours, fibrosis and loss of β-cells (Fig. 4), while those of age-matched control Wistar rats had a normal appearance. The islets of GK rats treated with the 40 mg miglitol/100 g control diet for 8 weeks showed good islet shape, and those of GK rats treated with 0·1 mg voglibose/100 g control diet were similar to those of control GK rats.

Discussion

In the present study, we planned two separate experiments to explore the effects of acute and chronic oral administration of miglitol on GK rats, an animal model of non-obese, type 2 diabetes.

First, we examined the concentrations of blood glucose and plasma insulin after an oral administration of sucrose with or without miglitol in GK rats. At a dose of 10 mg miglitol/kg body weight, the AUC0–2h of blood glucose after sucrose-loading decreased by 45% (P<0·05; see Table 2). Our results clearly showed that blood glucose concentrations after sucrose-loading were decreased by a single dose of miglitol. For voglibose at a dose of 0·125 mg/kg body weight, the AUC0–2h of blood glucose after sucrose-loading decreased by 25% compared with control GK rats, but the difference was not significant. Odaka et al. reported that blood glucose concentrations in 0·1 mg/kg voglibose-treated GK rats decreased by more than 50% compared with control GK rats. Such discordant results may be attributable to differences between the colonies or ages of GK rats used for these studies because the glucose tolerant rates of the experimental animals, that is, fasting blood glucose or peak value of increasing blood glucose after sucrose-loading, were different between the present experiment and theirs. In GK rats, the reduction in β-cells becomes more pronounced and the frequency of diabetic syndrome, which is characterised by hyperglycaemia and impaired glucose tolerance, tends to rise with increasing age. Therefore, the age of the animals used in an experiment would appear to be very important.

Next, we investigated the effects on glycaemic status when GK rats were fed a diet containing miglitol for 8 weeks. During the 8-week experimental period, the ΔHbA1c in miglitol-treated GK rats decreased in a dose-dependent manner and was significantly decreased in rats treated with 40 mg miglitol/100 g control diet compared with control GK rats, although ΔHbA1c in GK rats treated with 0·1 mg voglibose/100 g control diet was similar to that of control GK rats (see Fig. 2). This result indicates that chronic blood glucose concentrations in GK rats were controlled by miglitol.

It should be noted that ΔHbA1c was markedly reduced by treatment with the 0·2 mg voglibose/100 g control diet. Treatment with the latter diet induced diarrhoea and reduced food intake in GK rats (see Table 4). The high-sucrose and high-fat diet used in the present study may have accelerated the induction of gastrointestinal symptoms such as diarrhoea, which appeared only in rats treated with 0·2 mg voglibose/100 g control diet. Thus, carbohydrate malabsorption

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<th>Test substance</th>
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<td>18·2 ± 0·8</td>
<td>16·7 ± 0·4</td>
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Mean values were significantly different from those of control GK rats (Dunnett’s test): *P<0·05, **P<0·01, ***P<0·001.
Fig. 2. ΔHbA1c concentrations for 8 weeks in miglitol- and voglibose-treated Goto-Kakizaki (GK) rats. Mean values and their standard errors ($n = 5–7$). Mean values were significantly different from those of control GK rats (Dunnett’s test): **$P < 0.01$.

Fig. 3. Effects of miglitol (A) and voglibose (B) on plasma glucose concentration in glucose-loaded Goto-Kakizaki (GK) rats. Mean values and their standard errors ($n = 5–7$). (C) Incremental blood glucose concentration integrated over a period of 2 h ($\Delta\text{AUC}_{0–2h}$) in glucose-loaded GK rats treated with miglitol or voglibose. Mean values and their standard errors ($n = 5–7$).
occurs following a slight increase in the dose of a non-absorbable α-glucosidase inhibitor. Undigested carbohydrates enter the lower region of the small intestine, resulting in gastrointestinal disorders such as soft stools or diarrhoea. This suggests that the dosage range of voglibose for which gastrointestinal symptoms do not develop but for which the pharmacological action is seen is very narrow (0·1–0·2 mg voglibose/100 g control diet). Miglitol did not produce diarrhoea even though it was administered at up to 100 mg/100 g diet in a toxicity study in normal Wistar rats for 12 months. Due to this attribute, miglitol exhibits a more potent inhibitory action on postprandial hyperglycaemia than other α-glucosidase inhibitors, and without any adverse effects.

Table 5. Pancreas weight and islet morphometry of miglitol- and voglibose-treated Goto-Kakizaki (GK) rats

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<tr>
<th>Test substance</th>
<th>Dose (mg/100 g control diet)</th>
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<th>Pancreas weight (mg) (relative weight)</th>
<th>Volume density of β-cells (%)</th>
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<tr>
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Mean values were significantly different from those of control GK rats (Dunnett's test): *P<0.05, **P<0.01.

![Fig. 4](image-url) Islet structures and distribution of immunoreactive insulin-positive cells (β-cells) in miglitol- or voglibose-treated Goto-Kakizaki (GK) rats. Section from a control Wistar rat showing a normal structure: the islet is round in shape, with a clearly defined contour, and the β-cells (insulin-positive cells) are stained brown. Control GK rat and GK rats treated with 0·1 mg voglibose/100 g control diet, showing an irregular islet shape, a rough distribution of the β-cells and strands of fibrous tissue traversing the islet. GK rat treated with 40 mg miglitol/100 g control diet, showing good preservation of the islet. Scale bar = 100 μm. (A) Haematoxylin and eosin staining; (B) azan staining; (C) immunostaining for insulin.
Finally, we examined the effects of miglitol on histological changes in the islets of GK rats. Histological changes in the islets of GK rats that have been reported include progressive fibrosis and the disappearance of β-cells with increasing age. The mechanism for the progressive loss of β-cells in GK rats is apoptotic cell death. Furthermore, recent reports in which clinical information was better characterised have concluded that β-cell mass decreased in type 2 diabetes. In the present study, histological examination of the pancreas revealed that miglitol tended to inhibit the loss of β-cells as well as lessen irregular contouring and fibrosis of the islets in GK rats (see Fig. 4). Thus, the controlled blood glucose concentrations may be attributable to preservation of the islet β-cell mass.

The STOP-NIDDM trial has shown that decreasing postprandial blood glucose concentrations, as a consequence of acarbose treatment, could reduce the risk of diabetes in patients with impaired glucose tolerance. A reduced demand for endogenous insulin by α-glucosidase inhibitors, including miglitol, lessens the burden on a pancreas with decreased secretory capacity, which will potentially enable the preservation of pancreatic function over a long period in patients with type 2 diabetes.

In conclusion, miglitol ameliorates the hyperglycaemic state and impaired function of the pancreatic islets, and tends to inhibit the development of histological changes in the islets of GK rats.

Acknowledgements

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References