Altered dipeptidyl peptidase-4 activity during the progression of hyperinsulinemic obesity and islet atrophy in spontaneously late-stage type 2 diabetic rats

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Kirino Y, Sato Y, Kamimoto T, Kawazoe K, Minakuchi K. Altered dipeptidyl peptidase-4 activity during the progression of hyperinsulinemic obesity and islet atrophy in spontaneously late-stage type 2 diabetic rats. Am J Physiol Endocrinol Metab 300: E372–E379, 2011. First published December 7, 2010; doi:10.1152/ajpendo.00319.2010.—Altered dipeptidyl peptidase-4 (DPP4) activity during the progression of late-stage type 2 diabetes was measured in Otsuka Long-Evans Tokushima fatty (OLETF) rats. Compared with OLETF rats subjected to 30% food restriction, food-satiated OLETF rats exhibited spontaneous hyperphagic obesity, insulin resistance, hyperglycemia, hyperinsulinemia, and increased plasma DPP4 activity during the early phase of the experiment (up to ~30 wk). Subsequently, their plasma DPP4 activity as well as their body weight, body fat, and plasma insulin concentration declined to control levels during the late phase, resulting in excessive polyuria, proteinuria, dyslipidemia, pancreatic islet atrophy, hypoinsulinemia, and diabetes, which changed from insulin-resistant diabetes to hypoinsulinemic diabetes secondary to progressive islet insufficiency, and their fasting blood glucose level remained high. Since plasma DPP4 activity demonstrated significant positive correlations with body weight and the fasting plasma insulin level but not with the fasting blood glucose level during the late stage of diabetes, body fat and fasting plasma insulin levels may be useful factors for predicting the control of plasma DPP4 activity. In contrast, pancreatic DPP4 activity was significantly increased, and the expression of pancreatic insulin was significantly reduced in late-stage diabetic OLETF rats, suggesting that a relationship exists between the activation of pancreatic DPP4 and insulin depletion in pancreatic islet atrophy. In conclusion, it is suggested that plasma DPP4 activity changes in accordance with the progression of hyperinsulinemic obesity and pancreatic islet atrophy. DPP4 activity may play an important role in insulin homeostasis.

Otsuka Long-Evans Tokushima fatty rat; pancreatic islet atrophy

IN THE PAST FEW DECADES, type 2 diabetes has become a major worldwide public health problem due to changes in human behavior and lifestyle (22). Recently, incretin mimetics, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) receptor agonists, and dipeptidyl peptidase-4 (DPP4) inhibitors have been focused on as new classes of antidiabetic agents that do not cause weight gain and have a low incidence of hypoglycemia (5, 9, 17).

DPP4 (CD26, EC3.4.14.5) is a complex enzyme that is present on the surface of most cell types, including kidney, liver, pancreas, and fat cells, as well as in soluble form in the circulation (12, 13). DPP4 is a serine protease that cleaves the penultimate l-proline or l-alanine found at the NH2 termini of several polypeptides, such as GLP-1, GIP, and neuropeptide Y1–36. GLP-1 and GIP are members of the incretin system that stimulate pancreatic insulin secretion. Many studies in humans and animal models have established that the inhibition of DPP4 activity increases the circulating levels of intact bioactive GLP-1 and GIP, leading to improved glucose tolerance (3, 4, 14, 20, 21), which implies that similarities in the roles of DPP4 activity could exist across species. Additionally, DPP4 inhibition has also been reported to exert protective effects on pancreatic β-cell function, because GLP-1 and GIP were found to be involved in insulin biosynthesis and the proliferation of β-cells in preclinical studies (16, 19). Moreover, recent studies have suggested that DPP4 inhibition followed by neuropeptide Y1–36 elevation enhances its antilipolytic action in adipose tissue (12) and angiotensin II-mediated renal vasoconstriction (6). Nevertheless, only a few studies have investigated whether DPP4 activity is correlated with the onset or severity of diabetes and diabetes-related diseases.

Previously, we found that both high-fat and high-sucrose diet-fed rats demonstrated impaired glucose tolerance and visceral fat accumulation, possibly due to increased plasma DPP4 activity (10). Additionally, it was found that, while DPP4-deficient rats are resistant to diabetes development, they are also more susceptible to dyslipidemia and reductions in the glomerular filtration rate when treated with streptozotocin (STZ) (11). These taken together, it is likely that plasma DPP4 activity changes during the progression of diabetes and diabetic complications such as nephropathy. However, there have been no reports of an association between DPP4 activity and late-stage type 2 diabetes symptoms such as progressive islet atrophy.

In the present study, the role of DPP4 activity in late-stage type 2 diabetes was investigated using Otsuka Long-Evans Tokushima fatty (OLETF) rats (7, 8). OLETF rats display a spontaneously hyperphagic and obese phenotype in combination with hyperglycemia and hyperinsulinemia. Most male OLETF rats develop diabetes by 25 wk of age, and their pancreatic islets gradually atrophy by 30–40 wk of age, resulting in excessive polyphagia, polydipsia, polyuria, nephropathy, weight loss, and hypoinsulinemia (7, 8). In addition, it has been confirmed that OLETF rats subjected to food restriction (FR) or exercise are resistant to the development of metabolic abnormalities. Taking these findings together, we consider OLETF rats to be appropriate as a model of spontaneous late-stage type 2 diabetes and diabetic nephropathy. We determined the difference in DPP4 activity between OLETF rats subjected to food satiation (FS) and those subjected to FR.
MATERIALS AND METHODS

Animals. Four-week-old male OLETF rats were generously donated by the Tokushima Research Institute, Otsuka Pharmaceutical, Tokushima, Japan. All rats were housed in an air-conditioned room at 23 ± 2°C and 50 ± 10% humidity under controlled lighting conditions (12:12-h light-dark cycle). The rats were given free access to their diet and water and then acclimatized for 1 wk before the experiments on a standard diet (MF: Oriental Yeast, Tokyo, Japan). OLETF rats are recognized as an animal model of hyperglycemia accompanied by severe dyslipidemia, hepatic steatosis, and renal damage; therefore, all animal care procedures and treatments were conducted in accordance with the guidelines of the Animal Use and Care Committee of the University of Tokushima. No abnormal behavior or lack of voluntary movement was observed in any of the rats during the experimental period. No rats suffered from other diseases such as microbial infection.

Experimental design. At 5 wk of age, the rats were randomly divided into the following two groups: the food satiation (FS, n = 10) and food restriction (FR, n = 10) groups. Body weight at the baseline was not significantly different between two groups (FS, 90.1 ± 1.0 g; FR, 88.9 ± 1.4 g). Food intake in the FS group was monitored daily, and the rats in the FR group received an allotment of food equal to 70% of the food intake of the FS group. Blood samples were obtained from the tail veins of the rats at 9:00–10:00 AM after overnight fasting at the times indicated in Fig. 1. Fifty-five weeks after the start of the experiment, each rat was placed in a metabolic cage containing a urine collection funnel to measure the amount of urine excreted during 24 h, and the collected urine samples were stored at −20°C until the measurement of several parameters. Then, an oral glucose tolerance test (OGTT) was performed at 56 wk. At the end (58 wk) of the experiment, the right kidney, liver, pancreas, stomach, epididymal fat, and abdominal subcutaneous fat were immediately collected and

Fig. 1. Body weight (A), fasting blood glucose (B), fasting plasma insulin (C), HOMA-IR (D), blood glucose in the OGTT at 56 wk (E), and the AUC<sub>0–120 min</sub> of blood glucose in the OGTT at 56 wk (F) in the food-satiated (FS, n = 10, ■) and food-restricted (FR, n = 10, ○) groups. Data are shown as means ± SE. *P < 0.05, **P < 0.01, ***P < 0.001 vs. FR group (Student’s unpaired t-test).
weighed after the rats had been killed under anesthesia with urethane (5 g/kg ip; Sigma, St. Louis, MO). The tissues collected for the DPP4 enzyme assay were immediately frozen and stored at −80°C.

**Measurement of blood biochemical parameters.** After the blood samples had been collected, fasting blood glucose concentrations were immediately measured using a glucose analyzer (Glucose Pilot; Avenitir Biotech, Carlsbad, CA). Fasting plasma insulin was determined via an enzyme-linked immunosorbent assay using an Ultra-Sensitive Rat Insulin Kit (Morigina Institute of Biological Science, Yokohama, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from the blood glucose and insulin values of the rats by use of the standard formula to estimate insulin resistance and insulin-secretory capacity, respectively. The levels of triglycerides (TG), total cholesterol (T-CHO), high-density lipoprotein (HDL)-cholesterol, and creatinine were measured using commercial reagents according to the manufacturer’s recommendations (Wako Pure Chemical Industries, Osaka, Japan).

**Measurement of urinary parameters.** Proteinuria was assessed by the Bradford method (Bradford Protein Assay; Bio-Rad Laboratories, Hercules, CA). Urinary glucose concentrations were determined using a fluorescent analyzer (Glucose Pilot; Avenitir Biotech), and the data are shown as urinary excretion (ml/24 h), protein excretion (mg/24 h), and glucose excretion (mg/24 h).

**DPP4 enzyme assay in plasma.** DPP4 activity was determined by the rate of cleavage of 7-amino-4-methylcoumarin (AMC) from the resultant supernatants were collected and centrifuged twice at 20,000 g. After a 5-min preincubation at room temperature, the reaction was initiated by the addition of 40 μl of substrate Gly-Pro-AMC. After 20 min of incubation, fluorescence was determined using a spectrophotometer (Tecan Infinite M200; Tecan Japan, Yokohama; excitation: 380 nm/emission: 460 nm). A standard curve for free AMC was generated using 0–50 μmol/l solutions of AMC (Sigma). Plasma DPP4 activity is expressed as the amount of cleaved AMC per minute per ml (nmol-min⁻¹·ml⁻¹).

**DPP4 enzyme assay in tissues.** Frozen tissues were homogenized in cold buffer (25 mmol/l HEPES, 140 mmol/l NaCl, 80 mmol/l MgCl₂, and 1% BSA; pH 7.8) containing 1% Triton X-100. Following homogenization, the samples were centrifuged at 10,000 g for 10 min at 4°C. The resultant supernatants were collected and centrifuged twice at 20,000 g for 10 min at 4°C. The final supernatants were immediately subjected to the DPP4 enzyme assay as described above. The DPP4 activity in each tissue is expressed as the amount of cleaved AMC per minute per gram of tissue weight (nmol-min⁻¹·g tissue⁻¹).

**Quantitative real-time PCR.** Total RNA was isolated using the RNasy Lipid Tissue Mini Kit (Qiagen) according to the manufacturer’s methods. cDNA was synthesized using 1 μg of total RNA and SuperScript III reverse transcriptase (Invitrogen, Carlsbad, CA). Real-Time PCR was performed using SYBR Premix Ex Taq (Takara, Tokyo, Japan) and the AB 7500 real-time PCR system (Applied Biosystems, Foster City, CA) with the following thermal cycling profile: initial denaturation at 95°C for 10 s followed by 40 cycles of amplification (denaturation at 95°C for 10 s, annealing at 60°C for 10 s, and extension at 72°C for 34 s), and the results were normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The primers used in the real-time PCR were as follows: rat DPP4 sense 5′-CTCCAGGACACCTCTG-3′; rat GAPDH sense 5′-CTGAGAATGGGAAGCT-GGTTCAT-3′; antisense 5′-TGTTGCAGCGTGGCCT-3′. The primer used in the real-time PCR was as follows: rat DPP4 sense 5′-CTCCAGGACACCTCTG-3′; rat GAPDH sense 5′-CTGAGAATGGGAAGCT-GGTTCAT-3′; antisense 5′-TGTTGCAGCGTGGCCT-3′.

**OGTT.** After the rats had been fasted for 18 h, glucose was orally administered (1 g/kg). Blood samples were obtained before and at 30, 60, 90, and 120 min after glucose loading. Blood glucose concentrations were measured immediately, and the data were quantified by calculating the area under the curve (AUC0–120 min) using the trapezoidal rule.

**Immunohistochemistry.** The pancreas was dissected from the surrounding tissue, fixed overnight in 10% (vol/vol) formaldehyde, and embedded in paraffin. Immunostaining was conducted according to the standard peroxidase reaction method. Briefly, the sections were incubated with 3% (vol/vol) H₂O₂ for 10 min to avoid nonspecific peroxidase reactions. Histologic sections were immunostained for insulin using monoclonal anti-insulin (1:1,000 dilution, Sigma) as the primary antibody and peroxidase-conjugated rabbit anti-mouse IgG (1:200 dilution, Sigma) as the secondary antibody. The sections were then incubated with 3,3′-diaminobenzidine tetrahydrochloride (DAB) solution for 15 min. After being immunostained, the sections were lightly counterstained with Mayer’s hematoxylin, and immunoreactive cells were observed under a light microscope.

**Pancreatic insulin content.** Pancreatic insulin was extracted according to the acid-ethanol method [0.18 mmol/l hydrochloric acid in 70% (vol/vol) ethanol], and insulin concentrations were determined (Ultra Sensitive Rat Insulin Kit; Morigina Institute of Biological Science).

**Data analysis.** All values are expressed as means ± SE. Student’s unpaired t-test was used for comparisons between the two groups. Differences were considered significant at P < 0.05.

**RESULTS**

**Body weight, blood biochemistry, and OGTT.** The body weight of the rats in the FS group was significantly greater than that of the FR group from 2 to 48 wk, but it subsequently decreased to the level of the FR group, as shown in Fig. 1A (FS: 557.6 ± 21.9 g, FR: 593.0 ± 11.7 g at 58 wk). The fasting blood glucose level of the FS group was increased after 6 wk and was significantly higher than that of the FR group at 6–35, 41, and 56 wk (Fig. 1B). In the FS group, the fasting plasma insulin level (Fig. 1C) and HOMA-IR (Fig. 1D) increased from 6 to 26 wk but subsequently decreased to significantly lower levels compared with the FR group at 52–56 wk. Next, to determine the differences in glucose tolerance between the two groups, an OGTT was performed at 56 wk. The FS group showed a significantly greater increase in blood glucose than the FR group at every point after glucose loading (Fig. 1E). The AUC0–120 min of blood glucose in the FS group was also significantly higher than that in the FR group (Fig. 1F).

**Quantitative and histological studies of insulin content in the pancreas at 58 wk.** Insulin content in the pancreas was measured to assess pancreatic islet atrophy at the end of the experiment. Insulin content was significantly lower in the FS group than in the FR group (Fig. 2A). The histological study also showed pancreatic insulin depletion and islet atrophy in the FS group compared with the FR group (Fig. 2B).

Table 1 shows the blood and urinary parameters of the two groups at 55 wk. The FS group showed significant increases in TG, T-CHO, and HDL-cholesterol compared with the FR group. The serum creatinine levels were not different between the two groups. On the other hand, the FS group showed significantly greater increases in urinary excretion, protein excretion, and glucose excretion over 24 h than the FR group.

**Tissue weight.** Table 2 shows the differences in tissue weight between the FS and FR groups at 58 wk. In a comparison of the FS group with the FR group, significant increases in kidney and liver size and a significant reduction in epididymal fat mass were observed.

**Plasma DPP4 activity.** Plasma DPP4 activity in the FS group was significantly increased from 8 to 38 wk, but it subsequently decreased to the level of the FR group (Fig. 3).
Next, we investigated the correlations between plasma DPP4 activity and metabolic parameters (body weight, fasting plasma insulin, and fasting blood glucose). The level of plasma DPP4 activity was found to be positively correlated with each parameter in the FS group. In particular, plasma DPP4 activity demonstrated stronger correlations with body weight and the fasting plasma insulin level than with the fasting blood glucose level (Fig. 4). Figures 5 and 6 show the correlations between these parameters during the early phase (0–26 wk) and the late phase (26–56 wk), respectively. In the early phase, strong positive correlations were found between the level of plasma DPP4 activity and each parameter (body weight, fasting plasma insulin, and fasting blood glucose), as shown in Fig. 5. In contrast, the level of plasma DPP4 activity showed significant positive correlations with body weight and the fasting plasma insulin level but not with the fasting blood glucose level during the late phase (26–56 wk) in the FS group (Fig. 6), whereas in the FR group the level of plasma DPP4 activity was found to be positively correlated with each parameter (Fig. 7).

**DISCUSSION**

OLETF rats were first developed in 1984 as spontaneously diabetic obese rats and have been maintained at Otsuka Pharmaceuticals ever since (8). OLETF rats develop hyperglycemia (after 18 wk of age) and undergo changes to their pancreatic islets, which are classified into three stages: I, the early stage (at less than 9 wk of age), which involves mild lymphocyte infiltration; II, the hyperplastic stage (at 10–40 wk of age), which involves hyperplastic changes and fibrosis in or

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**Table 1. Blood and urinary parameters in OLETF rats at 55 wk**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FS</th>
<th>FR</th>
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<tr>
<td>Blood biochemistry</td>
<td></td>
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<tr>
<td>Triglycerides, mg/dl</td>
<td>231.8 ± 28.4*</td>
<td>139.0 ± 17.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>251.8 ± 15.2‡</td>
<td>105.6 ± 7.3</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>65.1 ± 7.2‡</td>
<td>36.0 ± 3.7</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.88 ± 0.10</td>
<td>0.78 ± 0.16</td>
</tr>
<tr>
<td>Urinary parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary excretion, ml/24 h</td>
<td>113.6 ± 16.2‡</td>
<td>16.7 ± 1.7</td>
</tr>
<tr>
<td>Protein excretion, mg/24 h</td>
<td>2,036.2 ± 223.8‡</td>
<td>253.4 ± 53.2</td>
</tr>
<tr>
<td>Glucose excretion, mg/24 h</td>
<td>18,135.3 ± 4,025.5‡</td>
<td>20.3 ± 2.6</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. *P < 0.05, ‡P < 0.001; Student’s t-test.

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**Table 2. Tissue weight in OLETF rats at the end of the experiment**

<table>
<thead>
<tr>
<th>Tissue weight, g</th>
<th>FS</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>2.33 ± 0.12‡</td>
<td>1.45 ± 0.05</td>
</tr>
<tr>
<td>Liver</td>
<td>20.79 ± 0.81‡</td>
<td>15.23 ± 0.49</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.76 ± 0.07</td>
<td>0.72 ± 0.04</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.69 ± 0.15</td>
<td>3.49 ± 0.10</td>
</tr>
<tr>
<td>Epididymal fat</td>
<td>7.43 ± 1.09†</td>
<td>15.24 ± 1.21</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>1.21 ± 0.66</td>
<td>4.97 ± 1.73</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. †P < 0.01, ‡P < 0.001; Student’s t-test.
around the islets; and III, the final stage (at more than 40 wk of age), which involves atrophy of the islets. Therefore, OLETF rats are recognized as an animal model of late-stage type 2 diabetes (1, 8).

In the present study, food-satiated OLETF rats exhibited a spontaneously hyperphagic and obese phenotype in combination with insulin resistance, hyperglycemia, and hyperinsulinemia at ~30 wk and subsequent marked reductions in their body weight (body fat) and plasma and pancreatic insulin levels. The increases in their fasting blood glucose levels were limited despite profound insulin depletion occurring during the late stage, suggesting that late-stage type 2 diabetic OLETF rats display impaired insulin secretion but that their insulin sensitivity spontaneously recovers. The recovery of insulin sensitivity may be due to the significant loss of adipose tissue, in which cytokines such as TNF-α and resistin are recognized as risk factors for insulin resistance during the late stage of diabetes. However, OGTT and urinary parameters showed that the late-stage type 2 diabetic OLETF rats suffered from severe postprandial hyperglycemia and proteinuria, indicating that pancreatic islet atrophy and glomerular damage were induced by long-term hyperglycemia in the food-satiated OLETF rats. On the other hand, 30% food restriction inhibited the development of late-stage type 2 diabetes in the OLETF rats; however, mild increases in their blood glucose and insulin levels and body weight were observed.

Fig. 4. Correlations of plasma DPP4 activity with body weight and levels of fasting plasma insulin and blood glucose in the FS group (0–56 wk).

Fig. 5. Correlations of plasma DPP4 activity with body weight and levels of fasting plasma insulin and blood glucose during the early phase (0–26 wk) in the FS group.
Interestingly, their plasma DPP4 activity was also increased at ~30 wk and then declined to the control levels, suggesting that plasma DPP4 activity changes according to the severity of hyperglycemic and hyperinsulinemic obesity, pancreatic islet atrophy, and renal damage. Previously, we (11) reported that DPP4 expression in plasma and some tissues increased progressively with the development of type 1 diabetes and nephropathy induced by STZ in rats. Additionally, we reported that plasma DPP4 activity was significantly greater in impaired glucose tolerance rats fed a high-fat or high-sucrose diet than in normal rats (10). Moreover, an in vitro study determined that exposure to high levels of glucose enhanced the biosynthesis of DPP4 in human glomerular endothelial cells (18). Considering all of the above, we confirmed that the increased plasma DPP4 activity observed in such conditions was due to enhanced DPP4 biosynthesis in some tissues (especially in the kidneys) and/or its leakage into the systemic circulation due to high blood glucose levels. In the present study, however, plasma DPP4 activity demonstrated stronger positive correlations with body weight and plasma insulin than with the blood glucose level in the food-satiated OLETF rats. In addition, positive correlations were found between the level of plasma DPP4 activity and every metabolic parameter (body weight, blood glucose, and insulin) during the early stage of diabetes. In contrast, the level of plasma DPP4 activity showed significant positive correlations with body weight and the plasma insulin...
level but not with the blood glucose level during the late stage of diabetes. These findings suggest that plasma DPP4 activity increases in accordance with the progression of hyperglycemic and hyperinsulinemic obesity (during the early stage) but decreases in accordance with insulin depletion and weight loss (during the late stage). Further studies are necessary to interpret these findings, because the changes in DPP4 activity are likely to be affected by multiple factors.

In contrast, higher pancreatic DPP4 activity and lower pancreatic insulin levels were observed during the late stage of type 2 diabetes in the OLETF rats. The mechanisms underlying the increased pancreatic DPP4 activity during the late stage of diabetic OLETF rats were not determined, since DPP4 mRNA expression was not significantly changed. Several studies have reported that systemic DPP4 inhibition promoted insulin biosynthesis and the proliferation of pancreatic β-cells, suggesting that DPP4 inhibition followed by incretin elevation exerts protective effects on pancreatic β-cell function (16, 19). Although the role of pancreatic DPP4 activity in pancreatic function remains unclear, a relationship may exist between the activation of pancreatic DPP4 and the inhibition of pancreatic insulin expression during the late stage of type 2 diabetes.

Decreased DPP4 activity in adipose tissue may be meaningful with regard to the risk of developing obesity. Recent studies have suggested that substrates for DPP4, such as GIP and neuropeptide Y1-36, play important roles in increased nutrient uptake, triglyceride accumulation, or antilipolytic activity in adipocytes (12, 15). In addition, Kos K. et al. (12) reported that lower DPP4 and higher Y1 receptor expression were detected in adipose tissue taken from obese subjects compared with those seen in adipose tissue collected from lean subjects, suggesting that DPP4 inhibition leads to the further accumulation of body fat in type 2 diabetic patients (hyperinsulinemic patients) via the augmentation of neuropeptide Y1-36-induced antilipolytic properties. In our previous study (10), decreased

Table 3. DPP4 mRNA expressions in OLETF rats at the end of the experiment

<table>
<thead>
<tr>
<th>DPP4/GAPDH mRNA</th>
<th>FS</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1.81 ± 0.14</td>
<td>2.33 ± 0.27</td>
</tr>
<tr>
<td>Liver</td>
<td>1.39 ± 0.07</td>
<td>1.73 ± 0.12</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.62 ± 0.06</td>
<td>0.92 ± 0.10</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.46 ± 0.02</td>
<td>0.69 ± 0.11</td>
</tr>
<tr>
<td>Epididymal fat</td>
<td>0.54 ± 0.14</td>
<td>0.33 ± 0.02</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. DPP4, dipeptidyl peptidase-4.
DPP4 activity was found in the visceral adipose tissue of impaired glucose tolerance rats fed a high-fat or high-sucrose diet. On the other hand, no changes in the DPP4 activity of adipose tissue were detected at the end of this experiment, probably because the late-stage diabetic OLETF rats were not obese at that point. Further studies are required to determine whether fat accumulation changes DPP4 expression in adipose tissue using obese OLETF rats (up to ~30 wk).

In conclusion, plasma DPP4 activity changed in accordance with the progression of hyperinsulinemic obesity and pancreatic islet atrophy. Therefore, plasma DPP4 activity may play an important role in insulin homeostasis.

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GRANTS

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DISCLOSURES

No conflicts of interest are reported by the authors.

REFERENCES