Characterization of STZ-Induced Type 2 Diabetes in Zucker Fatty Rats

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Abstract: The Zucker fatty (ZF) rat is a disease model of obesity and metabolic syndrome, such as hyperlipidemia and insulin resistance, resulting from hyperphagia owing to the loss of function of the leptin receptor, but it rarely develops hyperglycemia. We examined the effects of different doses of streptozotocin (STZ). A low dosage of STZ (30 mg/kg body weight, i.p.) elevated blood glucose levels in ZF rats up to 300 mg/dl within a week, and to nearly 500 mg/dl by 5 weeks after injection of STZ. Besides hyperglycemia, STZ-treated ZF (STZ-ZF) rats retained metabolic syndrome features such as hyperlipidemia and hyperinsulinemia. The stimulated insulin secretion in response to orally-loaded glucose disappeared completely in STZ-ZF rats. Although there were no significant differences in the morphology of pancreatic islets between vehicle-treated ZF (Cont-ZF) and STZ-ZF rats, the insulin content was markedly decreased in STZ-ZF rats. The hepatic gene expression for gluconeogenic enzymes was upregulated in STZ-ZF rats compared with Cont-ZF rats. Metformin lowered the blood glucose levels of STZ-ZF rats in a dose-dependent manner. These results suggest that STZ-ZF rats are useful for studies of T2DM and for the evaluation of the efficacy of anti-diabetic drugs.

Key words: streptozotocin, type 2 diabetes mellitus (T2DM), Zucker fatty rat

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disorder that is becoming a major health problem due to a global increase in its incidence. Moreover, it is a serious risk factor for fatal cardiovascular disease [26]. In the course of development of T2DM, augmentation of insulin secretion compensating for insulin resistance causes exhaustion of pancreatic β cells and, consequently, hyperglycemia [14]. T2DM patients share common pathophysiological features, including a decline in peripheral glucose utilization and extra hepatic glucose production, both of which are caused by insufficient insulin secretion [3, 6]. Various animal models have...
contributed to our understanding of the pathology of T2DM and/or to the discovery of new anti-diabetic drugs. T2DM is one component of metabolic syndrome that comprises obesity, abdominal fat deposition, hyperlipidemia and hypertension. Diabetic rat models with characteristics of metabolic syndrome are rarely available. The Zucker fatty (ZF) rat possesses some features of metabolic syndrome, such as hyperinsulinemia and insulin resistance. It has a phenotype associated with hyperphagia owing to the loss of function of the leptin receptor induced by a point mutation in the gene (fa) encoding this receptor; however, ZF rats do not exhibit hyperglycemia [9, 15, 19]. It is thought that the pancreatic β cells of ZF rats have a high capacity for insulin secretion which keeps blood glucose levels normal. The Zucker diabetic fatty (ZDF) rat, derived from ZF rats, is a well-known diabetic rat whose plasma insulin level is lower than that of ZF rats [20, 24]. Mild impairment of insulin secretion in ZF rats could lead to a diabetic condition preserving some features of the metabolic syndrome. If this is possible, such a rat model would contribute to our understanding of the transition state from a pre-diabetic to a diabetic condition, in the presence of metabolic syndrome. Streptozotocin (STZ) is known to be a diabetogenic agent, which acts by causing selective destruction of pancreatic β cells; it is used to induce both type 1 (T1DM) and type 2 diabetes [11, 23]. High doses of STZ (40 to 60 mg/kg body weight) can induce T1DM; on the other hand, low doses of STZ (35 mg/kg body weight) can induce T2DM in rats fed a high-fat diet [5, 22]. Boivin and Deshaies reported that STZ (45 mg/kg body weight) caused hyperglycemia in ZF rats; however, the diabetic phenotype of the STZ-treated ZF (STZ-ZF) rats was not fully characterized [1]. In this study, we induced T2DM by injecting a low-dose of STZ into ZF rats and characterized these STZ-ZF rats pathophysiologically. In addition, the efficacy of an anti-diabetic drug, metformin, was investigated in STZ-ZF rats.

### Measurement of blood glucose, hemoglobin A1c and plasma concentrations of biochemical markers

Blood samples were obtained from the tail veins. Blood glucose and hemoglobin A1c (HbA1c) levels were measured using a Glucocard Diameter (Arkray, Kyoto, Japan) and a DCA2000 Analyzer (Siemens, Munich, Germany), respectively. The plasma concentrations of triglyceride, total cholesterol and free fatty acids were measured using commercially available enzyme-linked colorimetric diagnostic kits (Wako, Osaka, Japan). Insulin concentrations were determined using an enzyme-linked immnosorbent assay kit (Seikagaku Corp., Tokyo, Japan).

### Extraction and determination of liver triglyceride content

Extraction of liver lipids was performed using the method of Folch et al. [4]. Briefly, a liver piece was homogenized in 3 volumes of saline. The homogenate was added to Folch reagent (2:1 chloroform-methanol) and rotated overnight for lipid extraction. The extracted solvent was evaporated and resuspended in 10 mM HEPES pH 7.4 containing 5% Triton-X 100. Triglyceride contents were determined as described above.

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**Materials and Methods**

**Animal experiments**

Male Zucker fatty rats (Japan SLC Inc., Hamamatsu, Japan), aged five weeks, were housed 2 per cage on a 12-h light/dark cycle at an ambient temperature of 20 to 26°C. The rats had free access to water and a low-protein chow diet consisting of 60% carbohydrate, 14% protein and 26% fat, as percentages of total calories (Labo MRDBT; Norsan Corp., Yokohama, Japan). This diet has been commercialized and facilitates the onset of diabetes. The care and handling of these animals was in accordance with the Guidelines for Animal Care and Use of Otsuka Pharmaceutical Co., Ltd., Revised on April 1, 2004. After 1 week of taming, the rats were subjected to overnight fasting and intraperitoneal injection with STZ (30 mg/kg body weight) dissolved in sodium citrate buffer (pH 4.5) or vehicle (citrate buffer). Three hours after the STZ injection, the rats were allowed to feed freely again. Body weight and biochemical indices were monitored once a week for 6 weeks. After 6 weeks of monitoring, each treatment group was divided into 2 groups (one group fasting overnight, the other feeding ad libitum), sacrificed the following day under ether anesthesia, and necropsied.
Oral glucose tolerance test
To assess oral glucose tolerance, animals were fasted overnight (16 h) and a 50% glucose solution was orally administered (2 g/kg body weight). Tail blood samples were taken before (time 0) and 30, 60, 90, and 120 min after administration of glucose, and blood glucose and plasma insulin concentrations were determined as described above.

Histopathology and immunohistochemistry
Pancreata were fixed in phosphate-buffered 10% formalin and processed routinely for paraffin sectioning. Specimens were stained with hematoxylin and eosin (HE). Immunohistochemistry procedures were performed using the Discovery HX system (Ventana Medical Systems, Inc., AZ, USA). Slides were incubated with an anti-insulin antibody (1:100, Santa Cruz, California, USA) at 37°C for 30 min. An anti-rabbit biotinylated IgG antibody (1:250, Vector Laboratories, Inc., California, USA) was used as the secondary antibody (for 20 min at 37°C), which was detected with horseradish peroxidase-conjugated streptavidin. Hydrogen peroxidase and 3,3’ diaminobenzidine (DAB) were added to visualize the bound antibody. Cell nuclei were counterstained with hematoxylin.

RNA preparation and real-time quantitative PCR
Total RNA was isolated from the liver using TRIzol reagent (Invitrogen Corp., California, USA). cDNA was synthesized from total RNA using an Omniscript RT kit (Qiagen, Maryland, USA) and oligo(dT)20 primer. Real-time quantitative PCR analysis was performed using an ABI Prism 7700 Sequence Detection System (Applied Biosystems, California, USA). The mRNA expression level of each gene was corrected using the expression of β2-microglobulin as an internal control. The results are represented as expression ratios relative to the expression levels in ZF rats in the non-fasting state. The sequences of gene-specific primers and FAM (5’)- and TAMRA (3’)-labeled hybridization probes for real-time quantitative PCR are listed in Table 1.

Table 1. Sequences for gene specific primers and hybridization probes used in the real-time quantitative PCR analyses

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer (5’–3’)</th>
<th>Reverse primer (5’–3’)</th>
<th>Hybridization probe (5’–3’)</th>
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<tr>
<td>Glucose-6-phosphatase (G6Pase: Catalytic subunit)</td>
<td>taaaacagttcccccggtcacc</td>
<td>cccgaatccatacgtgaccc</td>
<td>tgggccacagcagggtgataactacgttatgcga</td>
</tr>
<tr>
<td>Fructose-1,6-bisphosphatase (FBPase)</td>
<td>actttgaccctgccatcaat</td>
<td>tccagagctcatacgtgtccttg</td>
<td>acaatgtacgacagctgcatctctagag</td>
</tr>
<tr>
<td>Phosphoenolpyruvate carboxykinase (PEPCK)</td>
<td>atcgagaggccatatattttgg</td>
<td>tggacctctccctatgtgctg</td>
<td>acaatgtacgacagctgcatctctagag</td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptor-γ coactivator 1 (PGC-1α)</td>
<td>aatggtatacttaacggtcctgg</td>
<td>ttcagagctcatacgtgtccttg</td>
<td>acaatgtacgacagctgcatctctagag</td>
</tr>
<tr>
<td>Acetyl-coA carboxylase 1 (ACC1)</td>
<td>atcgagtagctgtcagttggg</td>
<td>agacgctctcagtgcagctcctg</td>
<td>tatcttagtggaacatcctcccaaccctt</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>accgagagcccgtatgtgcag</td>
<td>tggagcagcagctgcatctttgg</td>
<td>agtaaaaacagtcctctggagcccttaaaa</td>
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Efficacy of an antidiabetic agent
Eleven-week-old rats (5 weeks after STZ injection) were divided into 3 treatment groups (n=6). Vehicle (saline) or metformin (100 or 300 mg/kg body weight) was orally administered and the blood glucose concentration was monitored. Rats were kept fasting for 4 h during the monitoring.

Statistical analysis
Results are presented as means ± SD. The unpaired Student’s t-test was used to compare data between STZ-ZF and Cont-ZF rats. A first evaluation of metformin efficacy was performed using repeated measures ANOVA. If the result was significant, the blood glucose level at each time point was analyzed by Dunnett’s test. A value of P<0.05 was considered to be statistically significant.

Results

Determination of the proper dose of STZ
We attempted to determine the proper dose of STZ to
efficiently induce diabetes in ZF rats. ZF rats (6 weeks of age) were treated with STZ at doses of 0, 20, 30, or 40 mg/kg body weight. However, all rats treated with STZ at a dose level of 40 mg/kg died within one week after the treatment. Blood glucose levels of the surviving rats in a non-fasting state were measured 5 weeks after STZ treatment (Fig. 1). Twenty mg/kg of STZ failed to elevate blood glucose (except one of six rats). All rats receiving 30 mg/kg STZ were diabetic with high blood glucose levels (440.3 mg/dl in average). Therefore, we adopted a dose of 30 mg/kg STZ to induce diabetes in ZF rats.

**Body weight**

Vehicle-treated ZF (Cont-ZF) rats gained weight and reached approximately 500 g at 12 weeks of age. The body weights of STZ-ZF rats also increased to approximately 380 g, but the body weight gain in STZ-ZF rats was lower than that in Cont-ZF rats (Fig. 2A).

**Blood glucose level and HbA1c**

The blood glucose levels in Cont-ZF rats were almost constant throughout the experimental period. In STZ-ZF rats, blood glucose levels were elevated from 1 week after STZ treatment and reached approximately 500 mg/dl in the non-fasting state (Fig. 2B); STZ-ZF rats also showed hyperglycemia even in the fasting state (Table 2). Although the HbA1c levels of Cont-ZF rats were not elevated during the experimental period, those of STZ-ZF rats were gradually raised after the onset of hyperglycemia (Fig. 2C).

**Plasma insulin**

The insulin levels in Cont-ZF rats elevated with age and were more than 40 ng/ml. In contrast, the insulin levels in STZ-ZF rats were lower than those in Cont-ZF rats, but were largely unaltered, maintaining approximately 10 ng/ml for at least 6 weeks (Fig. 2D). This suggests that STZ-ZF rats were hyperinsulinemic rather than hypoinsulinemic. Such a high level of plasma insulin, whether the animal fed or not (Table 2), indicates that STZ-ZF rats retain both insulin resistance and some degree of insulin secretory potency.

**Lipids**

The plasma triglyceride levels in STZ-ZF rats were always significantly higher than those in Cont-ZF rats, from one week after STZ treatment (Fig. 2E). Plasma cholesterol was also elevated markedly in STZ-ZF rats. Although the plasma FFA levels in Cont-ZF rats increased remarkably in the fasting state, this response to fasting was diminished in STZ-ZF rats (Table 2). Moreover, although starvation normally induces elevation of plasma FFA, it is considered that STZ-ZF rats are always highly starved, despite their hyperphagia. The liver triglyceride content of STZ-ZF rats was higher than that of Cont-ZF rats in the non-fasting state, but these values were reversed in the fasting state.

**Glucose tolerance test**

The oral glucose tolerance test (OGTT) was performed at 6 weeks after STZ treatment (at 12 weeks of age). The STZ-ZF rats exhibited not only a significant elevation of fasting glucose, but also further deterioration of glucose intolerance compared with Cont-STZ rats (Fig. 3A). Unexpectedly, additional insulin secretion in response to glucose loading vanished in STZ-ZF rats (Fig. 3B). It is possible that the fasting hyperglycemia arises from lower basal insulin levels compared with the Cont-ZF rats, and that the deterioration of glucose intolerance arises from the disappearance of this insulin response.

**Pancreatic islets**

The pancreatic islets of Cont-ZF rat were enlarged and irregularly shaped with mild fibrosis, because ZF rats
Fig. 2. Body weight and biochemical indices. A: Body weight. B: Blood glucose (non-fasting). C: HbA1c. D: Plasma insulin. E: Plasma triglyceride (non-fasting). Open circles and filled circles represent Cont-ZF and STZ-ZF rats, respectively (n=8–12). Data represent means ± SD. *P<0.05, **P<0.01 vs Cont-ZF rats (unpaired Student’s t-test).

Table 2. Characteristics of STZ-ZF rats

<table>
<thead>
<tr>
<th></th>
<th>Non-fasting</th>
<th>STZ-ZF</th>
<th>Fasting</th>
<th>Cont-ZF</th>
<th>STZ-ZF</th>
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<tr>
<td>Body weight (g)</td>
<td>502.9 ± 19.4</td>
<td>381.7 ± 53.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>459.3 ± 8.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>355.2 ± 45.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>104.3 ± 18.6</td>
<td>465.8 ± 60.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69 ± 15.8&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;</td>
<td>313.2 ± 26.5&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Plasma insulin (ng/ml)</td>
<td>33.2 ± 14.4</td>
<td>15.3 ± 11.8</td>
<td>22.3 ± 13.4</td>
<td>11.0 ± 8.7</td>
<td></td>
</tr>
<tr>
<td>Plasma triglycerides (mg/dl)</td>
<td>243.0 ± 61.6</td>
<td>520.3 ± 237.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>230.0 ± 25.3</td>
<td>367.5 ± 234.6</td>
<td></td>
</tr>
<tr>
<td>Plasma cholesterol (mg/dl)</td>
<td>126.0 ± 7.8</td>
<td>158.8 ± 10.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>121.8 ± 11.9</td>
<td>160.7 ± 10.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Plasma FFA (mEq/l)</td>
<td>0.50 ± 0.13</td>
<td>0.72 ± 0.23</td>
<td>1.23 ± 0.20&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.92 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>Liver triglycerides (mg/g tissue)</td>
<td>11.1 ± 1.1</td>
<td>17.5 ± 4.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.1 ± 3.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14.1 ± 6.2</td>
<td></td>
</tr>
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</table>

Each value represents means ± SD from 4–6 rats of 12 weeks old. *P<0.05, **P<0.01 vs Cont-STZ rats. *P<0.01 vs non-fasting state.
per se show severe hyperinsulinemia (Fig. 4A). There were no significant morphological differences between Cont-ZF and STZ-ZF rats, except for the occasional loss and diffuse degeneration of islet cells in the diabetic pancreas. Immunohistochemical staining revealed that both the number of insulin-positive cells (that is, β cells) and the intensity of β cells (specifically, the staining of insulin granules) were markedly decreased in STZ-ZF rats (Fig. 4B).

Expression of gluconeogenesis- and lipogenesis-related genes

We compared the mRNA expression levels of gluco-
neogenesis- and lipogenesis-related genes in the livers of Cont-ZF and STZ-ZF rats. The mRNA expression levels of the gluconeogenic enzymes glucose-6-phosphatase (G6Pase), fructose-1,6-bisphosphatase (FBPase) and phosphoenolpyruvate carboxykinase (PEPCK) were markedly elevated in the livers of STZ-ZF rats, especially those in the non-fasting state. Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), a master regulator gene of G6Pase and PEPCK, was also expressed at a slightly higher level in the STZ-ZF rats (Figs. 5A–D). The expression levels of acetyl-CoA carboxylase, the rate-limiting enzyme in fatty acid synthesis, were not different between Cont-ZF and STZ-ZF rats (Fig. 5E).

Efficacy of an anti-diabetic drug

We examined the glucose lowering effect of metformin in STZ-ZF rats. The serial blood glucose concentration curve of the high-dosage (300 mg/kg body weight) metformin-treated group was significantly different from that of the saline-treated group (repeated measures ANOVA; \( P < 0.001 \)). Blood glucose concentrations were lowered in a dose-dependent manner, and the effect of metformin was significant at a high dose from 2 to 4 h after administration (Dunnett’s test, Fig. 6).

Discussion

A few rat models are available for the pathophysiological study of T2DM and the evaluation of new anti-diabetic molecular entities. Here, we have described the characteristics and utility of a T2DM rat induced by STZ-ZF rats, which exhibit severe hyperinsulinemia to compensate for insulin resistance and glucose intolerance, are able to maintain a normal blood glucose level in the ordinary nutrient state [15]. We hypothesized that the partial impairment of pancreatic β cells could lead ZF rats to become hyperglycemic as well as retaining their hyperinsulinemic features (such as insulin resistance and obesity). Indeed, a low dosage of STZ made them diabetic. STZ-ZF rats exhibited hyperglycemia and hyperlipidemia coupled with hyperinsulinemia. Kumano et al. reported that the body weights and plasma insulin levels of male Zucker lean rats (11-week-old, Japan SLC Inc.) were 281 ± 2.8 g and 1.58 ± 0.25 ng/ml (means ± SEM), respectively [12]. Therefore, we considered that STZ-ZF rats are diabetic rats exhibiting mild obesity and hyperinsulinemia in comparison with Zucker lean rats. In addition, STZ-ZF rats showed severe hyperglycemia.
Fig. 4. Morphology and immunohistochemistry of pancreatic islets. A: Hematoxylin and eosin staining. Degenerated cells were observed diffusely and gaps (arrows) were noticeable at the boundaries between cells in STZ-ZF rats. B: Insulin immunostaining. The number of insulin-positive cells and the staining-intensity of cells were markedly decreased in STZ-ZF rats. Scale bars are indicated in the photographs.
and hyperinsulinemia even in the fasting state. These features are partly considered to be proof of insulin resistance.

Reed et al. and Srinivasan et al. reported that fat-feeding and STZ induced non-obese T2DM in Sprague-Dawley rats [21, 22]. Their results and ours indicate that STZ can induce both obese and non-obese T2DM by using various recipient rats and feeding conditions. The

**Fig. 5.** Gluconeogenic and lipogenic gene expression in the liver. A: G6Pase. B: PEPCK. C: FBPase. D: PGC-1α. E: ACC1. White and black bars indicate Cont-ZF and STZ-ZF rats, respectively (n=4–6). Data represent means ± SD. *P<0.05, **P<0.01 vs Cont-ZF rats (unpaired Student’s t-test).
Spontaneously Diabetic Torii (SDT) rat is also known to be a non-obese T2DM rat that displays impaired insulin secretion [17]. Introduction of the fa mutation caused the SDT rat to develop obesity and hyperinsulinemia [16]. Evidently, a deficiency of leptin receptor, which causes abnormal hyperphagia, can induce some components of metabolic syndrome, namely obesity, hyperlipidemia, hyperinsulinemia and insulin resistance. This is a major reason why we adopted ZF rats as recipients of STZ. A notable characteristic of STZ-ZF rats is that they retain a high level of basal insulin; nevertheless, oral-loaded glucose does not induce additional insulin secretion. The Zucker Diabetic Fatty (ZDF) rat, which is derived from the ZF rat, spontaneously suffers from T2DM [2]. ZDF rats have some characteristics that are similar to those of STZ-ZF rats, especially the high level of basal insulin and the unresponsiveness of insulin to glucose. For comparison, we originally obtained the blood glucose concentrations of non-fasting and fasting male 14-week-old ZDF rats (ZDF/CrlCrlj-Lepr<sup>fa</sup>; Charles River Japan, Yokohama, Japan), which were 400.4 ± 103.1 mg/dl and 150.3 ± 41.1 mg/dl (n=18, mean ± SD), respectively. One of the major differences between STZ-ZF rats and ZDF rats is the fasting blood glucose level; indeed, STZ-ZF rats showed severe hyperglycemia (313.2 ± 26.5 mg/dl). STZ-ZF rats might be suitable for studying T2DM involving severe fasting hyperglycemia. STZ-ZF rats, which can be made by a single injection of STZ, have advantages over ZDF rats due to their availability and lower cost. Pathohistological observations showed that the pancreatic islets of STZ-ZF rats were comparable to those of Cont-ZF rats. However, the immunohistochemical detection of insulin revealed that both β cells and insulin granules were reduced in the pancreatic islets of STZ-ZF rats. The impaired β cells of STZ-ZF rats might exhaust themselves by keeping basal insulin, with the result that β cells could no longer secrete additional insulin in response to glucose. ZF rats can maintain normoglycemia owing to their high capacity for insulin secretion which surpasses their insulin resistance. This partial defect of β cell function, induced by STZ, could evoke imbalance of glucose homeostasis in STZ-ZF rats leading to hyperglycemia.

The plasma triglyceride levels of STZ-ZF rats were higher than those of Cont-ZF rats from the onset of T2DM. It has been reported that STZ treatment activates the enzymatic activity of intestinal acyl-coenzyme A:cholesterol acyltransferase / sterol O-acyltransferase (ACAT/SOAT), accompanied by upregulation of ACAT2 mRNA [7, 13]. This ACAT activation induced hyperlipidemia in STZ-treated rats. Excess hyperlipidemia in STZ-ZF rats might also be due to ACAT activation.

We examined the mRNA expression levels of gluconeogenesis-related genes, because STZ-ZF rats exhibited severe hyperglycemia in the fasting state. The mRNA levels of genes encoding gluconeogenic enzymes were remarkably elevated in STZ-ZF rats. Unexpectedly, this elevation was significant in the non-fasting state. It is possible that inadequate insulin secretion in STZ-ZF rats in response to feeding prevents downregulation of the expression of gluconeogenic enzymes in the non-fasting state.

Metformin, an anti-diabetic drug, reduced the blood glucose concentrations in STZ-ZF rats in a dose-dependent manner. Although metformin is widely regarded...
as a standard first-line agent in the US/EU, its mechanism of action is not yet fully elucidated. One candidate mechanism is the activation of AMP-activated protein kinase (AMPK) [25]. It has been recognized that metformin has multiple activities, including suppression of hepatic glucose production and improvement of peripheral insulin sensitivity, in T2DM patients [8, 10, 18]. These results suggest that STZ-ZF rats are useful not only for studies of diabetes, but also for the screening of pharmacologically hypoglycemic agents.

Acknowledgment(s)

We wish to thank Dr. Mari Kondo for pathological advice.

References


