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Non-Obese Type 2 Diabetic Rat Models-GK Rat and SDT Rat

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Abstract

The number of diabetic patients has recently been increasing all over the world together with lifestyle changes including sedentary life and high-calorie diet intake, and as a result the increase in these suffering from diabetes mellitus has become a global issue. Diabetic animal models play a key role in bettering our understanding of the pathophysiology of diabetes and in developing new therapies for the disease. Diabetes is classified into two types, type 1 and type 2, and type 2 diabetes is chiefly caused by a depletion of insulin secretion in the pancreas and insulin resistance in peripheral tissues. The Goto-Kakizaki (GK) rat and the Spontaneously Diabetic Torii (SDT) rat are genetic non-obese type 2 diabetic models, and the both rats are considered to be suitable models for investigating the etiology of the depletion of insulin secretion and impaired glucose tolerance. In this review, we overviewed the outline of pathophysiological features in GK rats and SDT rats, including biological parameters and pharmacological responses.

Keywords

Diabetic Model, GK Rat, SDT Rat, Type 2 Diabetes

1. Introduction

Metabolic diseases, including diabetes, have become health issues worldwide, and the population of patients is rapidly increasing [1] [2] [3]. The growing

population of diabetic patients has resulted in an increase in the number of patients who have micro-vascular complications, such as nephropathy, retinopathy, and neuropathy [4] [5] [6]. In addition to deterioration in the quality of life of such patients, the growing number of patients contributes to an increase in medical costs [7]. It is very important to prevent the development of diabetes; however, the etiology is complex, involving multiple mechanisms affecting multiple organs.

Diabetes is classified into two types, type 1 and type 2 diabetes, and most patients are suffering with type 2 diabetes. Type 2 diabetes is caused by a depletion of insulin secretion in the pancreas and a reduction of insulin sensitivity in peripheral tissues, such as the liver, muscles, and fat [8]. Animal models of type 2 diabetes have been established to assist better understanding of the pathophysiology of diabetes and its complications. Most of these models have abnormalities of single or multiple genes related to insulin deficiency, glucose intolerance, and/or insulin resistance leading to high blood glucose levels [9]. The development of diabetes and the progression of its complications are affected by various factors, including obesity, insulin resistance, hyperglycemia, and dyslipidemia. It is considered that in the future, diabetic animal models will play pivotal roles in development of new medical treatments.

The Goto-Kakizaki (GK) rat and the Spontaneously Diabetic Torii (SDT) rat are genetic non-obese type 2 diabetic models, and the rats are considered to be suitable models for investigating the etiology of the depletion of insulin secretion and impaired glucose tolerance. Non-obese type 2 diabetic models are classified into a non-genetic model and a genetic model. A neonatal rat injected with streptozotocin (nSTZ rat) is used as a non-genetic model. nSTZ rats show a chronic hyperglycemia with blood glucose concentrations ranging between 300 - 400 mg/dl, and a reduction of body weight occurs [10]. Moreover, the insulin secretion in response to glucose is markedly impaired [11] [12]. nSTZ rat model bears a resemblance to non-obese type 2 diabetes. In this review, we focus on a genetic model and introduce the pathophysiological features in GK rats and SDT rats.

2. GK Rat

2.1. Background—Breeding and Gene Analysis

GK rats were produced by a working hypothesis that posited that the repeating of the selective breeding of Wistar rats, a normal rat, with a slight glucose intolerance would lead to the production of a new spontaneous diabetic rat [13]. Firstly, 211 Wistar rats were prepared, and 18 rats were selected for breeding by an oral glucose tolerance test (OGTT). Furthermore, through the breeding, 162 offsprings (F_1 rats) were obtained. By repetition of the selective breeding, 204 F_2, 174 F_3 and 215 F_4 rats were obtained. As a result, the glucose tolerance curve became more diabetic with the increasing number of generations, and the positive rate in the urine sugar test during OGTT increased. In F_3 generations, the fasting

blood glucose levels were significantly increased (Male rats: 83 - 144 mg/dl, Female rats: 77 - 126 mg/dl). In the first experiment, sib-breeding has been avoided; however, in the subsequent experiment, brother-sister breeding was performed to intensify the nature of hyperglycemia in GK rats.

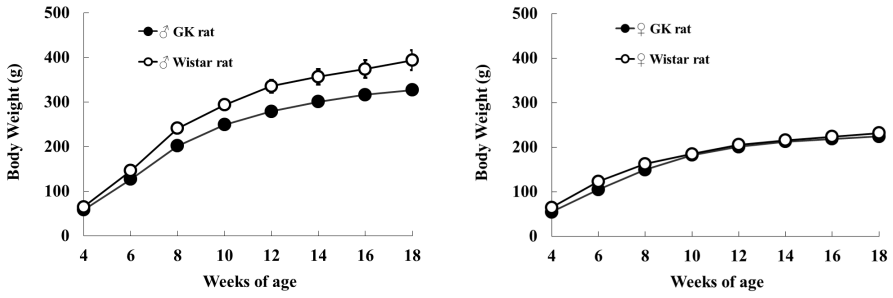
The GK rat is a polygenic strain and spontaneously develops diabetes. A comprehensive study of the genetic basis of diabetes in GK rats has been performed. The genetic dissection of non-insulin dependent diabetes mellitus (NIDDM) has allowed us to map three independent loci involved in the disease. Also, a major factor affecting body weight on chromosome 7 and map a further 10 regions that are suggestive for linkage are identified [14]. Furthermore, a combination of physiological and genetic studies was performed to identify quantitative trait loci (QTLs) responsible for the control of insulin secretion and glucose homeostasis in a F_2 cohort bred from GK rats. The genetic dissection of NIDDM allowed us to map up to six independently segregating loci predisposing to hyperglycemia, impaired glucose tolerance or impaired insulin secretion, and a seventh locus implicated in body weight [15].

2.2. Biological Profiles—Body Weight and Blood Chemical Parameters

Biological parameters, including body weight and blood biochemical levels, were determined in our institutes. Ten male and 10 female GK rats were prepared. Thirty male and 30 female Wistar rats were prepared as control rats. The body weights in GK rats and Wistar rats were measured every 2 weeks, from 4 to 18 weeks of age (**Figure 1**). The non-fasting glucose levels in GK rats were measured every 2 weeks, from 4 to 18 weeks of age, and the non-fasting glucose levels in Wistar rats, a normal control rat, were measured at 4, 10, and 18 weeks of age (**Figure 2**). The 2 g/kg OGTT (16 h fasting) was performed at 10 weeks of age in GK rats and Wistar rats (**Figure 3** and **Figure 4**). The rats were fed CE-2, a standard diet (CLEA Japan, Tokyo, Japan).

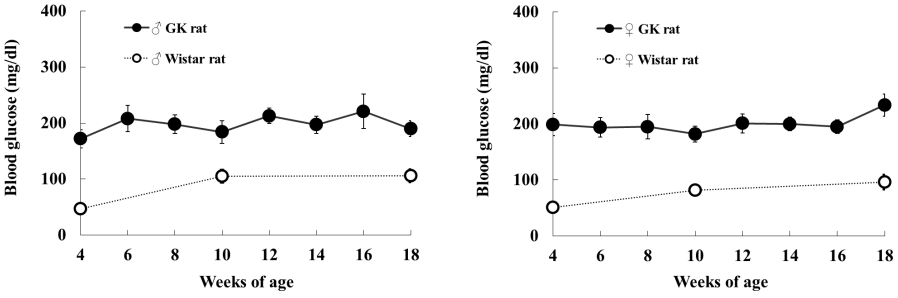
Changes in the body weight are shown in **Figure 1**. Body weights in male GK rats showed lower levels as compared with those in male Wistar rats during the observational period (body weights at 6 weeks of age, GK rats: 127.3 ± 4.0 g vs. Wistar rats: 146.2 ± 5.1 g; body weights at 18 weeks of age, GK rats: 327.4 ± 10.6 g vs. Wistar rats: 393.9 ± 22.5 g) (**Figure 1(A)**). On the other hand, body weights in female GK rats were comparable to those in female Wistar rats during the observational period (**Figure 1(B)**). It was suggested that the male GK rat was a non-obese diabetic model.

Changes in the non-fasting glucose levels were shown in **Figure 2**. The male GK rats showed an increase of the glucose levels at 4 weeks of age (GK rats: 172.0 ± 16.2 mg/dl vs. Wistar rats: 46.6 ± 6.8 mg/dl), and the hyperglycemia was sustained during the observational period (glucose levels at 18 weeks of age, GK rats: 190.0 ± 14.2 mg/dl vs. Wistar rats: 105.9 ± 11.4 mg/dl) (**Figure 2(A)**). Also, in female GK rats, the blood glucose level at 4 weeks of age increased as compared with that in female Wistar rats (GK rats: 199.0 ± 19.8 mg/dl vs. Wistar



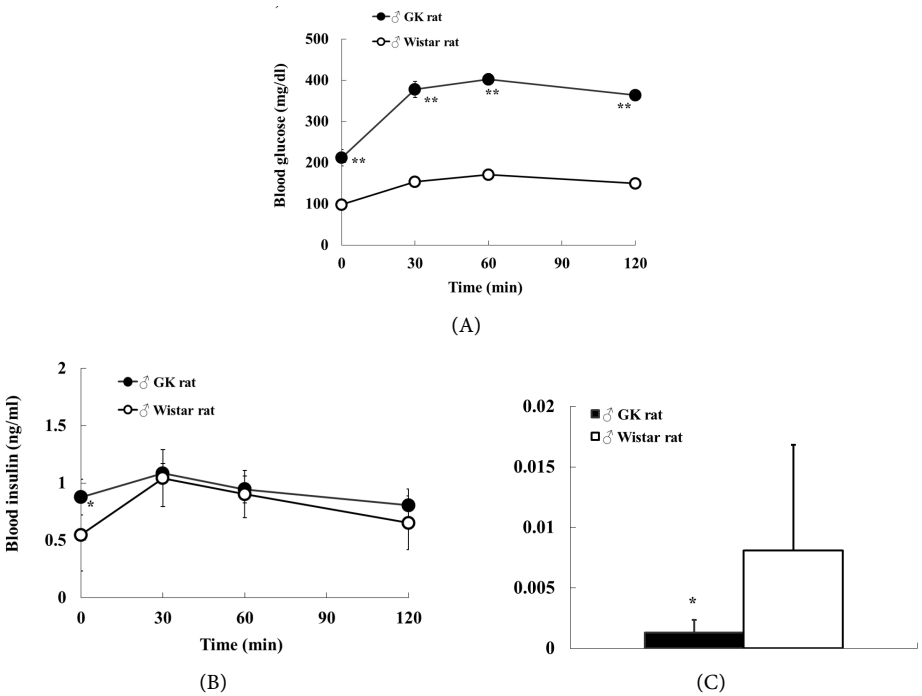
(A) (B)

Figure 1. Changes in body weights in GK rats and Wistar rats from 4 to 18 weeks of age. (A) Male GK rats (n = 10) and Wistar rats (n = 30); (B) Female GK rats (n = 10) and Wistar rats (n = 30).



(A) (B)

Figure 2. Changes in blood glucose levels in GK rats and Wistar rats from 4 to 18 weeks of age. (A) Male GK rats (n = 10) and Wistar rats (n = 30); (B) Female GK rats (n = 10) and Wistar rats (n = 30).



(A) (B) (C)

Figure 3. Changes in blood glucose (A) and insulin (B) levels in male glucose-loaded GK rats and Wistar rats at 10 weeks of age; (C) Insulinogenic index in glucose-loaded GK rats and Wistar rats. Insulinogenic index = ΔInsulin (increment from 0 - 30 min)/ΔGlucose (increment from 0 - 30 min). Data represent mean ± standard deviation (n = 10). *P < 0.05, **P < 0.01; significantly different from the Wistar rat.

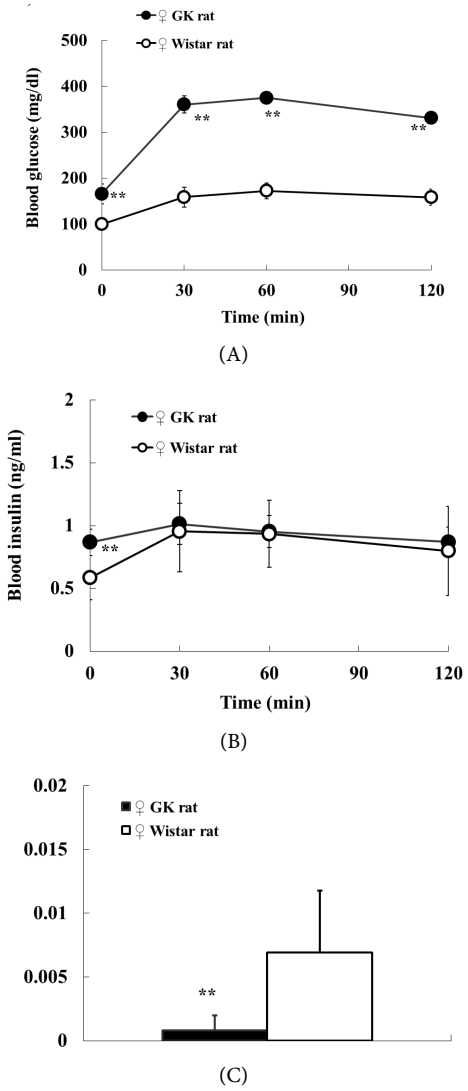


Figure 4. Changes in blood glucose (A) and insulin (B) levels in female glucose-loaded GK rats and Wistar rats at 10 weeks of age; (C) Insulinogenic index in glucose-loaded GK rats and Wistar rats. Data represent mean ± standard deviation (n = 10). *P < 0.05, **P < 0.01; significantly different from the Wistar rat.

rats: 51.4 ± 7.8 mg/dl), and the hyperglycemia was sustained until 18 weeks of age (GK rats: 234.0 ± 19.8 mg/dl vs. Wistar rats: 96.5 ± 13.0 mg/dl) (**Figure 2(B)**).

Changes in the blood glucose and insulin levels in OGTT were shown in **Figure 3** and **Figure 4**. In OGTT of GK rats, we investigated the GSIS as well as the glucose intolerance. Also, the insulin sensitivity was examined by measuring the fasted glucose and insulin levels. The blood glucose levels in male GK rats significantly increased at 30, 60, and 120 min. after glucose-loading, as compared with those in male Wistar rats (**Figure 3(A)**). Moreover, the fasting glucose level (0 min.) significantly increased in male GK rats (GK rats: 212.1 ± 19.9 mg/dl vs. Wistar rats: 98.3 ± 9.3 mg/dl). The blood insulin levels after glucose-loading in male GK rats were comparable to those in male Wistar rats; however, the fasting

insulin level (0 min.) significantly increased in the GK rats (GK rats: 0.877 ± 0.155 ng/ml vs. Wistar rats: 0.547 ± 0.312 ng/ml) (**Figure 3(B)**). Moreover, the insulinogenic index in GK rats was significantly reduced as compared with that in Wistar rats (**Figure 3(C)**). The insulinogenic index (ΔInsulin/ΔGlucose) was calculated using incremental plasma insulin and glucose levels for 0 to 30 min after glucose-loading. Also, in female GK rats, the blood glucose levels after glucose-loading significantly increased, and the fasting glucose level (0 min.) increased in female GK rats (GK rats: 166.0 ± 22.0 mg/dl vs. Wistar rats: 99.8 ± 10.3 mg/dl) (**Figure 4(A)**). The blood insulin levels after glucose-loading in female GK rats were comparable to those in female Wistar rats, and the fasting insulin level (0 min.) significantly increased in the GK rats (GK rats: 0.868 ± 0.104 ng/ml vs. Wistar rats: 0.586 ± 0.176 ng/ml) (**Figure 4(B)**). Furthermore, the insulinogenic index in GK rats significantly decreased as compared with that in Wistar rats (**Figure 4(C)**). GK rats showed an impaired glucose tolerance with the depletion of glucose-stimulated insulin secretion (GSIS). In addition, GK rats represented with a significant reduction of the insulinogenic index, suggesting that the early phase of insulin secretion after glucose-loading was characteristically impaired. In the previous reports, also, GK rats showed a reduction of GSIS, and in particular, the early phase of glucose-induced secretion was impaired [16] [17].

Several blood biochemical parameters were measured at 5, 10, and 18 weeks of age (**Table 1**). The TG levels in male and female GK rats were decreased by age (**Table 1(a)** and **Table 1(b)**). The decrease in TG levels may be related to the non-fasted insulin levels. Functional parameters in the kidneys, such as blood urea nitrogen (BUN) and blood creatinine, showed higher levels in GK rats than in Wistar rats.

2.3. Insulin Sensitivity

Villar-Palasi and Farese reported on the insulin sensitivity in peripheral tissues of GK rats in 1994 [18]. Glycogen synthase (GS) activity, GS phosphatase activity, and glucose 6-phosphatase (G6P) content after insulin treatment in skeletal muscle increased in Wistar rats, but, in GK rats, no increases in GS phosphate and G6P were observed. In adipose tissue, the activation of GS after insulin treatment was normal in GK rats. A defective activation of glucose accumulation into glycogen in skeletal muscle may be related to the impaired glucose tolerance and hyperglycemia in the GK rat. In the liver of GK rats, the G6P and the fructose-1,6-diphosphative activities increased, and the phosphofructokinase (PFK) was reduced, suggesting that the gluconeogenesis increased and the glycolysis decreased. Meanwhile, the activities of insulin-inducible enzyme, such as glucokinase and pyruvate kinase increased in the liver at 4 and 12 weeks of age in GK rats [19]. Those changes in hepatic enzyme are similar with those in adult-onset diabetic patients [20]. GK rats showed increases in fasting blood glucose and insulin levels (**Figure 3** and **Figure 4**), indicating that insulin sensitivity in the liver was reduced in GK rats.

Table 1. (a) Blood chemical parameters in male GK rats and Wistar rats; (b) Blood chemical parameters in female GK rats and Wistar rats.

(a)

		5 weeks-old	10 weeks-old	18 weeks-old
GK rat	TG (mg/dl)	139.9 ± 30.0	72.4 ± 10.7	59.2 ± 9.0
	TC (mg/dl)	63.8 ± 1.8	54.5 ± 4.2	65.4 ± 7.5
	GPT (U/l)	48.7 ± 4.6	43.5 ± 4.9	44.0 ± 10.1
	GOT (U/l)	55.2 ± 13.3	45.3 ± 8.9	58.9 ± 11.9
	TP (g/l)	5.47 ± 0.14	6.28 ± 0.22	6.38 ± 1.40
	BUN (mg/dl)	24.8 ± 1.6	22.3 ± 1.3	24.7 ± 3.7
	CRE (mg/dl)	0.42 ± 0.02	0.58 ± 0.06	0.64 ± 0.06
Wistar rat	TG (mg/dl)	132.5 ± 50.0	77.5 ± 15.7	128.9 ± 29.8
	TC (mg/dl)	89.4 ± 9.8	59.5 ± 7.0	67.4 ± 5.4
	GPT (U/l)	49.2 ± 8.2	34.0 ± 3.6	50.0 ± 6.9
	GOT (U/l)	78.2 ± 6.6	61.2 ± 6.8	66.2 ± 6.8
	TP (g/l)	5.11 ± 0.14	6.14 ± 0.19	6.75 ± 0.42
	BUN (mg/dl)	13.3 ± 2.0	15.9 ± 1.7	16.8 ± 1.5
	CRE (mg/dl)	0.16 ± 0.01	0.29 ± 0.06	0.30 ± 0.02

TG: triglyceride, TC: total cholesterol, GPT: glutamic pyruvic transaminase; GOT: glutamic oxaloacetic transaminase, TP: total protein, BUN: blood urea nitrogen; CRE: creatinine.

(b)

		5 weeks-old	10 weeks-old	18 weeks-old
GK rat	TG (mg/dl)	258.0 ± 25.0	125.7 ± 26.0	70.9 ± 19.7
	TC (mg/dl)	73.5 ± 4.2	58.6 ± 4.8	70.4 ± 12.8
	GPT (U/l)	41.2 ± 3.4	36.2 ± 2.5	37.6 ± 9.1
	GOT (U/l)	56.2 ± 6.6	39.0 ± 5.7	47.9 ± 3.4
	TP (g/l)	5.59 ± 0.12	6.27 ± 0.25	6.72 ± 1.05
	BUN (mg/dl)	22.5 ± 1.0	17.2 ± 1.7	20.4 ± 5.1
	CRE (mg/dl)	0.42 ± 0.04	0.54 ± 0.03	0.66 ± 0.11
Wistar rat	TG (mg/dl)	148.4 ± 35.0	51.1 ± 14.2	67.8 ± 13.3
	TC (mg/dl)	82.1 ± 11.1	57.9 ± 8.8	66.7 ± 6.8
	GPT (U/l)	38.8 ± 3.5	35.9 ± 6.7	34.6 ± 4.0
	GOT (U/l)	70.0 ± 5.7	65.7 ± 12.3	55.2 ± 5.1
	TP (g/l)	5.29 ± 0.34	5.99 ± 0.45	6.87 ± 0.25
	BUN (mg/dl)	15.2 ± 2.5	15.6 ± 3.2	17.4 ± 2.0
	CRE (mg/dl)	0.17 ± 0.02	0.27 ± 0.02	0.33 ± 0.04

TG: triglyceride, TC: total cholesterol, GPT: glutamic pyruvic transaminase; GOT: glutamic oxaloacetic transaminase, TP: total protein, BUN: blood urea nitrogen; CRE: creatinine.

2.4. Diabetic Complications

Peripheral neuropathy in GK rats has been been examined by Yagihashi *et al.* [21]. The motor nerve conduction velocity (MNCV) of the tail was always lower in GK rats than in age-matched Wistar rats, from 2 to 8 months of age (MNCV at 2 months of age, GK rats: 36.6 ± 2.4 m/s vs. Wistar rats: 40.4 ± 1.8 m/s; MNCV at 8 months of age, GK rats: 53.6 ± 4.4 m/s vs. Wistar rats: 63.5 ± 4.8 m/s). In morphometrical analysis of peripheral nerves, GK rats showed a reduction in the caliber of unmyelinated axons at 2 months of age, and the endoneural space was widened at 3 months of age. Furthermore, loss of myelinated nerve fibers, and decreases in nerve fiber size and axonal size were observed at 6 months of age in GK rats. Metabolic abnormalities in the polyol pathway are considered to be related to the development of neuropathy. Sustained hyperglycemia promotes the polyol pathway and the accumulation of sorbitol in neural fibers, resulting in the deterioration of neural function via hyperosmosis [22]. In particular, the decrease in the activity of sodium-potassium-ATPase associated with defects of myo-inositol by sorbitol accumulation is closely related with the decrease in MNCV [23].

Urinary albumin excretion (UAE) was significantly higher in GK rats than in Wistar rats, from 2 to 14 months of age, and the UAE levels rose progressively over time [24]. Also, Yagihashi *et al.* have investigated the glomerular lesion in GK rats [25]. Creatinine clearance decreased over time in GK rats, but not in Wistar rats. Blood pressure in GK rats was in the normotensive range. In GK rats at 8 weeks of age, there was no significant difference in ultrastructure from age-matched Wistar rats. At 12 weeks of age, GK rats showed thickening of basement membrane and accumulation of basement membrane-like materials in the mesangial regions. After 16 to 24 weeks of age in GK rats, hemispherical thickening in addition to diffuse thickening of the glomerular basement membrane was observed. Moreover, interstitial monocyte/macrophage influx in GK rats increased at 12 weeks of age, as compared with that in Wistar rats [26]. Glomerular macrophage infiltration was also elevated in GK rats at 35 weeks of age. The histological changes observed in GK rats are similar to those observed in prolonged type 2 diabetic patients who have not developed renal lesions. In brief, the GK rat is useful in investigating the mechanism involved in the pathogenesis of the consequences of sustained hyperglycemia.

There are some reports in which renal lesions in GK rats were investigated. The dye-dilution technique with scanning laser ophthalmoscope-based fluorescein angiopathy was performed to evaluate retinal circulation in GK rats at 1, 3, and 5 months of age [27]. The retinal mean circulation times (MCTs) in GK rats were always prolonged, as compared with those in Wistar rats. No significant differences were observed in the retinal arterial and venous diameters in GK rats at each time period, but the retinal segmental blood flows (SBFs) were reduced in GK rats. The endothelial/pericyte (E/P) ratio in the retinas of GK rats was also investigated [28]. The E/P ratio was found to be higher in GK rats at 8

months of age, and, in GK rats at 24 to 30 months of age, the E/P ratio was higher than at 8 months of age. Moreover, time-dependent changes of electroretinograms (ERGs) have been determined in GK rats, 4 to 48 weeks of age [29]. The amplitudes of the a-wave, b-wave, and oscillatory potentials in GK rats were reduced with aging, and the a-wave latencies in GK rats were prolonged, as compared with those in Wistar rats. Functional abnormalities of photoreceptors might be induced by the prolonged hyperglycemia in GK rats.

2.5. Pharmacological Study

In a previous study, we investigated the pharmacological effects of JTT-608, a glucose-sensor activator, in comparison with the sulphonylurea tolbutamide in GK rats [30]. In isolated perfused pancreases from GK rats, JTT-608 enhanced the insulin secretion depending on glucose concentration (2.8 - 11.1 mmol/l); however, the tolbutamide stimulated insulin secretion at low glucose concentration (2.8 mmol/l). Moreover, JTT-608 stimulated insulin secretion in the first and second phase, but the tolbutamide enhanced only the second phase of insulin secretion. Also, in *in vivo* study, JTT-608 enhanced early insulin secretion only with glucose-loading. Furthermore, we investigated the chronic effect of JTT-608 in GK rats [31]. The fasting glucose and hemoglobin (Hb) A1c levels were reduced by JTT-608 treatment during the experimental period. In histopathological analysis, the decrease of insulin content in pancreas and the onset of renal lesions, vacuolation in renal tubules (Armanni-Ebstein changes), were improved with JTT-608 treatment (**Figure 5**).

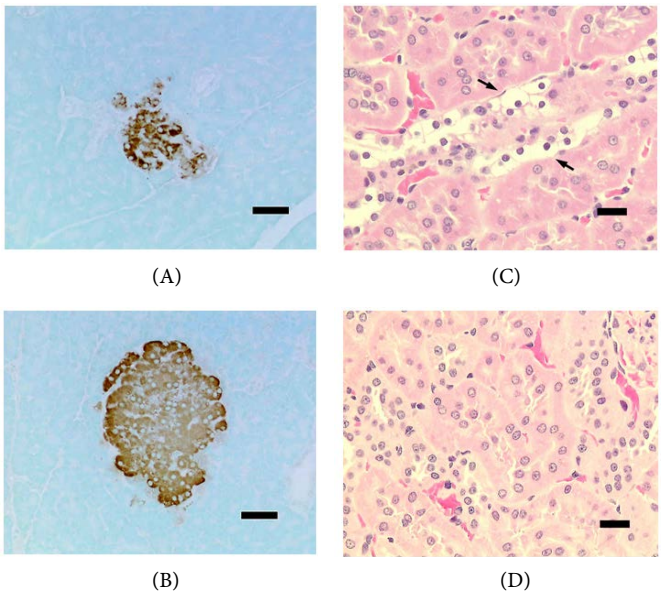


Figure 5. Histopathological analysis in GK rats with JTT-608 treatment. (A) Pancreas, GK rat at 18 weeks of age, immunostained with anti-insulin; (B) Pancreas, GK rat with JTT-608 treatment, immunostained with anti-insulin; (C) Kidney, GK rat at 18 weeks of age, hematoxylin and eosin staining. Arrows show Armanni-Ebstein changes; (D) Kidney, GK rat with JTT-608 treatment, hematoxylin and eosin staining. Bar = 20 μm.

The effects of dipeptidyl peptidase (DPP)-4 inhibitors on the pancreas in GK rats were investigated. Chronic administration of vildagliptin for 18 weeks improved the glucose tolerance and insulin secretion, and suppressed hyperglucagonemia in GK rats [32]. Moreover, vildagliptin enhanced the β cell and α cell proliferation, and increased the number of small neogenetic islets. It is reported that the perturbations of exocrine pancreatic function and structure in GK rats are improved by the long-term administration of vildagliptin [33].

The effects of sodium-glucose cotransporter (SGLT) inhibitor T-1095 were also investigated in GK rats [34]. T-1095 was administered as a dietary admixture for 32 weeks, from 7 to 9 weeks of age. As a result, T-1095 treatment decreased blood glucose and HbA1c levels in GK rats. Furthermore, T-1095 treatment prevented the development of diabetic neuropathy, such as reduction of the thermal response in tail-flick testing, in GK rats. In this way, the GK rat has been used for the development of new anti-diabetic drugs.

3. SDT Rat

3.1. Background—Breeding and Gene Analysis

SDT rat is an inbred strain of Sprague-Dawley (SD) rat established by Shinohara in 1997. Some non-obese diabetic rats which show polyphagia, polyposia, polyuria, and urinary sugar among approximately 1-year-old male SD rats were bred at the laboratory of Torii Pharmaceutical Co. Ltd. (Tokyo, Japan). These male SD rats were mated with normal female SD rats to generate diabetic F_1 [35] [36] [37]. In the process of strain breeding, the incidence of diabetes in male rats was 90% or more in the F_4 generation and 100% in the F_9 and subsequent generations [35]. Diabetes tended to develop earlier in later generations and developed at approximately 4 months of age in the F_7. Hypoinsulinemia accompanied by hyperglycemia appeared at approximately 20 weeks of age in male SDT rats. The cumulative incidence of diabetes was 100% by 40 weeks of age in male SDT rats, while it was only 33% in females even at 65 weeks.

Onset and development of diabetes in SDT rats are genetically regulated, and seven QTLs involved in glucose intolerance were mapped on the rat genome [38] [39]. In a backcross analysis with Brown Norway rats, QTLs involved in glucose intolerance in SDT rats were identified on chromosomes 1, 2, and X (*Gisdt*1, *Gisdt*2, and *Gisdt*3, respectively). In an intercross analysis with F344 rats, QTLs involved in glucose intolerance in SDT rats were identified on chromosomes 3, 8, 13, and 14 (*Dmsdt*1, *Dmsdt*2, *Dmsdt*3, and *Dmsdt*4, respectively). Moreover, *Dmsdt*1 was the major locus responsible for the pancreatic lesions in SDT rats [39].

3.2. Biological Profiles—Phenotype and Blood Chemical Parameters

Male SDT rats developed diabetes around 20 weeks of age and at 40 weeks of age, all animals developed diabetes (**Figure 6(A)**). However, only 1/3 of female

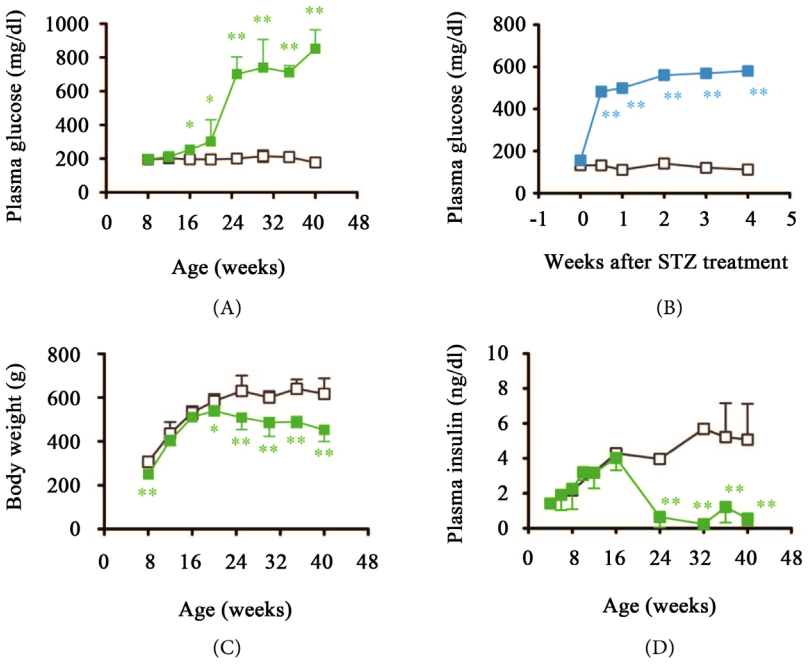


Figure 6. Biological profiles of male SDT rats. The plasma glucose levels in SDT rats become increase around 16 weeks of age and reached 700 mg/dl by 25 weeks (A); On the other hands, STZ-induced diabetic rats develop hyperglycemia immediately after STZ treatment (B); SDT rats show decreased body weight from 20 weeks of age (C); Blood insulin rapidly diminishes after 16 weeks of age (D). White square; male SD rats, green square; male SDT rats, blue square; STZ-induced diabetic rats. Data represent means ± standard deviation (n = 5 - 8). *P < 0.05, **P < 0.01; significantly different from the control SD rat. (A) - (C) are modified from [36] [37].

SDT rats developed diabetes, even at 65 weeks of age [37]. After the onset of diabetes, blood glucose level markedly increased and reached 800 to 1000 mg/dl at 30 weeks of age with polyuria/glucosuria as well as polyposia/polyphagia. HbA1c increased to more than 10%. One of the most popular animal models, STZ-induced diabetes rats, also showed severe hyperglycemia within a day after STZ injection (**Figure 6(B)**). This is a clear difference between spontaneous model and chemical induced models. Our preliminary study showed that polyphagia and obesity result from ventromedial hypothalamic (VMH) damage developed diabetes earlier than sham operated SDT rats (Ito and Sasase, unpublished observations).

Body weight and body-mass index were similar as normal SD rats before the onset of diabetes, but were decreased after the onset (**Figure 6(C)**) [37] [40] [41]. At the same time, blood insulin was diminished rapidly (**Figure 6(D)**) [42] [43]. Therefore, the hyperglycemia of SDT rat developed insulin dependently. mRNA expressions of glucokinase and glycogen content in the liver were reduced in SDT rats at 16 weeks of age, suggesting that glucose metabolism in the liver is already disturbed before the onset of diabetes. After the onset, mRNA levels of gluconeogenesis enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), and G6Pase, were elevated [44] [45].

SDT rats also developed dyslipidemia at 30 weeks of age and thereafter (**Table 2**) [37] [46]. Blood TG and total cholesterol (TC) levels increased after the onset of diabetes. However, in male SDT rats, the blood TG levels after fat-loading have already been high with normal TG absorption from the small intestine before the onset, suggesting that the TG clearance is already impaired. Increased TG absorption due to physical increase in TG inflow associated with polyhagia-induced hypertrophy of the small intestine occured after the onset of diabetes. Active ghrelin production, an orexigenic hormone, and suppression of insulin and leptin may be concerned with diabetic polyphagia in SDT rats [47]. In addition, enzymes involving in TG absorption in the small intestine increased in SDT rats [44] [46].

3.3. Impaired Glucose Tolerance and Pancreatic Lesions

The SDT rat is a good model of impaired glucose tolerance (IGT). Before 16-18 weeks of age, basal blood glucose levels in SDT rats were same as normal rats, means they do not develop diabetes at these points. However, after glucose-loading, insulin secretion decreased and blood glucose levels significantly increased (**Figure 7(A)** and **Figure 7(B)**). Glucose tolerance in SDT rats markedly decreased at least 2 months before the development of hyperglycemia and it got worse with age. After the onset of diabetes, insulin secretion disappeared and the increase of blood glucose levels was clearer (**Figure 7(C)** and **Figure 7(D)**) [41] [48] [49]. This blood glucose change in SDT rats at 24 weeks of age was similar to that of STZ-induced diabetes rats (**Figure 7(E)** and **Figure 7(F)**). Thus SDT rats after developing diabetes and STZ-induced diabetes rats are unsuitable model of IGT.

Table 2. Comparison of blood parameters, body weight, and food consumption of SD rat and SDT rat.

	8 weeks-old		30 weeks-old	
	SD rat	SDT rat	SD rat	SDT rat
Body weight (g)	319.0 ± 1.2	320.5 ± 11.2	649.4 ± 18.1	469.7 ± 7.6**
Glucose (mg/dl)	138.7 ± 2.2	138.2 ± 2.5	119.6 ± 1.4	686.2 ± 36.4**
Insulin (ng/ml)	1.41 ± 0.40	1.65 ± 0.22	1.61 ± 0.57	0.23 ± 0.01*
NEFA (mEq/ml)	0.49 ± 0.14	0.49 ± 0.14	0.56 ± 0.21	0.76 ± 0.36
TG (mg/dl)	155.0 ± 8.0	168.3 ± 36.3	148.8 ± 15.1	478.1 ± 155.0**
TC (mg/dl)	80.4 ± 3.9	83.9 ± 1.2	114.5 ± 9.3	132.2 ± 7.7
HDL-C (mg/dl)	60.3 ± 5.0	63.0 ± 1.2	91.6 ± 10.8	62.6 ± 2.7**
Non HDL-C (mg/dl)	20.5 ± 1.9	20.5 ± 0.4	22.8 ± 2.3	69.6 ± 22.4**
Food consumption(g/day)	25.2 ± 0.9	24.6 ± 0.5	22.6 ± 1.5	48.3 ± 3.8**
Leptin (ng/ml)	4.3 ± 0.2	4.3 ± 0.2	17.4 ± 2.0	0.4 ± 0.1**

Biochemical parameters of non-fasted SD and SDT rats were measured at both 8 and 30 weeks of age. Each value represents mean ± SEM (n = 5 - 9). *P < 0.05, **P < 0.01 (vs. age-matched SD rats, unpaired *t*-test). Table is modified from Sasase *et al.*, 2007 [46].

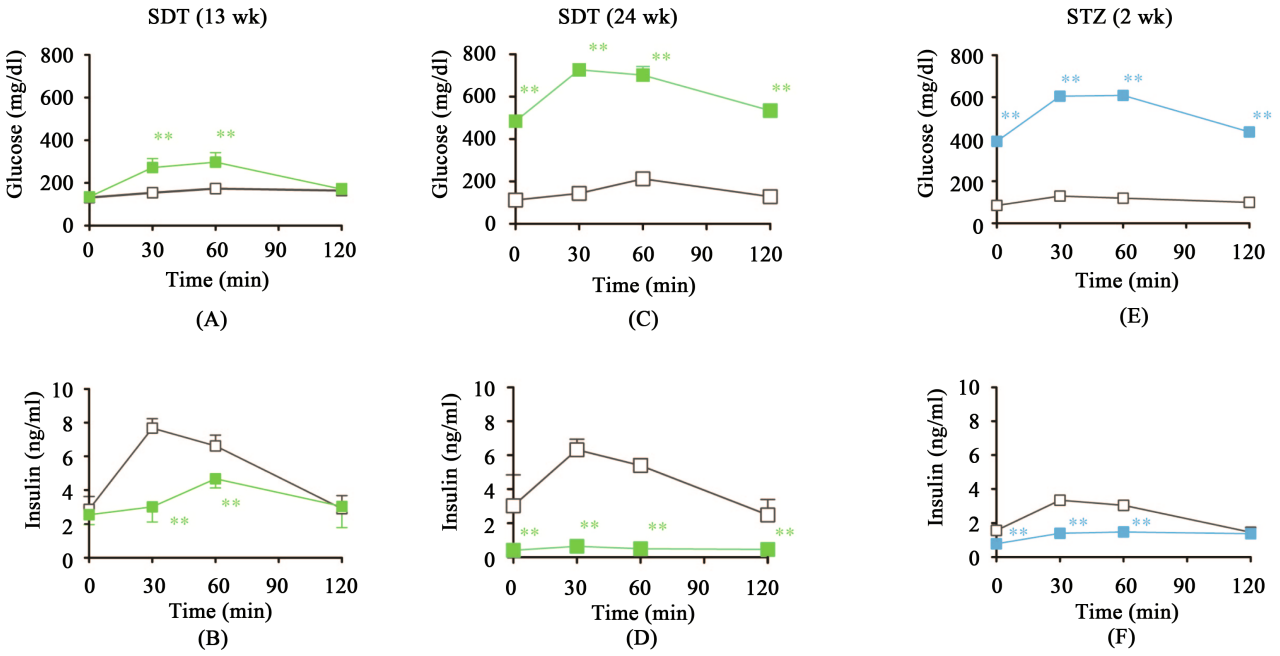


Figure 7. Changes in plasma glucose and insulin concentrations during oral glucose tolerance test (OGTT; 2 g/kg). At 13 weeks of age, SDT rats were non-diabetic but the marked elevation of plasma glucose and lower insulin concentration were observed after glucose-loading (impaired glucose tolerance; IGT) ((A), (B)). At 24 weeks of age, SDT rats become diabetic and show further elevation of plasma glucose level because of diminished insulin secretion ((C), (D)). STZ-induced diabetic rat show similar blood glucose changes as 24 weeks-old-SDT rat even at 2 weeks after STZ treatment ((E), (F)). White square; male SD rats, green square; male SDT rats, blue square; STZ-induced diabetic rats. Data represent means ± standard deviation (n = 6). **P < 0.01; significantly different from the control SD rat. (A) - (D) are modified from [41] [48].

In addition, *in vitro* study showed that the insulin secretion after glucose treatment in isolated pancreatic β-cells from SDT rats markedly decreased at 12 weeks of age compared with normal SD rats [50]. In female rats, glucose tolerance also decreased at 25 weeks of age without insulin diminution, suggesting involvement of some factors in insulin resistance in the females SDT rats [51]. It has also been reported that increased insulin secretion from hypertrophic pancreatic islets delayed the onset of hyperglycemia in SDT rats fed a high-fat diet [52].

At 8 weeks of age, microcapillary extension and congestion were frequently observed in pancreatic islets in SDT rats (**Figure 8(A)**). At 10 weeks of age, the number of pancreatic islets and the area of β-cells gradually decreased. Hemorrhages were also observed in pancreas (**Figure 8(B)**). Inflammation and fibrosis in or around the pancreatic islets extended, and fibrosis, hemosiderin deposition, and marked decrease in β-cells were observed in almost all pancreatic islets at 20 weeks of age (**Figure 8(C)** and **Figure 8(E)**). After development of diabetes, atrophy of pancreatic islets occupied by collagenous fibers and virtual disappearance of β-cells were observed (**Figure 8(D)** and **Figure 8(F)**) [35] [37] [41]. Such changes in pancreatic islets starting from hemorrhage were found in female SDT rats [51]. These pancreatic damages were considered as results of transient increase of IL-18 concentration and the local macrophage infiltration

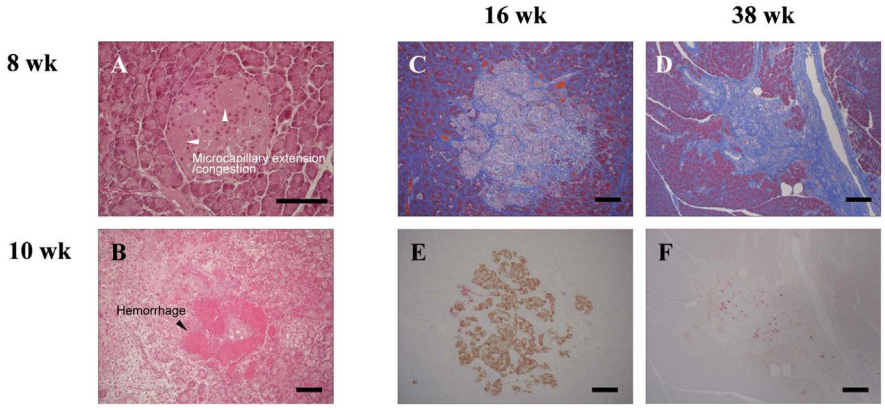


Figure 8. Histopathological observations in pancreas (islet) of SDT rats. Congestion or microcapillary extension (A) and hemorrhage (B) in the pancreatic islets were observed (HE stain). Replacement of islet cells by connective tissues with advanced fibrosis ((C), (D)) (MT stain). Immunohistochemistry of islet showed almost all of the β-cells (brown, insulin-immunoreactive) disappeared from the islets, whereas α-cells (pink, glucagon-immunoreactive) were still observed at 38 weeks of age ((E), (F)). Bar = 100 μm. Figures are modified from [41].

[53] [54]. Weakness of pancreas in SDT rats was also suggested by higher sensitivity to STZ [43].

3.4. Diabetic Complications

Long-term duration of diabetes can cause severe microvascular complications such as diabetic retinopathy, diabetic nephropathy, or diabetic peripheral neuropathy. In the eye, retinopathy, cataract, and neovascular glaucoma (hemorrhagic glaucoma) are the clinically important complications. Proliferative retinopathy with tractional retinal detachment was found in some aged SDT rats. Vitreous hemorrhage and fibrovascular membrane were resulting from retinal neovascular vessels (**Figure 9(A)**). Capillary narrowing and pericyte loss were also found, but capillary aneurysms that are frequently observed in human diabetic retinopathy was not found in SDT rats (**Figure 9(B)**). Severe fluorescein leakage (**Figure 9(C)** and **Figure 9(D)**) and abnormal retinal vasodilatation that may correspond to venous beading in human retinopathy was observed [35] [37] [55] [56] [57] [58] [59]. At 44 weeks of age, ERG revealed delay and reduction of oscillatory potentials (OPs) and a- and b-waves [58] [60], as is the case with human diabetic retinopathy. Kakehashi *et al.* [57] reported that the prevalence of diabetic retinopathy was 8% at 35 to 50 weeks of age, but was increased to approximately 80% at 51 to 60 weeks and finally reached 100% at 61 to 82 weeks. Increased expression of vascular endothelial growth factor (VEGF) is deeply involved in angiogenesis as in human diabetic retinopathy. Gene therapy with soluble VEGF receptor (sFlt-1) into the retina prevented fluorescein leakage from the retina at 57 weeks of age SDT rat [61] [62]. In some severe human diabetic retinopathy, excess VEGF produced by advanced retinal ischemia develops angiogenesis in the iris or anterior chamber angle to cause neovascular glaucoma,

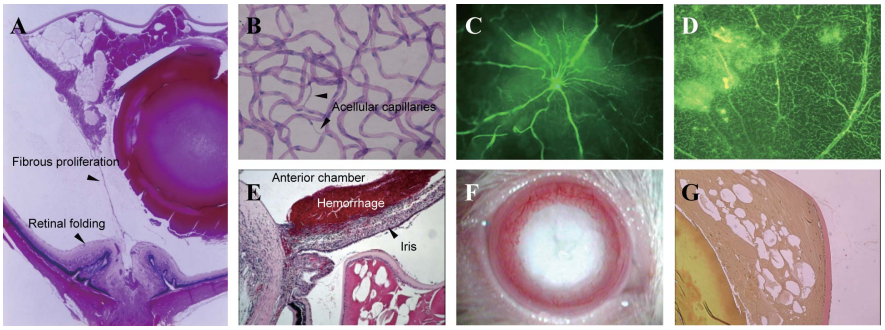


Figure 9. Typical ocular observations in SDT rats. Large retinal folds were seen in the midperipheral retina and around the optic disk. A tractional retinal detachment was observed with fibrous proliferation (A) (HE stain); Retinal trypsin digestion showed acellular capillaries (B) (HE stain); Tortuous vessels and extensive fluorescein leakages were observed in retinal flat mounts from SDT rats ((C), (D)); Massive hemorrhage in the anterior chamber associated with proliferation around the iris was seen in some severe case (E) (HE stain); The mature cataract was observed clearly in the dilated pupil (F); The sclerotic nucleus floats in a liquefied lens cortex. Vacuolation, disintegration of the lens fibers, and Morgani's globules were observed in the lens cortex (G) (Elastica van Gieson stain). Figures are modified from [37] [55] [57] [58] [59].

one of the most severe ocular complications. Currently, there is no animal models show neovascular glaucoma. SDT rats with advanced retinopathy developed fibrovascular membrane around the iris and sometimes with anterior chamber hemorrhage (**Figure 9(E)**) [35] [37] [55] [57]. Although there is no report that evaluates ocular pressure, SDT rat may have potential to be a model of neovascular glaucoma. After 40 weeks of age, male SDT rats showed opacity at the posterior pole of the lens and finally developed hypermature cataract (**Figure 9(F)** and **Figure 9(G)**). Nuclear sclerosis progresses and the cortex is highly opacified. Swollen of lens fibers, liquefaction, vacuolation, abnormal configuration, and formation of Morgagnian droplets, and partial proliferation of fibroblastoid cells were found pathologically [35] [37] [55] [56] [57] [58] [59]. Controlling blood glucose level with long-term insulin treatment or pancreas transplantation prevented all these ocular abnormalities. Therefore these ocular complications are considered accompanied by sustained hyperglycemia [58] [63].

Some renal lesions were found in SDT rats at 24 weeks of age, such as thickening of the glomerular loop, glycogen deposition in the tubular epithelium (Armanni-Ebstein lesion), dilatation of the renal tubule lumen, and increased hyaline casts. Slight thickening of the glomerular loop was consistent with mesangial proliferation, Masson's trichrome stain, and type IV collagen immunostaining (**Figures 10(A)-(F)**). Mesangial proliferation developed with age, and nodular lesions (Kimmelstiel-Wilson-like nodules) that suggest more severe glomerular lesions were slightly observed at 68 weeks of age (**Figure 10(G)**). The renal tubular lesions also increased with a marked increase in tubular glycogen deposition at 50 and 68 weeks of age (**Figure 10(H)**). In addition, urine volume, urine protein, and urine albumin increased with blood glucose at 24 weeks of age and thereafter, and these changes may be consistent with the development of

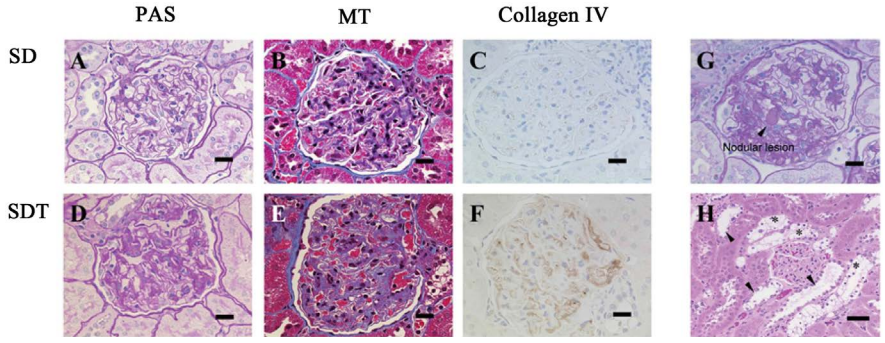


Figure 10. Histological and immunohistological analysis of glomeruli in SD rats ((A) - (C)) and SDT rats ((D) - (F)). In the glomeruli of SDT rats, basement membrane thickening and mesangial matrix proliferation were observed at 50 weeks of age (Bar = 20 μm). Nodular lesions were found in a few glomeruli from 68-weeks-old SDT rats (G) (PAS stain, Bar = 20 μm). In the renal tubules of SDT rats, dilation (arrowhead) and glycogen deposition in the epithelium (*) were observed (H) (HE stain, Bar = 50 μm). Figures are modified from [65].

renal lesions [64] [65]. These renal lesions were also improved by blood glucose control with insulin and thus shown to result from exposure to high blood glucose [64] [65]. The blood asymmetric dimethylarginine (ADMA) concentration, urinary excretion of oxidative stress markers 8-hydroxydeoxyguanosine (8-OHdG), and nitrogen oxide (NOx) increased in SDT rats at 36 weeks of age. In addition, glomerular hypertrophy and mesangial proliferation were found pathologically. From immunohistopathological study, increase of glomerular 8-OHdG, endothelial NO synthase (eNOS), and nitrothyrosine were also reported. These findings indicated an important role of oxidative stress on the progression of diabetic nephropathy [66] [67].

In diabetic peripheral neuropathy (DPN), both motor and sensory nerves are impaired. In an electrophysiological and morphological study, the MNCV and sensory nerve conduction velocity (SNCV) in SDT rats were same as in normal SD rats until 6 months of age, but gradually decreased to less than 80% of that in normal SD rats at 12 months (**Figure 11(A)**). Increased nerve sorbitol and fructose contents and decreased myo-inositol contents in SDT rats indicated that the polyol pathway was prominently involved in DPN [68] [69]. Neurologic deficit was not observed in the sural nerve cross-section, but degenerated nerves increased in SDT rats. The myelinated nerve area in SDT rats was not clearly different from normal rats at 6 months of age, but decreased at 12 months compared with normal rats. Morphologically, the number of blood vessels in the nerve sheath was not clearly different; however, occluded/thickened epineurial arterioles were observed in SDT rats (**Figures 11(B)-(E)**). Thickened intima disturbs nerve perfusion and accelerates DPN. Therefore, SDT rats developed peripheral neuropathy associated with type 2 diabetese, including functional/morphological abnormalities of peripheral nerves and vascular lesions [68] [69]. Autonomic nerve is part of the peripheral nervous system and transmits impulses from the central nervous system to peripheral organ systems. Diabetic

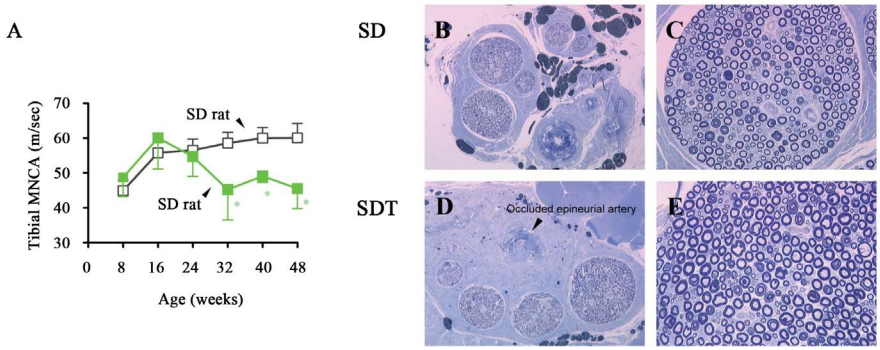


Figure 11. Diabetic peripheral neuropathy and histopathology in sural nerves of SDT rats. Serial changes of tibial motor nerve conduction velocity (MNCV) in male SD rats (white square) and male SDT rats (green square) (A). MNCV reduced after the onset of diabetes. Data represent means ± standard deviation (n = 6). *P < 0.05; significantly different from the control SD rat. Morphologically, SDT rats revealed significant atrophy in myelinated nerve at 48 weeks of age. Occluded/thickened epineurial arterioles were found in SDT rats. Typical low ((B), (D)) and high ((C), (E)) magnification microphotographs of sural nerves from SD rat and SDT rat (toluidine blue stain). Figures are modified from [68].

autonomic nerve dysfunction was also evidenced in SDT rats. Diabetic diarrhea and increased gastrointestinal motility with higher fecal water content were observed in SDT rats [70]. In a study of voiding function, voiding pressure, voided volume per micturition, and inter-micturition interval tended to increase in SDT rats [71].

At 36 weeks of age, bone formation and resorption decreased in SDT rats compared with normal SD rats. Bone density and strength also decreased in SDT rats (**Figure 12**). As a result of mechanical stress test, energy absorption significantly decreased in SDT rat, indicating decrease of bone strength. Decreased bone density and low-turnover bone lesions are found as seen with type 2 diabetes primarily due to decreased insulin secretion. Actually, the diabetic osteoporosis was improved with insulin treatment, indicating involvement of insulin on bone metabolism [72] [73].

3.5. Pharmacological Study

Use of animal models is essential to development of diabetes drugs. Currently, SDT rats are used for development and application of several diabetes drugs. In addition to insulin treatment [58] [65], sulfonylurea (tolbutamide) and DPP IV inhibitor (JTP-76209) [50], α-glucosidase inhibitor (voglibose) [74], SGLT inhibitor (phlorizin) [44] [49], and perilla (shiso) tea [75] were treated to SDT rats to control blood glucose levels. Diabetic microangiopathy was reportedly caused by increased tissue protein kinase C-beta (PKCβ) activity at high blood glucose levels. Twelve week-treatment of a PKCβ inhibitor JTT-010 improved retinal dysfunction such as delayed OPs in ERG, neuropathy such as decreased caudal MNCV, electrocardiographic coefficient of variation of R-R interval ($CV_{R\text{-}R}$), and thermal hypoalgesia in diabetic SDT rats [76]. Also, a transketolase activator benfotiamine that reduces major pathways related to diabetic microvascular

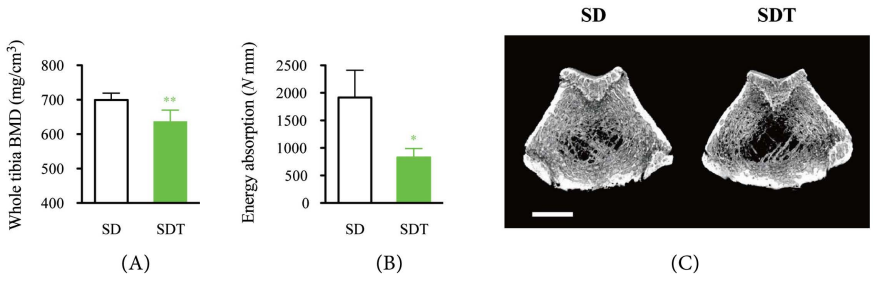


Figure 12. Bone properties (osteoporosis) of SDT rats. Bone mineral density (BMD) of the whole tibia (A) and mechanical property of the femur midshaft (B) were clearly indicating diabetes-induced osteoporosis in SDT rats. White column; male SD rats, green column; male SDT rats (40 weeks of age). Data represent means ± standard deviation (n = 5). **P < 0.01, *P < 0.05; significantly different from the control SD rats. The reconstructed bone microstructure 3D images of femur from 40 weeks SDT rats showed the obvious bone loss (C) (Bar = 2 mm). Figures are modified from [73].

complications, such as polyol pathway, hexosamine pathway, advanced glycation end product (AGE) pathway, and diacylglycerol (DAG)-PKC pathway, showed preventive effects on peripheral nerve dysfunction in SDT rats [68]. An angiotensin II type 1 receptor blockers (ARBs) are known to inhibit the development of retinopathy in type 2 diabetes patients [77]. In SDT rats, blood glucose level was not controlled by telmisartan, but blood pressure decreased; delayed OPs and a-wave in ERG were improved and fluorescein leakage from retinal vasculature in SDT rats was inhibited, suggesting that the ARB may suppress the development of proliferative retinopathy in SDT rats [78]. In addition, candesartan decreased the pentosidine content in the lens/vitreous body in SDT rats, and the drug inhibited accumulation of pentosidine in the retinal vascular wall and decreased retinal VEGF mRNA expression [79]. These findings indicated that ARBs can suppress the development of proliferative diabetic retinopathy by inhibiting AGE formation. Furthermore, cataract and retinopathy in SDT rats were reportedly prevented by aldose reductase inhibitors, fidarestat [80] and ranirest [81], AGE inhibitor aminoguanidine [82], and $\alpha 1/\beta$ blocker nipradilol [83].

4. Conclusion

The GK rat is a non-obese type 2 diabetic rat, showing impaired glucose tolerance and sustained hyperglycemia with a reduction of GSIS. In particular, the reduction of the first phase in GSIS is an important property, and a similar change is also found in type 2 diabetes in humans. With sustained hyperglycemia, diabetic complications, including nephropathy and neuropathy, are shown in GK rats. GK rats have contributed to development of anti-diabetic drugs. The SDT rat shows ocular complications similar to those in human diabetes, and severe diabetic neuropathy and nephropathy are caused by long-term hyperglycemia. Also, SDT rats show IGT before they develop diabetes. The diabetic rat models have played an important role in elucidating the pathogenesis of human

type 2 diabetes and developing the new anti-diabetic drugs. In the future, the diabetic rat models may be necessary for developing of new therapies in Unmet Medical Needs for diabetic complications.

Conflicts of Interest

TO and TS are employees of Japan Tobacco Inc. TG and MS are employee of CLEA Japan Inc. PS, SF, RT, and TK are employees of Nomura Siam International Co., Ltd.

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