Characteristics of Diabetes in the SDT Rat

Taku Masuyama*

Toxicology Research Laboratories, Central Pharmaceutical Institute, Japan Tobacco Inc., Japan

Abstract: The Spontaneously Diabetic Torii (SDT) rat is a useful animal model of type 2 diabetes mellitus without obesity. The diabetes in this model manifests as severe hyperglycemia and hypoinsulinemia. However, insulin treatment is not required for survival despite marked hyperglycemia. Pancreatic islets display unique pathologic changes such as hemorrhage and fibrosis before the onset of hyperglycemia as well as marked atrophy. Islet injury is associated with macrophage infiltration of the islets and excess production of nitric oxide. Impaired glucose tolerance results from impaired insulin secretion following by decrease in beta cell mass and glucose-stimulated insulin release from beta cells. Beta cells in these animals have low insulin-secreting capacity in response to glucose stimulation, but retain normal responses to sulfonylurea and incretin. Although insulin resistance is less presented by body composition without obesity, the SDT rat has the potential contributions of hepatic insulin resistance and low energy expenditure to the development of diabetes. This article provides an overview of the pathologic features of pancreatic islets such as beta cell function and possible insulin resistance in SDT rats.

Keywords: SDT rat, hyperglycemia, insulin secretion, insulin resistance, pancreatic islets.

INTRODUCTION

Type 2 diabetes is a complex disease that results either from decreased insulin secretion from the pancreas or ineffective insulin function and metabolism in the body, and affects millions of people worldwide [1]. Appropriate experimental models are essential for understanding genetics, molecular basis, and pathogenesis of this disease as well as functioning of therapeutic agents. Because available animal models develop type 2 diabetes spontaneously, numerous rat models have been reported and utilized in diabetes research. Spontaneously Diabetic Torii (SDT) rats are animal models of type 2 diabetes mellitus without obesity, and develop diabetic complications such as proliferative retinopathy [2, 3]. The diabetes in this model manifests as severe hyperglycemia and hypoinsulinemia, but does not require insulin treatment for survival despite the marked hyperglycemia. Interestingly, pancreatic islets in this model display unique pathologic changes such as hemorrhage and fibrosis before the onset of hyperglycemia as well as marked atrophy [4]. No findings suggestive of autoimmunity, such as infiltration of lymphocytes into the islets, have been reported. Since there are patients with type 1 diabetes without apparent evidence for autoimmune mechanism, the SDT rat might be considered as a model animal for diabetes mellitus, not only for type 2, but possibly for type 1 and other types of diabetes such as called maturity-onset diabetes of the young (MODY). This article provides an overview of the available information on the pathologic features of diabetes in SDT rats.

*Address correspondence to this author at the Toxicology Research Laboratories, Central Pharmaceutical Institute, Japan Tobacco Inc., 23 Naganuki, Hadano, Kanagawa 257-0024, Japan; Tel: +81-463-81-1201; Fax: +81-463-82-3444; E-mail: taku.masuyama@jt.com

CLINICAL PATHOLOGY

SDT rats develop hyperglycemia spontaneously in both sexes. Males demonstrate higher incidence and earlier age at onset. In males, hyperglycemia and glucosuria are noted by 20 weeks of age, and the cumulative incidence of diabetes reaches 100% at 40 weeks of age under normal nutritional conditions [2]. In contrast, females display signs of diabetes by 45 weeks of age, and the cumulative incidence of diabetes is 33% at 65 weeks of age [2]. This gender difference in the development of diabetes is believed to be partially associated with suppressive effects of the female steroid hormone estrogen on the onset of diabetes [5]. It is interesting that diabetic SDT rats can survive for a long period without insulin treatment despite marked hyperglycemia. The survival rate up to 65 weeks of age was high, and was 92% in males and 97% in females [2]. Body weight and body mass index of prediabetic SDT rats are comparable to those of normal Sprague-Dawley rats; both values reduce in SDT rats after the onset of diabetes [6].

Blood glucose levels, either in fasting or nonfasting conditions, are markedly elevated by 20 weeks of age in male SDT rats, and reach 700 mg/dL or higher at around 30 weeks of age [4]. Diabetic SDT rats display not only hyperglycemia but also hyperphagia, polyposia, and polyuria with glycosuria [2]. Before acquiring hyperglycemia, plasma insulin levels in SDT rats were similar to or tended to be lower than those in age-matched normal Sprague–Dawley rats. SDT rats with hyperglycemia showed marked hypoinsulinemia [4].

Impaired glucose tolerance (IGT) often precedes clinically overt hyperglycemia and glucosuria [7]. SDT rats also exhibit IGT around 8 weeks of ages, which is much earlier than the onset of overt hyperglycemia [6]. In an oral glucose tolerance test (OGTT), marked elevation in postload

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plasma glucose concentration further increased concomitantly with age in SDT rats, although fasting plasma glucose concentrations were indistinguishable between SDT and age-matched control Sprague–Dawley rats. When SDT rats developed diabetes at 24 weeks of age, they exhibited marked fasting hyperglycemia, and plasma glucose concentrations were further elevated and sustained during the 2-h postload study period (Fig. **1**). The area under the curve of blood glucose concentration following an oral glucose load at an age before the onset of diabetes correlated positively to the age at onset of diabetes [6], indicating that the magnitude of IGT in prediabetic conditions in SDT rats is a biomarker for estimating the age at onset of diabetes. Female as well as male SDT rats also developed IGT at 16 weeks of age, well before the appearance of diabetes [8].

INSULIN SECRETION

The IGT that occurs in SDT rats is believed to be associated with an impaired insulin response to glucose stimulation. Indeed, the OGTT revealed lower plasma insulin levels before and after glucose loading in prediabetic SDT rats at a young age compared to age-matched Sprague–Dawley control rats [4]. The plasma insulin concentration in the OGTT was lower in SDT rats than in age-matched Sprague–Dawley control rats 30 min after the load at 18 weeks of age (Fig. **1**). At 24 weeks, SDT rats exhibited significant fasting hypoinsulinemia on becoming diabetic, and hardly any increase was observed in the plasma insulin level after a glucose challenge (Fig. **1**).

As mentioned, SDT rats exhibited significant fasting hypoinsulinemia and vanishingly low response in insulin secretion to an oral glucose load on developing diabetes [4]. Matsui *et al*. [9] investigated the *in vivo* response to insulin secretagogues other than glucose. Arginine, tolbutamide, and a dipeptidyl peptidase IV inhibitor increased the amount of insulin released after glucose loading and improved GT. In addition, *in vitro* studies using isolated islets from SDT rats revealed that glucose-stimulated insulin secretion was markedly lower in isolated islets from prediabetic SDT rats compared with those from age-matched normal Sprague–Dawley rats. However, when the islets were treated with tolbutamide or glucagon-like peptide-1 (7-36) amide in the presence of 11.2 mM glucose, the insulin level normalized. This indicated that beta cells of SDT rats have low insulin secretory capacity in response to glucose stimulation, but retain normal responses to sulfonylurea and incretin.

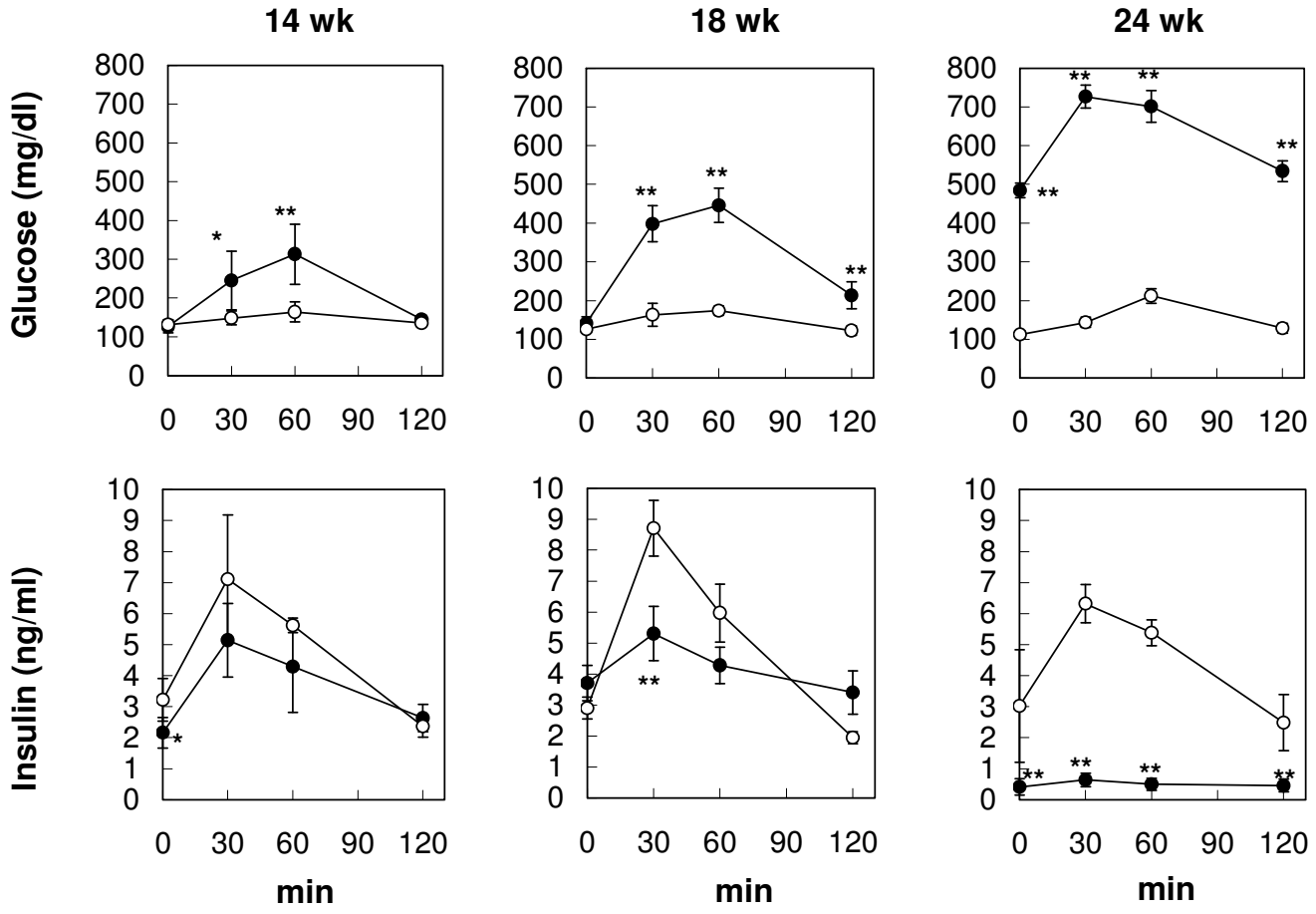

Fig. (1). Plasma glucose and insulin responses in the OGTT. Fasted animals were orally administered 20% glucose solution at a dose level 2 g/kg body weight. Plasma concentrations for glucose (upper panels) and insulin (lower panels) during the OGTT performed at 14, 18 and 24 weeks of age are plotted. Open and closed circles indicate control Sprague–Dawley and SDT rats, respectively. Data are expressed as mean ± S.D. (n = 6). Asterisks indicate statistically significant differences (*P < 0.05, **P < 0.01) between SDT and age-matched control rats. The SDT rats were nondiabetic at 14 and 18 weeks of age and diabetic at 24 weeks of age.

INSULIN RESISTANCE

Insulin resistance and obesity are key factors influencing the development of type 2 diabetes mellitus. Because prediabetic SDT rats have a normal body composition and lower plasma insulin levels than normal Sprague–Dawley rats [2, 4], the contribution of peripheral insulin resistance to the development of diabetes is presumably small. In contrast, homeostasis model assessment of insulin resistance index tended to be higher in SDT rats than in normal Sprague–Dawley rats as reported by Matsui *et al*. In addition, Morinaga *et al*. [10] reported decreased hepatic glucokinase mRNA levels and activity, glycogen synthase activity, and glycogen content in prediabetic SDT. Sasase *et al*. [11] reported impaired lipid catabolism preceding hypoinsulinemia/hyperglycemia in SDT rats. One interpretation of these reports is that SDT rats may have the potential to develop hepatic insulin resistance and abnormalities in hepatic glucose and lipid metabolism, leading to the onset of diabetes. In another approach, Ookawa *et al*. [12] reported clearly lower locomotor activity and higher food efficiency in SDT rats compared with Sprague–Dawley rats. A repeated water immersion–restraint stress burden during the prediabetic period improved GT and delayed the development of diabetes [12]. These results imply that SDT rats inherently have poor energy expenditure. Further investigations are needed to estimate insulin resistance in SDT rats.

PANCREATIC ISLETS

The first histologic change seen in pancreatic islets in male SDT rats was dilatation of the microvasculature, which occurred sporadically by approximately 8 weeks of age, when the animals were normoglycemic with normal glucose tolerance [4]. Congestion or hemorrhage is often observed in islets, and these phenomena are regarded as consecutive events in intraislet microcirculation. Inflammatory cells and fibroblasts subsequently infiltrate the pancreatic islets after the intraislet microcirculation followed by connective tissue invasion, and eventual fibrosis [4]. Deposition of hemosiderin is also observed in peri-islet areas and within the islets. These islets are irregular in shape, enlarged with fibrous tissue proliferation, and divide into small pseudo-lobules by 10–20 weeks (Fig. **2**). Fibrosis in islets was also reported in humans with type 2 diabetes [13]. The inflammation observed in SDT rat islets was qualitatively different from autoimmune-mediated inflammation, such as the typical lymphocyte infiltration that is consistently

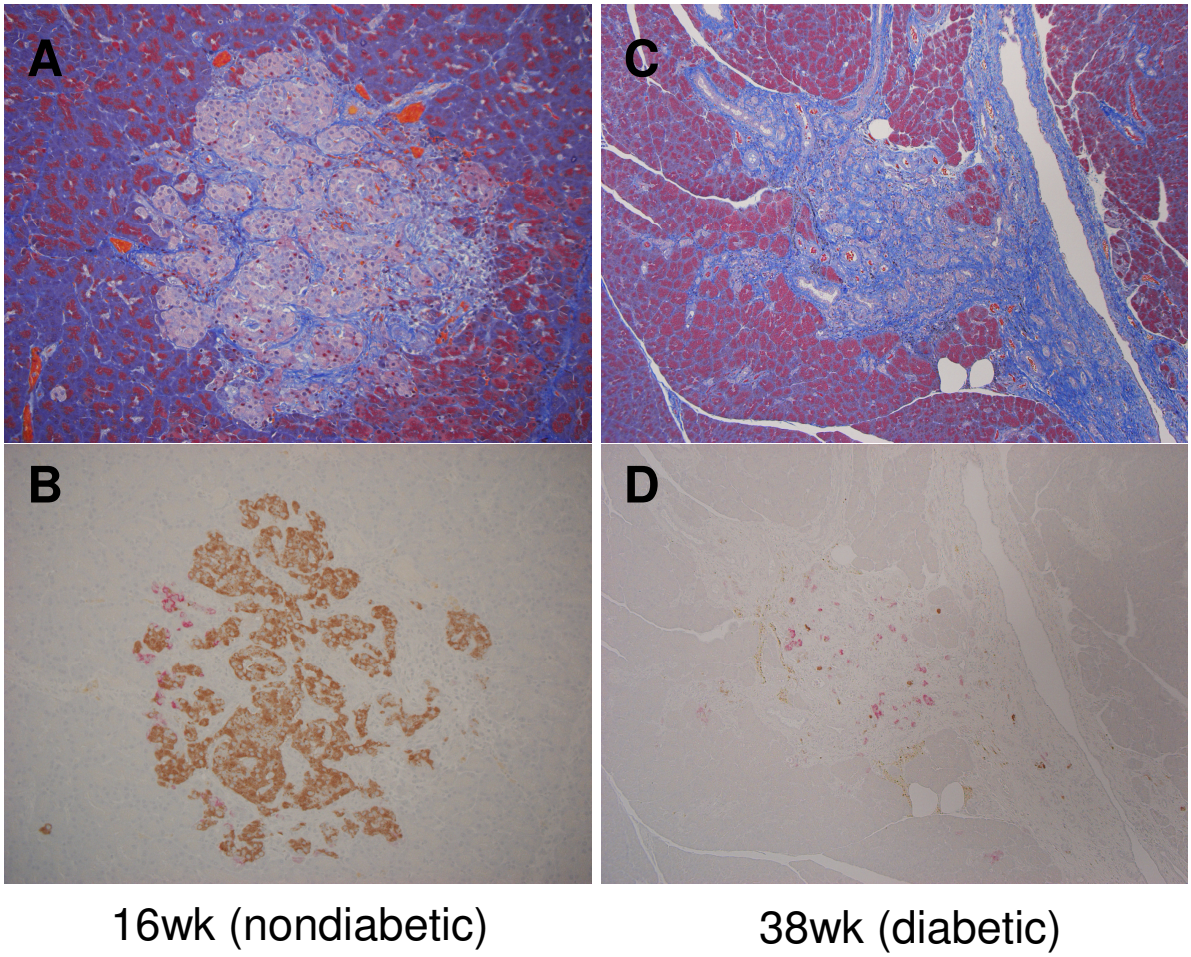

Fig. (2). Fibrosis in pancreatic islets. Fibrosis and hemosiderin deposition in and around the islets were seen at nondiabetic 16 weeks of age (**A**: Masson's trichrome staining, **B**: Immunohistochemistry for insulin (brown), glucagons (red) and somatostatin and pancreatic polypeptide (blue)). The islets are divided into pseudolobules by connective tissue and are irregular in shape. An islet at 38 weeks of age is atrophied and replaced by connective tissues with advanced fibrosis (**C**: Masson's trichrome staining, **D**: Immunohistochemistry for insulin (brown), glucagons (red) and somatostatin and pancreatic polypeptide (blue)). Insulin positive cells were disappeared.

observed in autoimmune diabetes. With regard to inflammatory cell infiltration, Inokuchi *et al*. [14] reported marked infiltration of $CD68^+$ cells (macrophages) in islets of SDT rats. Macrophage infiltration was associated with abrupt increases in serum interleukin-18 levels and circulating monocyte counts by 9 weeks of age, leading to excessive production of interferon-gamma and nitric oxide.

Depletion of pancreatic beta cells evokes insulin deficiency, and leads to IGT followed by diabetes. Despite being normoglycemic, pancreatic islet mass was smaller in SDT rats at 6 weeks of age than in age-matched normal Sprague–Dawley rats, and further declined progressively with age [4, 9].

Almost all beta cells disappeared from the islets of mature, diabetic SDT rats [4]. Although the reason for this loss is unclear, possible contributory factors are exhaustion of surviving beta-cells by overwork and impaired proliferation (regeneration) of beta cells. In contrast, Simada *et al*. [15, 16] and Wiao *et al*. [17, 18] performed syngeneic or allogeneic pancreas transplantation to diabetic SDT rats. Interestingly, pancreas transplantation to diabetic SDT rats was beneficial in preventing glucose toxicity, and induced pancreatic duodenal homeobox-1 expression close to ductal structures in the recipient native pancreas. This resulted in regeneration of beta cells in the native pancreas.

Studies using an angiotensin II blocker (telmisartan or candesartan cilexetil) revealed the preventive effect of angiotensin II blockers on the development of diabetes in SDT rats [19, 20]. Hasegawa *et al*. [19] reported upregulation of local renin–angiotensin system (RAS) in the islets of SDT rats as well as prevention of islet damage and failure with telmisartan treatment, possibly through oxidative stress resulting from local RAS activation. Either intraislet circulatory dynamics or oxidative stress is believed to contribute to the pathologic changes occurring in islets including the depletion of beta cells [21].

CONCLUSIONS

The pathogenesis of hyperglycemia in SDT rats is believed to be heterogeneous, involving both a marked decrease in insulin-secreting capacity related to dysfunction in beta cells and probably hepatic insulin resistance. SDT rats have unique and important properties relevant to the understanding of type 2 diabetes. Thus, the SDT rat could play important role as an animal model for studying diabetes, and may yield insights useful in developing new treatments for diabetes.

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