Obese Type 2 Diabetic Model
SDT fatty rats
Rat Model with Early Onset of Diabetic Complications
SDT fatty rats become overtly obese just after weaning and are distinguishable from normal or original SDT rats, and show significant polyphagia. Body weights of male SDT fatty rats reach 500-600 g at 16 weeks (Figure 1). SDT fatty rats show hyperglycemia much earlier than original SDT rats and show slightly higher blood glucose level even just after weaning. Blood glucose level reaches 600 mg/dl at 8 weeks of age, and 800 mg/dl at 12 weeks and thereafter (Figure 2). Hyperlipidemia is also observed in SDT fatty rats2). Blood insulin levels increase at 4-8 weeks of age and decrease thereafter (Figure 3). Histopathologically, hypertrophy, vacuolation, and irregular shape in pancreatic islet are found (Figure 4, 13 weeks).

In addition, computerized tomography (CT) shows excess accumulation of abdominal/subcutaneous fat. Noticeable fatty liver is also observed in SDT fatty rats4). These features make SDT fatty rat a highly obese model associated with disorder of lipid metabolism. Furthermore, increased diastolic blood pressure6) (from 8 weeks of age) suggests use of SDT fatty rats as model of metabolic syndrome. All of these pathophysiological observations are found in both male and female SDT fatty rats5).

Background and Origin

In 2004, Dr. Masuyama and Dr. Shinohara (Research Laboratories of Torii Pharmaceutical Co., Ltd., Japan) established the congenic type 2 diabetes model Spontaneously Diabetic Torii fatty (SDT fatty) rat by introducing the fa allele of the Zucker Fatty rat into the genome of the original SDT rat1). SDT fatty rats were introduced to Central Pharmaceutical Research Institute, Japan Tobacco Inc. (Japan) and were characterized in detail by Dr. Ohta and Dr. Sasase. CLEA Japan has received right of production and sales from Japan Tobacco Inc., and has distributed the animals as SDT fatty rats from 2012.
**Diabetic ocular complications**

With elevated glucose level from young age, macroscopic opacity occurs in the SDT fatty rat from 8 weeks of age and progresses severely to mature cataract in almost all animals by 16 weeks of age\(^2\). Retinal lesions (retinal folding and thickening) and inflammation in the choroid (uveitis) are observed in SDT fatty rats at 50 weeks of age (Figure 5) \(^17\). Uveitis associated with diabetes has been reported in humans; however, there has been no report of a spontaneous diabetes animal model affected with uveitis.

SDT fatty rats after 16 weeks of age show a prolongation of the peak latency on an electroretinogram\(^2\). On the other hand, fibrous proliferation and following tractional retinal detachment observed in the original SDT rats are not observed in SDT fatty rats up to 60 weeks of age.

**Diabetic nephropathy**

SDT fatty rats show marked polyuria accompanied by glucosuria and proteinuria due to persistent hyperglycemia from early age. Histopathologically, glycogen deposition in the renal tubule (Armanni-Ebstein change) and tubular dilatation caused by polyuria are observed from 8 weeks of age. In the glomerulus, increased mesangial matrix and diffuse glomerulosclerosis are observed, and the nodular-like lesion appears in the mesangium from approximately 40 weeks of age (Figure 6). Tubulointerstitial lesions including fibrosis, inflammatory cell infiltration, and regeneration of tubules are observed after 50 weeks of age\(^18\).

**Diabetic neuropathy**

SDT fatty rats show diabetic peripheral neuropathy concomitant with severe hyperglycemia. In an electrophysiological study, the caudal motor nerve conduction velocity (MNCV) in SDT rats was decreased at 24 weeks of age and it became clear with age (Figure 7). Decreased caudal blood flow and excess sorbitol accumulation in sciatic nerve were also observed. Morphologically, the number of aural nerve fibers was lower at 40 weeks of age, and occluded/thickened epineurial arterioles were frequently found in SDT fatty rats\(^16\). SDT fatty rats are susceptible to diabetic diarrhea, suggesting development of diabetic autonomic neuropathy.

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**Figure 5.** Histopathological findings in ocular of female SDT fatty rat (50 weeks of age)

**Figure 6.** Histopathological findings in kidney of male SDT fatty rats (24, 40 weeks of age)

**Figure 7.** Changes in MNCV of male SDT fatty rats (*P < 0.05, **P < 0.01**)*
SDT fatty rats show osteoporosis with low bone turnover, unlike an ovariectomized model. Levels of serum osteocalcin, a bone formation marker, and urine deoxypyridinoline (DPD), a bone resorption marker, are decreased from 8 weeks of age in SDT fatty rats (Figure 8). At 40 weeks of age, SDT fatty rats show low bone mineral density (BMD), shortening of bone length, and deterioration in trabecular bone microstructure (Figure 9) of the long bones. Furthermore, high serum homocysteine levels in SDT fatty rats at 32 weeks of age suggest deterioration in bone quality. Parathyroid hormone (PTH) injections suppress a decrease in BMD and also decrease serum glucose levels in SDT fatty rats.

Diabetic osteoporosis

Several anti-diabetic drugs such as biguanide (metformin), thiazolidinedione (pioglitazone), and DPPIV inhibitors improve hyperglycemia in SDT fatty rats. Controlling blood glucose level from early stage can retard progression of insulin hyposecretion\(^9\) and diabetic complications, such as diabetic peripheral neuropathy\(^19\).

Pharmacological treatment

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Conclusion

In addition to early development of hyperglycemia, multiple features such as obesity, hypertension, and osteoporosis make SDT fatty rat a useful model for diabetes, diabetic complications, and metabolic syndromes. The characteristics of SDT fatty rat are also suitable for use in drug discovery of these diseases.
In SDT fatty rats, glucosuria appears on ingestion of standard diet for mice and rats. Their diet intake increases (more than 2 to 3 times that of SD rats, approximately 60 g/day) and water intake also significantly increases (300 to 400 ml/day and more) with the onset of diabetes. It is therefore important for the rats to always have sufficient amounts of diet and drinking water.

SDT fatty rats urinate often and their bedding easily becomes soiled after onset of diabetes, exposing them to development of urinary tract infections. To avoid such infections, rats should be reared individually, and a large amount of bedding should be provided in plastic cage housing. Frequent replacement of cages should be recommended in both plastic cages and bracket cages.

**Notes on rearing and handling SDT fatty rats**

**Diet and drinking water**

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**High-volume bedding and frequent cage-change are recommended**

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References
17) 正崎佐也, 萩賀香彦, 安井雄三, 益山拓, 太田敏: 萩賀香彦, 齋本知之. Spontaneously Diabetic Torii (SDT) fatty ラットにおける自然発生性どうぶつの現象について：病理組織学的検討. 第26回日本動物病院学会誌. 大宮, 2011年.

Remarks: Strain name
Please note that the common name of “SDT fatty” is shown on the shipping documents while the strain has the nomenclature of “SDT.Cg-Lepr<sup>α</sup>/JttJcl” according to the Guidelines for Nomenclature of Mouse and Rat Strains.