

PhysioGenix Disease Rat Models

Delivering Solutions

The rapid worldwide growth in the incidents of cardiovascular, metabolic and renal disease has lead to an accelerated effort to find cures for these diseases. PhysioGenix supports these research efforts with our best in class research models.

Type II Diabetic Nephropathy (T2DN) Rat: Non-obese, type II diabetes and renal disease model.

The T2DN rat was developed by combining the genomes of the Goto-Kakizaki (GK) rat, which develops diabetes but not renal disease, with important regions of the genome of the Fawn Hooded Hypertensive (FHH) rat, which develops renal disease but not diabetes.

Our patented T2DN rat model displays early-onset of type II diabetes with insulin-resistance and lipid disorders. The model also recapitulates the chronology of events in diabetes and the histological changes in diabetic-nephropathy that are characteristic of diabetic patients. The model is typically used for proof-of-concept studies in younger animals and as a model system for progressive renal disease resembling those seen in humans, in the older animals.

Reference: Nobrega, M.A. Initial characterization of a rat model of diabetic nephropathy. *Diabetes*. 2004 March; 53(3):735-742.

Zucker Diabetic Fatty (ZDF) Rat: Obese, type II diabetes model.

Obese males develop sustained hyperglycemia and hyperlipidemia while insulin levels evolve from hyperinsulinemic to hypoinsulinemic. The model also develops renal hypertrophy and progressive focal segmental glomerulosclerosis.

References: Leonard B.L., et al. Insulin resistance in the Zucker diabetic fatty rat: a metabolic characterization of obese and lean phenotypes. *Acta Diabetol*. 2005 December; 42(4):162-170.

Schmidt, R.E., et al. Analysis of the Zucker Diabetic Fatty (ZDF) type 2 diabetic rat model suggests a neurotrophic role for insulin/IGF-I in diabetic autonomic neuropathy. *Am J Pathol*. 2003; 163(1), 21-28.

Obese Zucker Rat: Obese metabolic syndrome model.

With increasing age obese Zucker rats spontaneously develop proteinuria and focal segmental glomerulosclerosis, ultimately leading to renal failure.

References: Augstein, P. & Salzsieder, E. Morphology of Pancreatic Islets: A time of Pre-diabetes in Zucker Fatty Rats. *Methods Mol Biol*. 2009; 560,159-189.

Frisbee JC. Hypertension-independent microvascular rarefaction in the obese Zucker rat model of the metabolic syndrome. *Microcirculation*. 2005 July-August; 12(5):383-392.

Dahl/Salt Sensitive (Dahl/SS) Rat: Hypertensive and renal failure model.

Developed from a congenic group of Dahl/SS rats that develops hypertension and renal failure when fed diets with high salt content.

References: Mattson DL, et al. Chromosome substitution reveals the genetic basis of Dahl salt-sensitive hypertension and renal disease. *Am J Physiol Renal Physiol*. 2008 September 1; 295(3):F837-F842.

Mattson DL, et al. Influence of diet and genetics on hypertension and renal disease in Dahl salt-sensitive rats. *Physiol Genomics*. 2004 January 15; 16(2):194-203.

Dahl/SS - SS-13BN Rat: Normotensive control model.

A consomic rat developed at the Medical College of Wisconsin, in which chromosome 13 from the normotensive inbred Brown Norway rat was introgressed into the background of the Dahl/Salt Sensitive rat. The model is used as a control for the hypertensive Dahl/SS rat. The model is insulin resistant, hyperinsulinemia, hypertriglyceridemia and normotensive control.

References: Cowley Jr., A.W., et al. Genetically defined risk of salt sensitivity in an intercross of Brown Norway and Dahl S rats. *Physiol Genomic*. 2002 2,107-115.

Liang, M., et al. Renal medullary genes in salt-sensitive hypertension: a chromosomal substitution and cDNA microarray study. *Physiol Genomics*. 2002; 28.8,139-149.

Spontaneously Hypertensive (SHR) Rat: Hypertensive model.

The model was initiated with an outbred Wistar Kyoto male with marked elevation of blood pressure mated to a female with slightly elevated blood pressure.

References: Okamoto, K. Spontaneous hypertension in rats. *Int Rev Exp Pathol.* 1969; 7, 227-270.

Swislocki A, & Tsuzuki A. Insulin resistance and hypertension: glucose intolerance, hyperinsulinemia, and elevated free fatty acids in the lean spontaneously hypertensive rat. *Am J Med Sci.* 1993 November; 306(5):282-286.

Goto-Kakizaki (GK) Rat: Non-obese, type II diabetes model.

The Goto-Kakizaki rat is a non-obese Wistar substrain that develops adult onset type II diabetes early in life.

References: Cowley AW Jr. Genetically defined risk of salt sensitivity in an intercross of Brown Norway and Dahl S rats. *Physiol Genomic.* 2002; 2,107-115.

Ostenson, C.G. The Goto-Kakizaki Rat. *Animal Models of Diabetes Frontiers in Research*, 2nd edition. Edited by Eleazar Shafir. CRC Press 2007; 119-137.

| Characteristic | T2DN | ZDF | Zucker | Dahl/SS | Dahl/SS - SS-13BN* | SHR | GK |
|---------------------------|------|-----|--------|---------|--------------------|-----|----|
| Insulin Resistance | + | + | + | + | + | + | + |
| Hyperinsulinemia | + | + | + | + | + | + | + |
| Type II Diabetes | + | + | - | - | - | - | + |
| Fasting Hyperglycemia | + | + | - | - | - | - | + |
| Hypertension | - | - | - | + | - | + | - |
| Obesity | - | + | + | - | - | - | - |
| Cardiovascular Disease | - | - | - | - | - | - | - |
| Hypertriglyceridemia | + | + | + | + | + | + | - |
| Hypercholesterolemia | + | + | + | + | + | + | - |
| Nephropathy | + | +,1 | +,1 | + | + | - | + |
| Leptin Receptor Defect | - | + | + | - | - | - | - |
| Special Diet Requirements | - | + | - | + | + | - | - |
| Genetics | H | I | O | I | C | I | I |

+ = Exhibits the Characteristic
 - = Does Not Exhibit the Characteristic
 1 = Hydronephrosis (Interference)
 I = Inbred
 O = Outbred
 H = Hybrid
 C = Consomic
 * Dahl/SS Control

Lab Induced Characteristics

We have become a leader in preclinical contract research by providing value add customization to every study that precisely meets our clients' needs.

Surgical

Diabetes

- STZ - Chemically induced pancreatic necrosis of the insulin producing beta cells to produce an animal model that has type I diabetes.
- 5/6 Nephrectomy - Surgical removal of one kidney and 2/3 of the other kidney leading to distinct rises in blood urea nitrogen and in renal excretion of proteins indicate the impairment of the kidney.

Technique

Diabetes

- Clamp - The hyperglycemic clamp is a way to quantify beta-cell response to glucose. The hyperinsulinemic euglycemic clamp is a way to quantify sensitivity to insulin.

Chemical

Diabetes

- High Fructose Diet
- High Sucrose/Low Copper Diet

Hypertension

- L-Name - A non-selective inhibitor of nitric oxide synthase.
- High Salt Diet
- High Fructose Diet

Our highly skilled team is capable of delivering a wide-range of studies utilizing research models, surgical procedures and diets not listed. Call PhysioGenix at 1-888-PGNX-CRO to work with our Senior Study Director to build a study based on your specific needs.