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The Zucker Diabetic Fatty (ZDF) Rat

Diet Evaluation Study for the Induction of Type 2 Diabetes in Obese Female ZDF Rats

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Strain Origin

A mutation occurred in a colony of outbred Zucker rats in the laboratory of Dr. Walter Shaw at Eli Lilly Research Laboratories in Indianapolis, IN, in 1974-75. In 1977, part of this colony containing the mutation was moved to the laboratory of Dr. Julia Clark at Indiana University Medical School (IUMS). Several groups of animals with diabetic lineage were identified and rederived in 1981. Inbreeding of selected pairs from this rederivation was performed in the laboratory of Dr. Richard Peterson at IUMS. An inbred line of the Zucker Diabetic Fatty (ZDF) rat was established by Dr. Peterson in 1985. This colony was transferred to Genetic Models, Inc., in 1991 and then to Charles River in 2001.

Characteristics

Characteristics of the obese male ZDF rat maintained on Purina 5008 diet include hyperinsulinemia and hyperglycemia, type 2 diabetes (T2D), insulin resistance and obesity beginning at six to seven weeks of age. By 10-12 weeks of age, glucose levels steadily increase, reaching an average of approximately 500 mg/dL. During this same period, insulin production gradually decreases until the plasma insulin concentration reaches approximately 1 ng/mL or less.

Unlike the male, the female ZDF does not develop diabetes on the Purina 5008 diet as assessed by the oral glucose tolerance test. However, it does develop metabolic syndrome as characterized by raised insulin and glucose levels.

Introduction

The obese male ZDF rat plays a pivotal role in studying the cascade of physiologic events associated with the onset and treatment of T2D. The female ZDF can also be used as a model for T2D, but unlike the male, the female requires dietary modification to induce the diabetic state.

Historically, females fed Research Diets (RD) C13004 diet starting at six weeks of age consistently developed diabetes by 12 weeks of age. The C13004 diet consists of a grain base supplemented with added fat. During the fall of 2007, several research groups reported to Charles River that female ZDF rats fed C13004 did not reliably develop diabetes. Charles River conducted a 14-week study feeding obese female ZDF rats the C13004 diet and confirmed that this specialized diet no longer induced diabetes in this model. In conjunction with RD and Purina Lab Diets, Charles River learned that a modification in a specific fat component of the diet had occurred just prior to the initial customer reports. Subsequently, Charles River implemented a number of studies with the objective of identifying a diet that reliably induced diabetes in female obese ZDF rats.

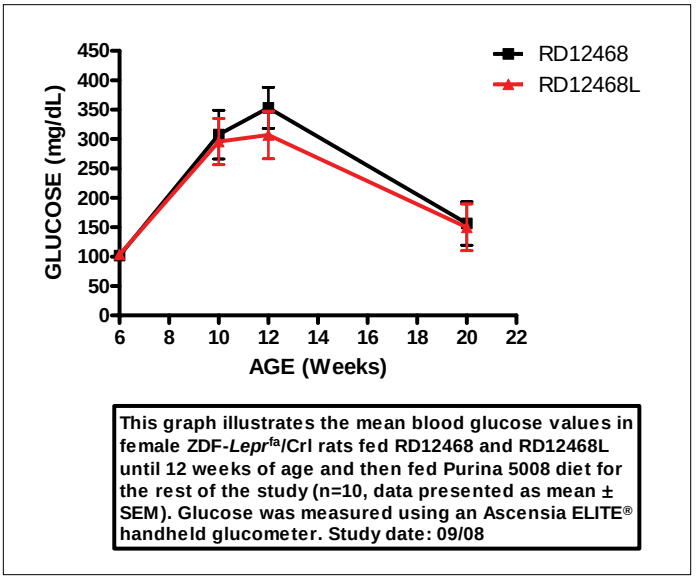
Study

An initial study using RD 12468 and 12468L (in which lactoalbumin was added as an additional protein source) was conducted. Both diets were reported to induce hyperglycemia in ZDF females. However, upon removing each of the test diets and placing the animals on Purina 5008 (at 12 weeks of age), the hyperglycemic state resolved in the animals (see Figure 1).

Next, a follow-up study was conducted to determine whether diabetes could be induced and maintained if the study animals were kept on RD 12468 for a longer time period. A group of ZDF females (N=20) were fed diet RD 12468 from five weeks of age through 20 weeks of age. The RD 12468 with lactoalbumin was not evaluated because we found no statistical difference between the two diets with regards to induced raised glucose levels in the first test. Insulin and glucose values were collected from 12 to 18 weeks of age and the results demonstrated that a continuous diet of RD 12468 resulted in a sustained hyperglycemia accompanied by a gradual decrease in serum insulin levels (see Figure 2), both of which indicate that the study animals became diabetic.

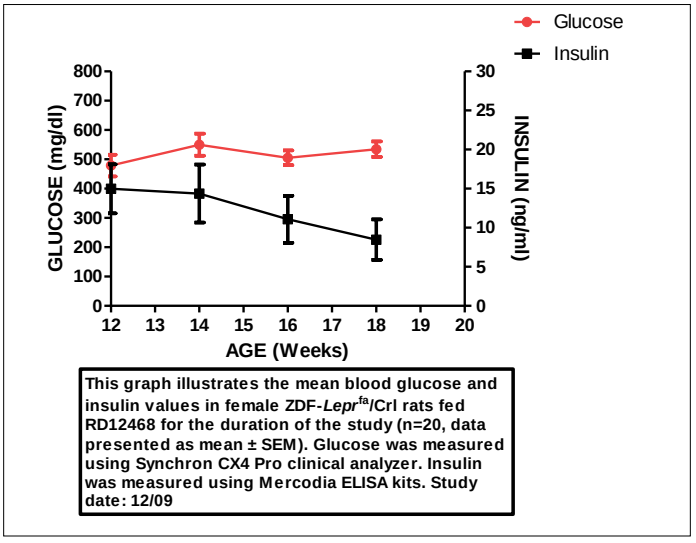
For further validation, two follow-up studies, each consisting of 20 female ZDF rats, were conducted following a similar protocol to the one above. In Study 1, the females (N=20) received RD 12468 until 18 weeks of age, followed by a diet of Purina 5008. The females in Study 2 remained on diet RD 12468 throughout the 26-week study period. Figures 3 and 4 illustrate that a diabetic phenotype was achieved and maintained in both studies regardless of whether the diet switched back to Purina 5008.

Figure 1: Fed Glucose, Obese Female ZDF Rats



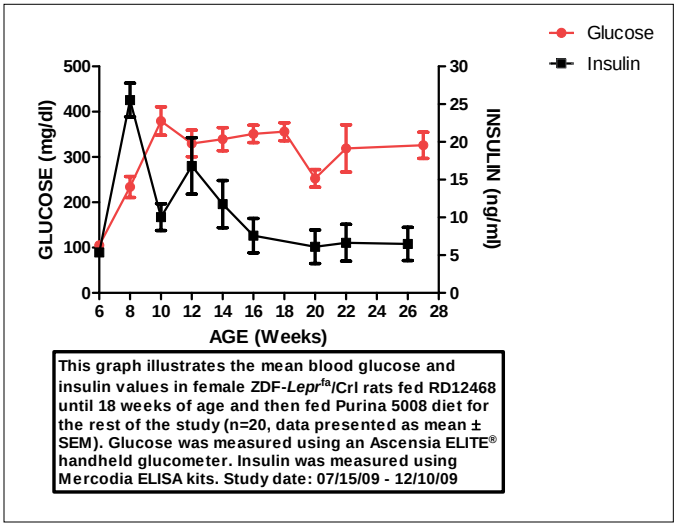
Glucose level of female obese ZDF rats fed RD 12468 and 12468L, respectively, over a period of six weeks.

Figure 2: Fed Glucose and Insulin, Obese Female ZDF Rats



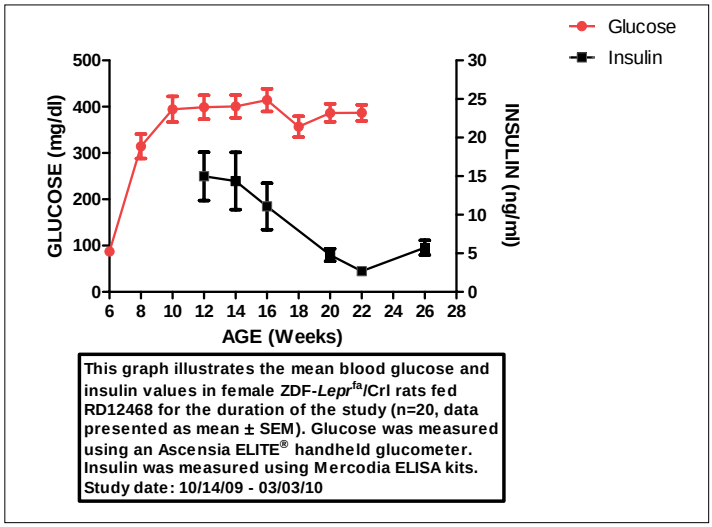
Glucose and insulin values of female obese ZDF rats fed RD 12468.

Figure 3: Fed Glucose and Insulin, Obese Female ZDF Rats



Glucose and insulin levels of female obese ZDF rats fed RD 12468 until 18 weeks of age, at which time the diet was replaced with Purina 5008 (Study 1).

Figure 4: Fed Glucose and Insulin, Obese Female ZDF Rats



Glucose and insulin values of female obese ZDF rats fed RD 12468 over a period of 26 weeks (Study 2).

Summary

Although older studies documented that obese female ZDF rats became diabetic when fed RD C13004, beginning in 2007, Charles River received several reports from researchers that these rats no longer developed diabetes when placed on this diet. Subsequently, Charles River learned that certain nutritional components of RD C13004 had been modified. After first ruling out environmental and genetic factors as possible causes of the loss of the diabetic phenotype, Charles River experimentally evaluated the RD C13004 diet and confirmed that it no longer reliably produced diabetes in the obese female. Subsequently, Charles River performed a series of studies that indicated that the semi-purified diet RD 12468 reliably produced a diabetic phenotype, indicated by hyperglycemia and insulinopenia, in the female ZDF rat.

Charles River recommends that investigators consider utilizing RD 12468 to reliably induce a diabetic phenotype in the female ZDF rat. Alternatively, Charles River can provide preconditioned female ZDF rats fed RD 12468 upon request.

References

Shafrir, E. *Animal Models of Diabetes: Frontiers in Research*. 2nd ed. 1-357 (CRC Press, Boca Raton, 2007).

technical sheet

Charles River Disease Models

As the prevalence of certain diseases continues to increase worldwide, the need for new ways to explore the mechanisms of disease has become paramount. Charles River's portfolio of research animal models, which includes cardiovascular, metabolic, renal and oncologic disease models, helps ensure that you will have the optimal resources available in your chosen area of research.

Characteristic	THE POUND MOUSE™	OP-CD	OR-CD	Dahl/SS	SS-13^{BN}*	SHR	Stroke Prone
Insulin Resistance	+	+	+	+	+	+	+
Hyperinsulinemia	+	+	+	+	+	+	+
Type 2 Diabetes	–	–	–	–	–	–	–
Fasting Hyperglycemia	+	+	+	–	–	–	–
Hypertension	?	+	+	+	–	+	+
Obesity	+	+	–	–	–	–	–
Cardiovascular Disease	–	–	–	–	–	–	–
Hypertriglyceridemia	–	+	+	+	+	+	+
Hypercholesterolemia	+	–	–	+	+	+	+
Nephropathy	–	–	–	+	+	–	+
Leptin Receptor Defect	+	–	–	–	–	–	–
Special Diet Requirements	–	+	+	+	+	–	+
Genetics	I	O	O	I	C	I	I

Characteristic	SHROB	SHROB Lean	GK	ZDF	ZSF1	Zucker
Insulin Resistance	+	+	+	+	+	+
Hyperinsulinemia	+	+	+	+	+	+
Type 2 Diabetes	–	–	+	+	+	–
Fasting Hyperglycemia	–	–	+	+	+	–
Hypertension	+	+	–	–	+	–
Obesity	+	–	–	+	+	+
Cardiovascular Disease	–	–	–	–	–	–
Hypertriglyceridemia	+	+	–	+	+	+
Hypercholesterolemia	+	+	–	+	+	+
Nephropathy	+	–	+	+, 1	+, 2	+, 1
Leptin Receptor Defect	+	–	–	+	+	+
Special Diet Requirements	–	–	–	+	+	–
Genetics	I	I	I	I	H	O

+ = Exhibits the characteristic
– = Does not exhibit the characteristic
? = Unknown at this time
1 = Hydronephrosis (Interference)
2 = Hydronephrosis (Interference) is found infrequently

I = Inbred
O = Outbred
H = Hybrid
C = Consomic
**Dahl/SS control*

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