The highly immunodeficient SRG Rat™ for modeling diabetes

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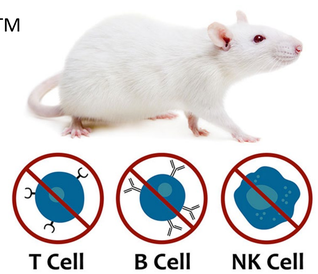
Abstract

Immunocompromised rodents are essential for pre-clinical testing of cell-based therapies. The SRG rat (Sprague Dawley Rag2-/-, Il2rg-/-) lacks mature B, T, and NK cells, and is normoglycemic under standard conditions. Compared to mice, the SRG rat offers more human-like metabolism, easier surgical manipulations, and greater volume and frequency of blood collection. Compared to nude rats, the SRG is more permissive to a wider range of human xenografts. Given the advantages of the SRG rat, we determined whether it could serve as a model of streptozotocin-induced (STZ) Type 1 Diabetes or diet-induced obesity (DIO) as a model of Type 2 Diabetes. We compared the effects of STZ on blood glucose levels in SRG versus wild-type Sprague Dawley (SD) male rats. Rats were given vehicle, STZ 40 mg/kg, or STZ 65 mg/kg. After low dose STZ, day 6 non-fasting glucose was 262 ± 41 (SEM) mg/dL in SD rats and 565 ± 64 (SEM) mg/dL in SRG rats. After high dose STZ, day 6 non-fasting glucose was 679 ± 23 (SEM) mg/dL in SD rats and 505 ± 72 mg/dL in SRG rats. Weight loss associated with hyperglycemia was more pronounced in SRG rats compared to SD rats. To induce T2D, obesity, and insulin resistance, SRG rats were fed control or high fat diet (60% kcal from fat). Food intake and body weight were measured weekly. SRG rats underwent IPGTT (after 10 and 24 weeks of high fat diet) and ITT (after 11 weeks of high fat diet). Compared to low fat diet, DIO rats had increased caloric intake and body weight throughout the study. After 10 weeks, DIO rats had impaired glucose tolerance without elevated fasting insulin. Insulin tolerance did not differ at 11 weeks. At 24 weeks, glucose tolerance did not differ between diet groups, but DIO SRG rats displayed elevated fasting insulin ($P < 0.01$). In conclusion, SRG rats display increased sensitivity to 40 mg/kg STZ when compared to SD rats, with rapid induction of weight loss and hyperglycemia. The SRG glycemic response to chronic DIO is complex and changes over time.

Background

The SRG Rat™



- Severe combined immunodeficient (SCID) rat
- Sprague-Dawley background
- Rag2, Il2Rγ double knockout
- Lacks B-cells, T-cells, and NK-cells.
- Enhanced xenograft engraftment versus Nude rats
- Allows for early in vivo testing of cell-based therapeutics
- Combined efficacy, PK/PD/tox, and biomarker studies

STZ-induced diabetes in SRG vs SD

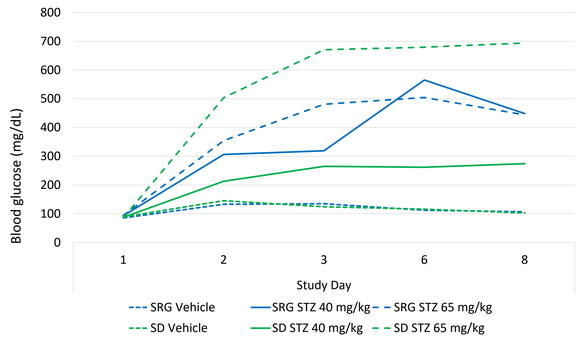


Figure 1. Compared to the parental Sprague Dawley strain, the SRG is more sensitive to streptozotocin (STZ)-induced diabetes. In SRG rats, 65 mg/kg STZ caused severe weight loss (data not shown). All rats were 8-week-old males. N = 5/vehicle group. N = 10/STZ group.

Diet-induced obesity in the SRG Rat

Study Design

Male rats were 8-10 weeks old at start of study.

Diets: Research Diets D12450K-I, 10% kcal from fat, N = 6
Research Diets D12492-I, 60% kcal from fat, N = 27-29

Week						
0		10	11	12	24	26
Begin high fat diet		GTT	ITT	Serum lipids	GTT	Serum lipids

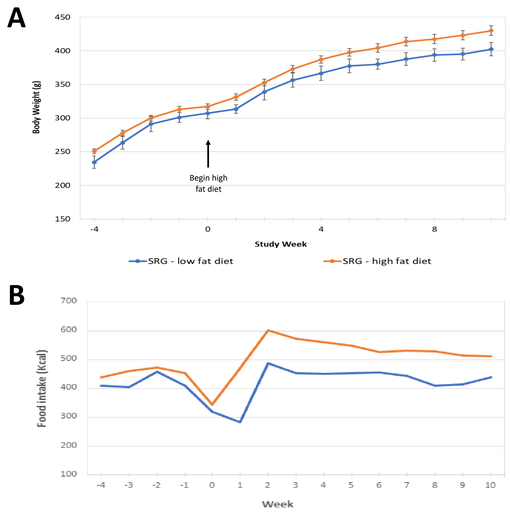


Figure 2. The SRG Rat exhibits moderate increases in A) body weight, and B) caloric consumption when fed high fat diet.

Table 1. Serum lipid summary in HFD versus LFD

Week	Triglycerides	Total Cholesterol	NEFA
12	=	↑	=
26	=	↑	=/↓

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Diet-induced obesity in the SRG Rat

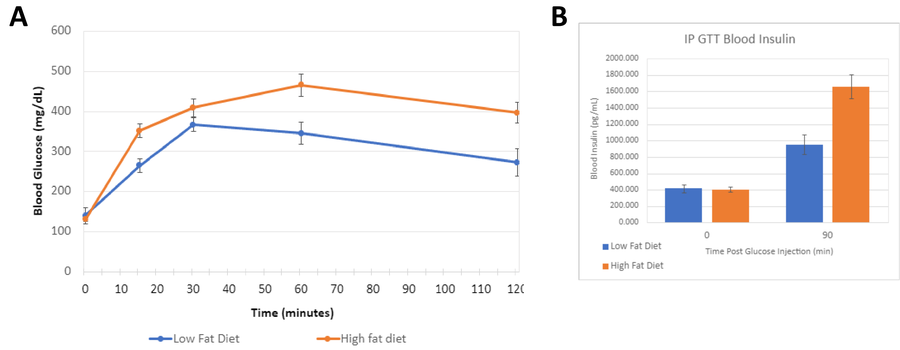

Figure 3. Impaired glucose tolerance following 10 weeks of high fat diet. A) High-fat-fed SRG rats show prolonged hyperglycemia after i.p. injection of 3 g glucose/kg body weight. B) High-fat-fed SRG rats display increased insulin at 90 minutes after glucose injection. Insulin measured using the MSD electrochemiluminescent platform.

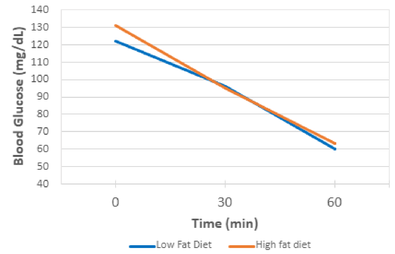

Figure 4. 11-week insulin tolerance. The SRG Rat does not exhibit impaired insulin tolerance following 11 weeks of high fat diet. Rats received 1.5U insulin/kg body weight.

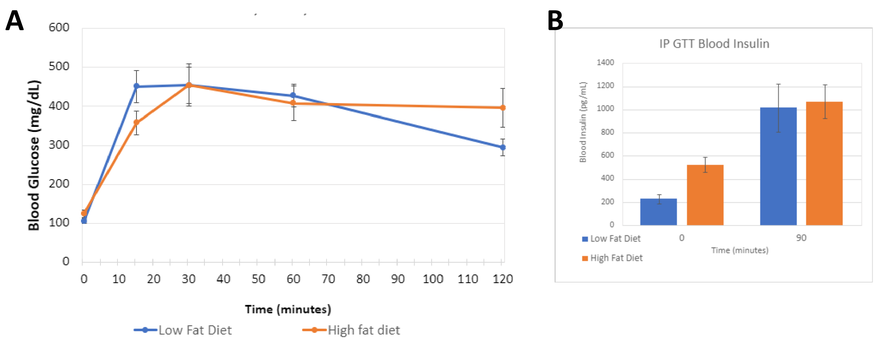

Figure 5. 24-week glucose tolerance. After 24 weeks of high fat diet, glucose tolerance did not differ from low-fat-fed. A) Both high- and low-fat-fed SRG rats show hyperglycemia after i.p. injection of 3 g glucose/kg body weight. B) High-fat-fed SRG rats display increased fasting insulin at baseline, with no difference in insulin levels at 90 minutes after glucose injection.

Conclusions

- Compared to Sprague Dawleys, SRG rats are more sensitive to STZ-induced diabetes, with marked hyperglycemia and rapid weight loss. 65 mg/kg STZ is not tolerated by SRG rats.
- With chronic fed high fat diet feeding, SRG rats exhibit a complex phenotype, with impaired glucose tolerance after 10 weeks of high fat diet. After 24 weeks on high fat diet, glucose tolerance did not differ from low-fat-fed rats, potentially due to increased age of all rats, or due to compensatory hyperinsulinemia in high-fat-fed rats.