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Research Horizons Day

Liver *Ubd* is Upregulated in the Lew.1WR1 Rat

Helen Gibson[1], Amelia Clopp[1], Genoah Collins[2], Sharifa Love-Rutledge[2]
Department of Biology[1] Department of Chemistry[2],

Abstract

Diabetes prevention is a large topic of research that is focused on nutritional and exercise-based interventions with some genetic predisposition based interventions. Ubd is a ubiquitin-like protein and Type 1 Diabetes (T1D) susceptibility gene that may play a role in age-related inflammation, adiposity, cancer, and kidney disease. The young T1D susceptible, LEW.1WR1 rat overexpresses *ubd* in the pancreatic lymph node during the induction of type 1 diabetes,[1] but little is known about the *ubd* expression profile of other organs in this model. It is also unclear if the insulin sensitivity of this animal model plays a role in T1D disease susceptibility. In an aging study of these rats, we observed an increase in body mass, epididymal fat mass, and glucose intolerance by 14 weeks of age relative to a control strain of rat containing a parental haplotype.[2] Because Ubd has been proposed to regulate beta-oxidation,[3] we hypothesized that young adult LEW.1WR1 rats have markers of increased insulin resistance like reduced gene expression of lipolytic genes. Although several lipolytic genes were downregulated. We have also confirmed that *ubd* expression is significantly upregulated. The objective of this study was to characterize gene expression in insulin-regulated pathways like lipid breakdown relative to a glucose-intolerant phenotype to identify if the expression of genes related to insulin sensitivity was affected in the livers of glucose-intolerant young adult LEW.1WR1 rats.

Results & Discussion

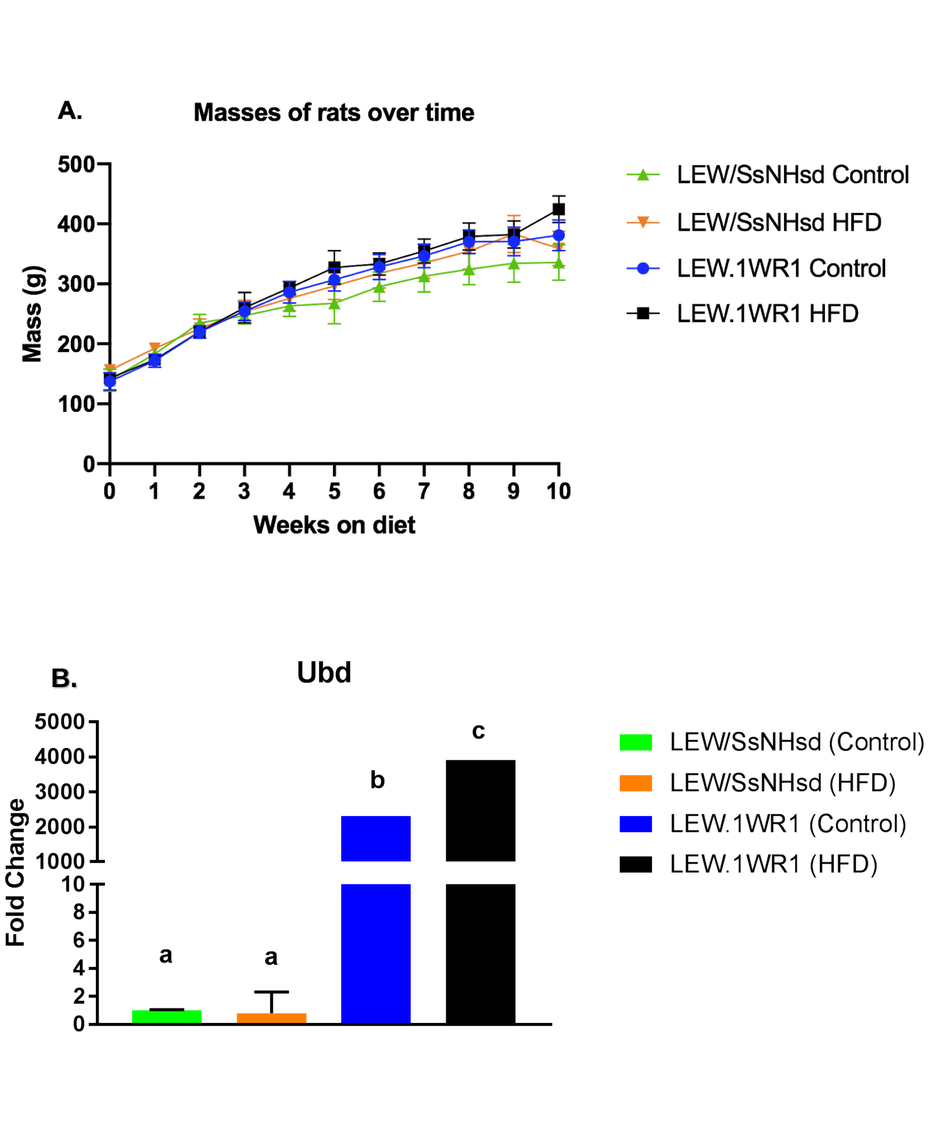

Figure 1. **Body Mass and Ubd Gene Expression.** A. Body Mass was measured twice weekly during the duration of the experiment. Throughout the experiment the WR1 Control, HFD, and SsNHsd HFD rat showed mirrored growth suggesting all three groups have increased adiposity. All groups of rats had no significant differences in food consumption. B. *Ubd* was significantly increased in the livers of the LEW.1WR1 rats as predicted.

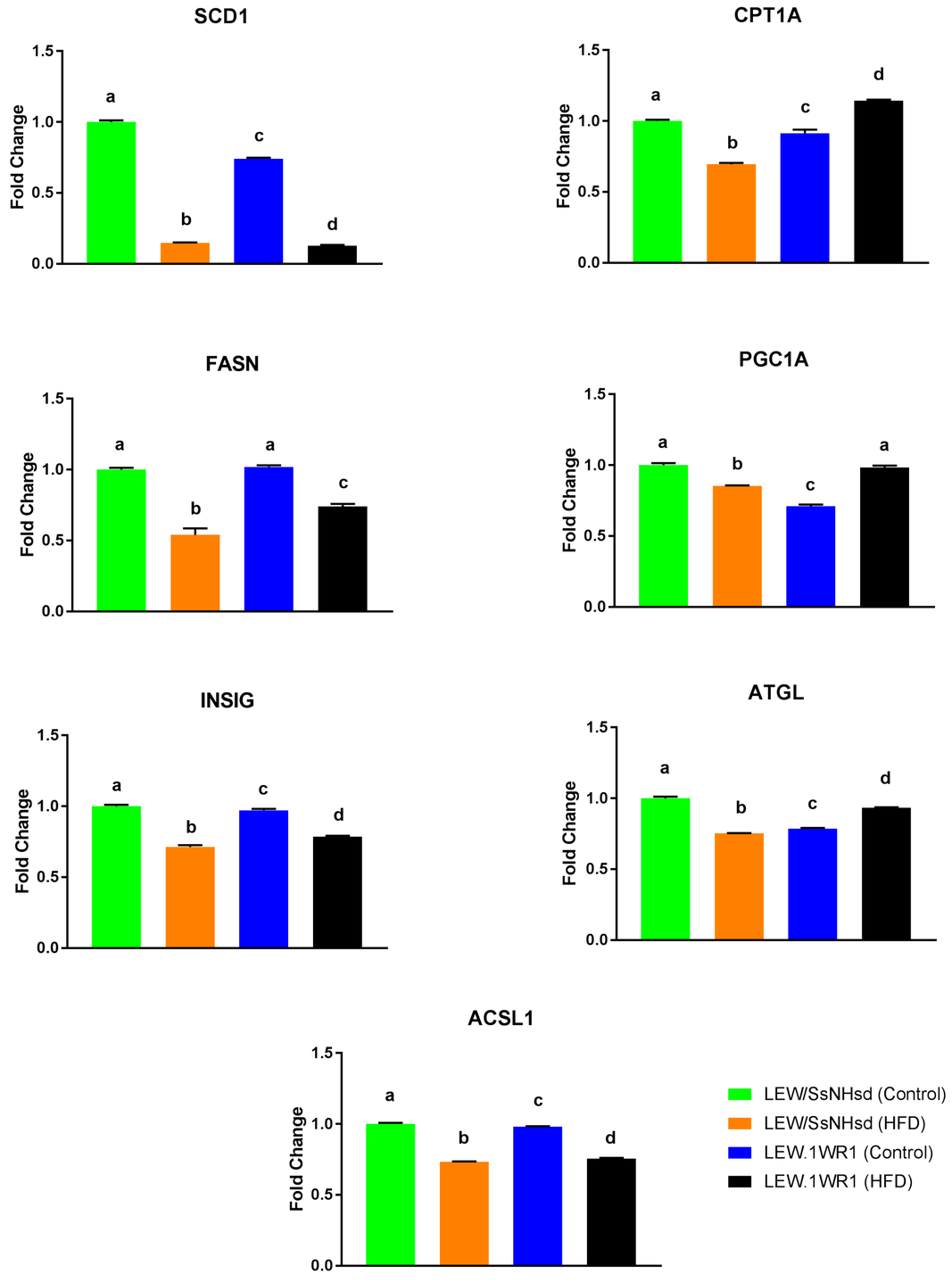

Figure 2: **Relative gene expression data.** Scd1 is downregulated in the rats fed a high fat diet. This is logical considering there is no need to synthesize fat when there is an excess in the diet. It was however interesting to see that it was decreased in the LEW.1WR1 control rat. The lipolytic genes *atgl, cpt1a,* and *pgc1a* were all significantly decreased in the control 1WR1 rats compared to the SsNHsd rats. *Acsl1* is predominant isoform of acetyl CoA synthase in the liver and can shuttle oleic acid into either cholesterol or triglyceride. Which suggests that triglyceride synthesis may be slightly reduced while lipolysis is reduced more significantly in fasting which could lead to an accumulation of lipid. Error bars represent SD of n=7 rats.

Conclusions

- LEW.1WR1 rats on control diet gain mass similar to LEW/SsNHsd rats on a high-fat diet
- LEW.1WR1 rats have significantly upregulated liver *ubd* expression while having diet-specific SCD1 gene expression changes, a gene that regulates MUFA production.
- There was a significant downregulation of lipolytic genes, a small yet significant downregulation of long chain lipogenic and cholesterol synthesis gene with the exception of FASN.
- storage genes in the liver to identify the underlying cause of glucose intolerance and increased adiposity in the LEW.1WR1 rat.

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