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Identification of genes that affect cardiac failure in diabetic Drosophila melanogaster

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Identification of genes that affect cardiac failure in diabetic *Drosophila melanogaster*

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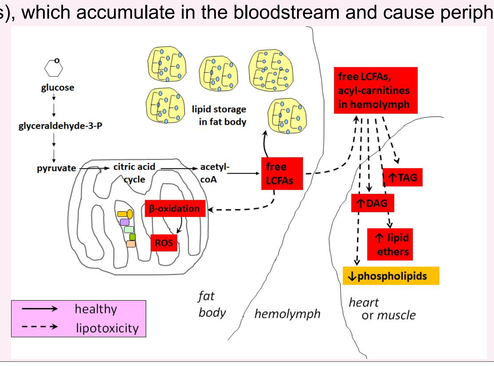
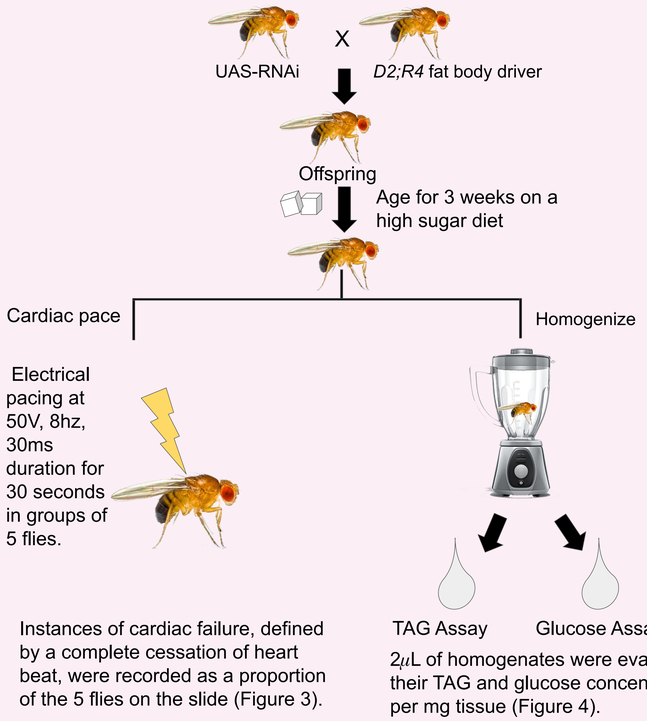
Background

- High-sugar diets exacerbate type two diabetes and cardiovascular disease in humans and model organisms, including *Drosophila melanogaster*. Type two diabetes is characterized by hyperglycemia and increased triglyceride (TAG) levels.
- High sugar diets are linked to cardiovascular disease through lipotoxicity (1).
- Lipotoxicity is thought to be a byproduct of limited fat storage where fatty acids produced beyond that limit lead to the accumulation of free floating fatty acids in the bloodstream and, ultimately, toxicity in peripheral tissues (2,3).
- While the lipids and mechanisms underlying lipotoxicity are not well understood, increased abundance of some lipids are strongly associated with impaired cardiovascular function, such as plasmalogens (4).
- Our goal is to identify lipids or proteins that ameliorate or exacerbate responses to cardiac stress-induced heart failure through tissue-specific genetic loss of function.

Figure 1. Model: High sugar feeding leads to lipotoxicity via the maximum expandability model . High sugar-induced lipogenesis makes free long chain fatty acids (LCFAs), which accumulate in the bloodstream and cause peripheral lipotoxicity.



Methods



Results

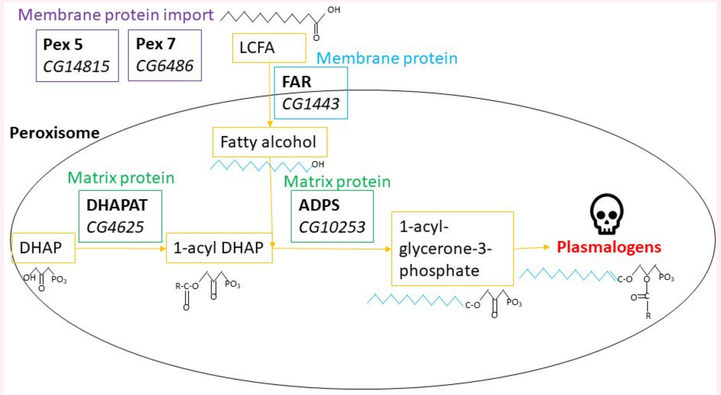


Figure 2: Plasmalogen and peroxisomal genes function in plasmalogen formation. Genes in the peroxisome were selected as genes of interest because they are responsible for the production of plasmalogen lipid species, which are seen at a higher concentration under high sugar feeding conditions. *CG14815* and *CG6486* encode a peroxisomal transport proteins Pex 5 and Pex 7, *CG1443* encodes for a fatty acyl reductase, *CG4625* encodes for dihydroxyacetone phosphate acyl transferase, and *CG10253* encodes for alkyldihydroxyacetonephosphate synthase.

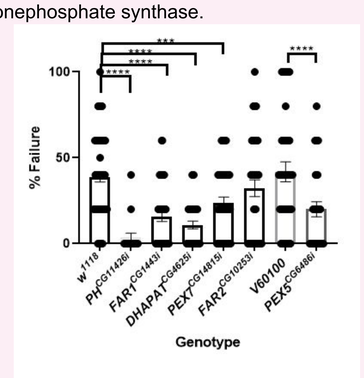


Figure 3: Plasmalogen and peroxisomal genetic knockdown show an increased resistance to cardiac pacing. Cardiac pacing phenotypes were evaluated for fat body specific (*r4-GAL4*) RNAi knockdown genotypes after three weeks of high sugar feeding. Control w^{1118} (n=345) was compared with *CG11426* (n=85,p<0.0001), *CG4625* (n=165, p<0.0001), and *CG14815* (n=205, p=0.0003).*V60100* (n=160) was compared with *CG6486* (n=150, p<0.0001). Significance was determined by a 2X2 chi squared test.

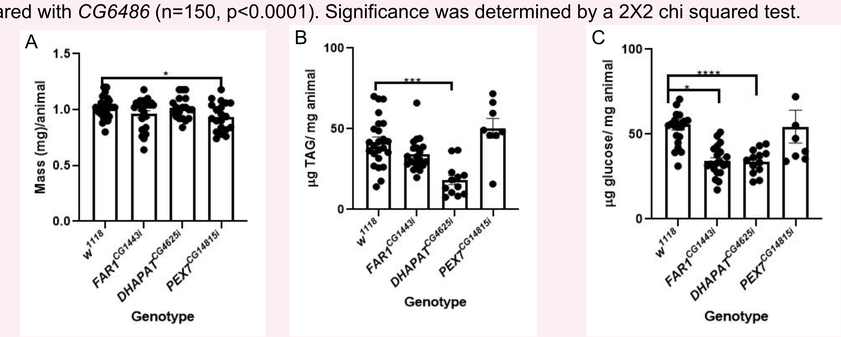


Figure 4: Diabetic phenotypes are ameliorated through plasmalogen synthesis and peroxisomal gene knockdowns. Phenotypes were evaluated for fat body specific (*r4-GAL4*) RNAi knockdown genotypes after three weeks of high sugar feeding. Genetic knockdowns in the fatty acid biosynthesis pathway revealed some statistically significant differences in weight: w^{1118} (n=20), *CG1443* (n=20,p=.1406), *CG4625* (n=8,p=0.0412),and *CG14815* (n=20,p<0.01) (A).TAG assays revealed statistically significant differences in TAG: Control w^{1118} (n=20), *CG1443* (n=20,p=.1939), *CG4625* (n=20,p=0.0002),and *CG14815* (n=20,p=.1939) (B). Genetic knockdowns revealed a decreased level in whole animal glucose compared to genetic control: w^{1118} (n=20), *CG1443* (n=20, p=0.0153), *CG4625* (n=20, p<0.0001), and *CG14815* (n=20, p=.8859)(C). Significance was determined by a Student's T Test.

Results

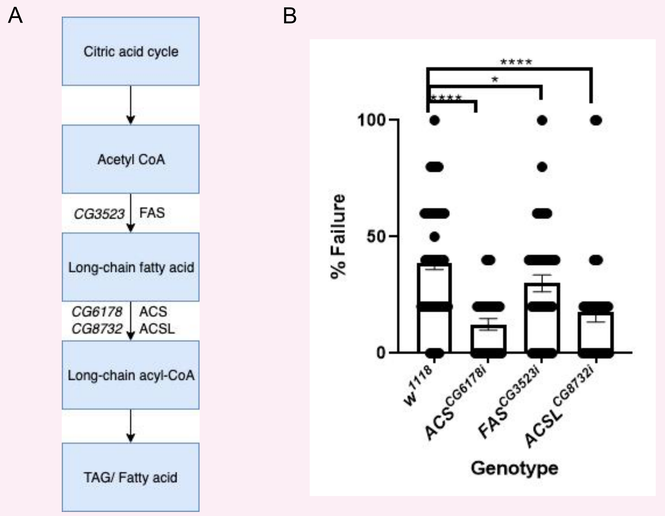


Figure 5: Fatty acid biosynthesis gene knockdowns increase resistance to cardiac stress. Cardiac pacing phenotypes were evaluated for fat body specific (*r4-GAL4*) RNAi knockdown genotypes after three weeks of high sugar feeding. Genes were selected based on their role in fatty acid biosynthesis as either a fatty acid synthase (*CG3523*), acyl-CoA ligase (*CG6178),*or a acyl-CoA synthetase long chain (*CG8732)* (A). Control w^{1118} (n=345) was compared with *CG3523* (n=220, p=0.0306), *CG6178* (n=155,p<0.0001), and *CG8732* (n=135, p<0.0001)(B). Significance was determined by a 2X2 chi squared test.

Conclusion and Future Direction

- Genetic knockdowns on the interface of the maximum expandability can ameliorate cardiac function after high sugar feeding.
- Knockdowns also display an improvement on other type two diabetes like phenotypes such as high glucose levels and high TAG levels.
- Future direction for this work is to identify and mechanistically define how these genes are contributing to cardiac lipotoxicity.

Acknowledgement

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