Analysis of the loss of Pyruvate Dehydrogenase Kinase (PDK1) on lipid metabolism

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Introduction

Pyruvate dehydrogenase kinase 1 (PDK1) inhibition has been studied as a cancer therapy due to its potent effects on decreasing tumor growth. PDK1 is the rate limiting step in the Kreb's Cycle. Intermediates of the Kreb's cycle can be used for glucose and lipid metabolism. Downregulation of other PDKs have been shown to ameliorate glucose sensitivity. The field has done more research on other isoenzymes of PDKs such as PDK2 and 4 and their role in glucose metabolism, but the effects of reduced PDK1 on metabolism has not been well studied. Here we try to identify the role of PDK1 on body weight, and lipid metabolism.

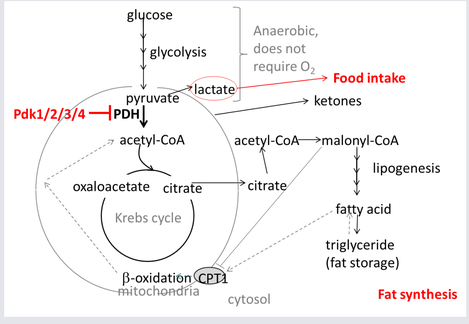

Figure 1: Role of PDKs in Glucose and Fat Metabolism. Pdk1 is a potential candidate gene for obesity and diabetes. Pdk1 inhibits Pyruvate dehydrogenase (PDH). PDH is an irreversible step. Pdk1 influences metabolism. Pyruvate flux into the Krebs cycle affects lipid metabolism.
Acetyl-CoA is a substrate for lipogenesis. Once this is converted pyruvate, it can no longer be used in gluconeogenesis. Thus Pdk1 may affect body weight, lipid and glucose metabolism.

Methods

- Pdk1 KO mice fed a High Fat Diet (HFD, D12492i Research Diets)

Body weight:

- Body weights from weaning (3 weeks- 10 weeks)
- Mesenteric fat was assessed at 16 weeks

Lipid Synthesis Test:

- Triglyceride appearance were tested using lipase inhibition with poloxamer 407 on 12 week old *Pdk1* KO mice

Lipid Tolerance Test:

- Oral lipid tolerance tests were performed on 14 week old *Pdk1* KO mice

Results

PDK1 loss on body weight

Loss of PDK1 did not change overall body weight, but reduced mesenteric weight.

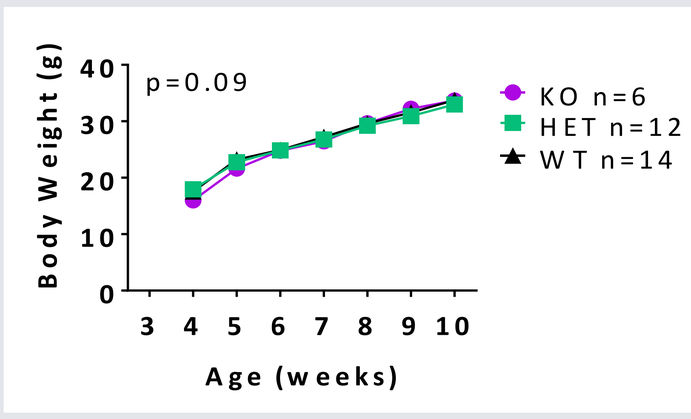

Figure 2: PDK1 KO Mice Growth Curves: body weights were measured with no significant difference (2-way ANOVA).

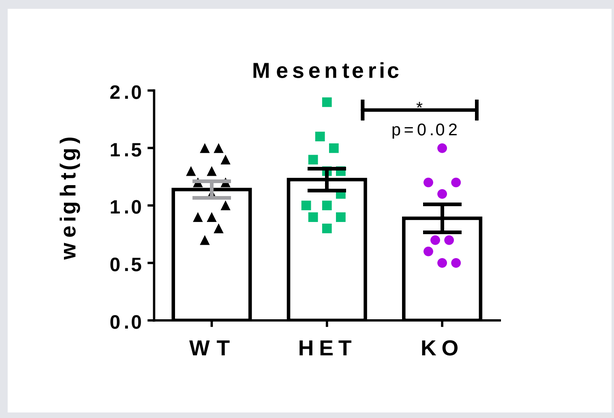

Figure 3: PDK1 mice were sacrificed at 16 weeks and were measured for their mesenteric fat. Significant difference between HET vs. KO (1-way ANOVA, *p<0.02).

PDK1 loss on lipid synthesis

To assess the effects of PDK1 loss on triglyceride synthesis, we used a triglyceride secretion assay.

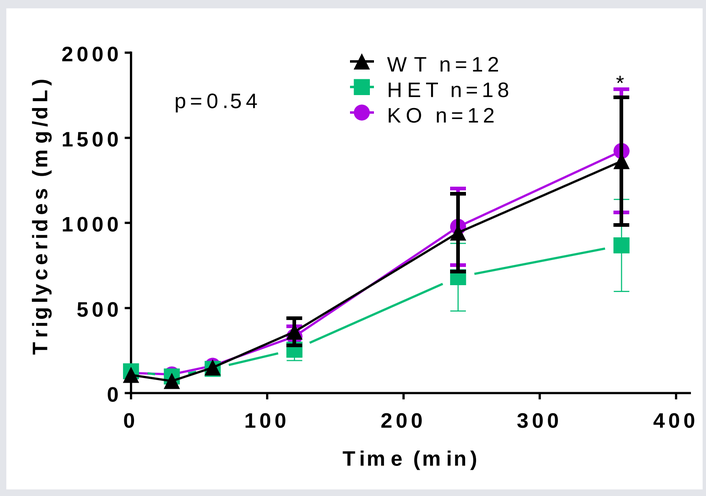

Figure 4: Triglyceride secretion in *Pdk1* mice at 12 weeks of age. (*p<0.05, for HET vs. KO) Tukey's pairwise comparison.

There was reduced triglyceride synthesis in PDK1 HET mice compared to KO.

PDK1 loss on lipid tolerance

However, lipid clearance can also cause a difference in fat stores.

To assess lipid clearance, a lipid tolerance test was conducted.

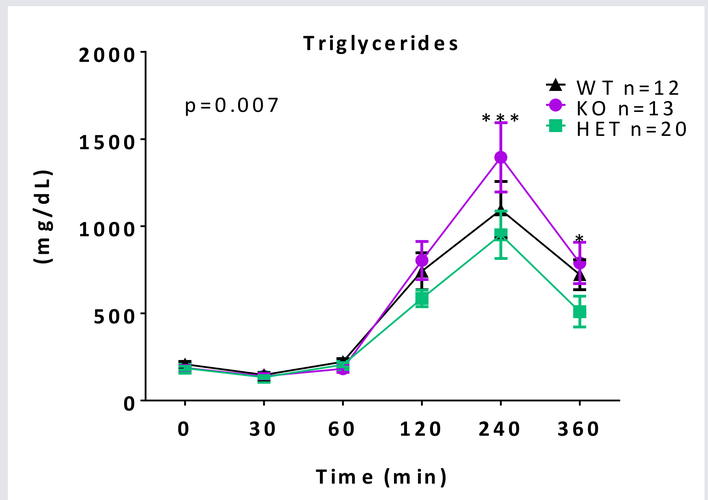

Figure 5: Lipid tolerance in *Pdk1* mice at 14 weeks of age. (*p<0.05, ***p<0.001, for HET vs. KO) Tukey's pairwise comparison.

There was increased triglyceride clearance in PDK1 KO mice compared to HET.

Discussion/Conclusion

There was increased lipogenesis and increased triglyceride clearance PDK1 KO mice compared to HET, causing a reduction in mesenteric fat in the KO mice.

The reason for the phenotype in HET mice not observed in KO is not clear. There could be compensation by other isoforms when PDK1 is lacking that does not occur when PDK1 is only partially reduced.

Together these findings suggest that having one functional copy of Pdk1, or a complete reduction may affect lipid metabolism.

Significance

- PDK1 inhibition has been studied in cancer therapy
- Dosing of PDK1 inhibition may be important to consider, as patients are put on different dosing regimens
- PDK1 could potentially be targeted for lowering triglycerides (more work needs to be done)

References

Jeoung, N. H et al. Biochem. J. 443, 829–39 (2012).

Sugden, M. C. et al. *Am. J. Physiol. Endocrinol. Metab.* **284,** E855–62 (2003)

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