Elucidating the mechanism by which the antianginal ranolazine mitigates obesity-induced nonalcoholic fatty liver disease

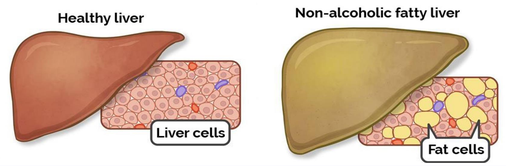
Christina T. Saed[1,2,3], Rami Al Batran[1,2,3], Keshav Gopal[1,2,3], Amanda A. Greenwell[1,2,3], Farah Eaton[1,2,3], John R. Ussher[1,2,3]

[1]Faculty of Pharmacy and Pharmaceutical Sciences.
[2]Alberta Diabetes Institute.
[3]Cardiovascular Research Centre.

INTRODUCTION

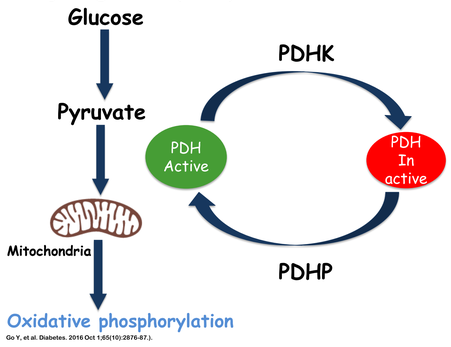
Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of excess fat (steatosis) in the liver, due to non-alcohol abuse (1).

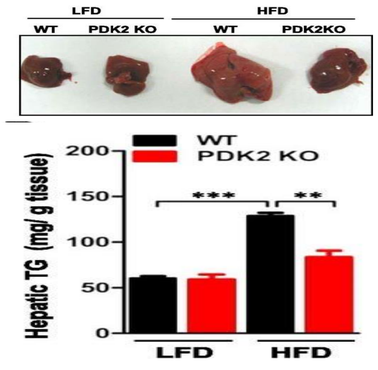
- Unfortunately, the prevalence rate of NAFLD is increasing at an alarming rate. According to the Canadian Liver Foundation, NAFLD affects over 7 million people.
- NAFLD is highly associated with increased risk for type 2 diabetes, insulin resistance, and dyslipidemia, which may contribute to cardiovascular diseases such as, hypertension and coronary artery disease (e.g. angina) (2).



Glucose oxidation as a target for NAFLD

Pyruvate dehydrogenase kinase 2 knockout mice (PDHK2 KO) mice fed with HFD showed a marked decrease in body weight gain compared to WT mice. Similarly, hepatic triglycerides was significantly decreased at PDHK2 KO fed HFD compared to WT. These findings highlighted the crucial importance of pyruvate dehydrogenase (PDH) (3).

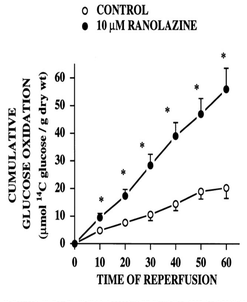


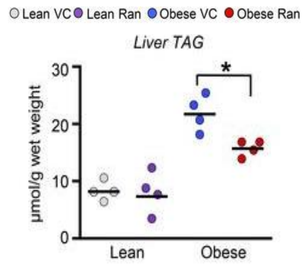


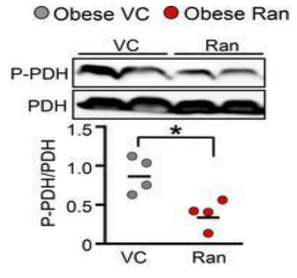
Ranolazine mitigates NAFLD

Ranolazine is a second-line antianginal treatment via inhibiting the late inward sodium current (INa) during cardiac repolarization (4) . Interestingly, our previous study showed that ranolazine mitigates obesity-induced hepatic steatosis and increased PDH(4) .

Ranolazine treatment improves glucose homeostasis & reverses obesity-induced hepatic steatosis







McCormack JG, Barr RL, Wolff AA, Lopaschuk GD.Circulation. 1996 Jan 1;93(1):135-42.
Al Batran R, et al. JCI insight. 2019 Jan 10;4(1).

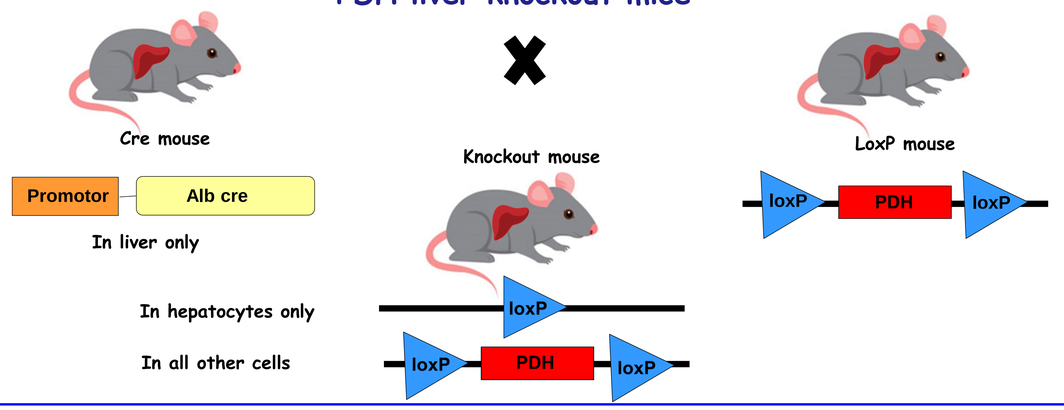
HYPOTHESIS/ OBJECTIVES

Our goal was to determine whether increases in pyruvate dehydrogenase (PDH) activity may explain how ranolazine decreases hepatic steatosis.

METHODS & EXPERIMENTAL DESIGN

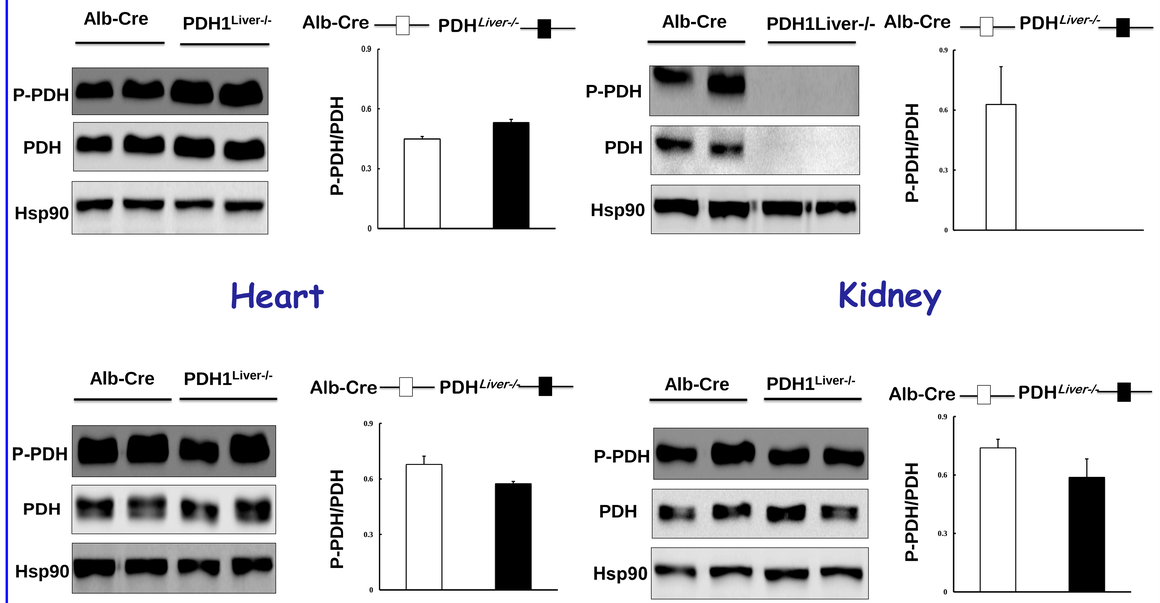
We will generate mice with a hepatocyte-specific deletion of PDH by crossing albumin-Cre mice with floxed PDH mice.

PDH liver knockout mice



RESULTS

Confirmation of successful generation of a Liver-Specific PDH knockout mouse model

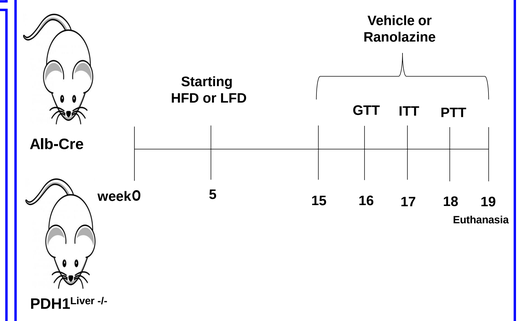


SUMMARY & CONCLUSIONS

- We have successfully generated a hepatocyte-specific PDH knockout (KO) mouse model. These animals demonstrate virtually absent PDH expression in their livers, while maintaining normal PDH expression in other peripheral tissues.
- Our previous results indicate that ranolazine has favourable actions on NAFLD in obesity , which we believe is potentially due to ranolazine's action on hepatic PDH activity(4).

FUTURE DIRECTIONS

Our future goals are to determine whether hepatic PDH activity explains these salutary actions of ranolazine through use of our new hepatocyte-specific PDH KO mouse model.



ACKNOWLEDGEMENTS

Ussher lab

- Keshav Gopal
- Rami Al Batran
- Farah Eaton
- Kim Ho
- Amanda A. Greenwell
- John R. Ussher

liver.ca
Canadian Liver Foundation
Fondation canadienne du foie

REFERENCES

1. Kudaravalli P, John S. Nonalcoholic Fatty Liver. InStatPearls [Internet] 2019 Apr 20. StatPearls Publishing.
2. Massart J, Begriche K, Moreau C, Fromenty B. Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. Journal of clinical and translational research. 2017 Feb;3(Suppl 1):212.
3. Go Y, Jeong JY, Jeoung NH, Jeon JH, Park BY, Kang HJ, Ha CM, Choi YK, Lee SJ, Ham HJ, Kim BG. Inhibition of pyruvate dehydrogenase kinase 2 protects against hepatic steatosis through modulation of tricarboxylic acid cycle anaplerosis and ketogenesis. Diabetes. 2016 Oct 1;65(10):2876-87.
4. Al Batran R, Gopal K, Aburasayn H, Eshreif A, Almutairi M, Greenwell AA, Campbell SA, Saleme B, Court EA, Eaton F, Light PE. The antianginal ranolazine mitigates obesity-induced nonalcoholic fatty liver disease and increases hepatic pyruvate dehydrogenase activity. JCI insight. 2019 Jan 10;4(1).
5. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation. 1996 Jan 1;93(1):135-42.