Macrophage Glucose transporter-1 mediates obesity induced Non-alcoholic fatty liver disease in mice.

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Introduction

Obesity is characterized by metabolic defects in the liver and adipose macrophages exhibiting inflammation, dyslipidemia, hyperglycemia, and insulin resistance[1]. It is now appreciated that obesity associated chronic inflammation, generated by Kupffer cells and infiltrating macrophages, promote the development of non-alcoholic fatty liver disease (NAFLD) and steatosis[2]. Classical inflammatory response in macrophages is accompanied by elevated glucose transporter-1 (Glut1), glycolytic flux and metabolic shifts, in-contrast to OXPHOS anti-inflammatory macrophages[3]. However, the importance of glucose regulations to NAFLD remains unknown.

Aim and Objective

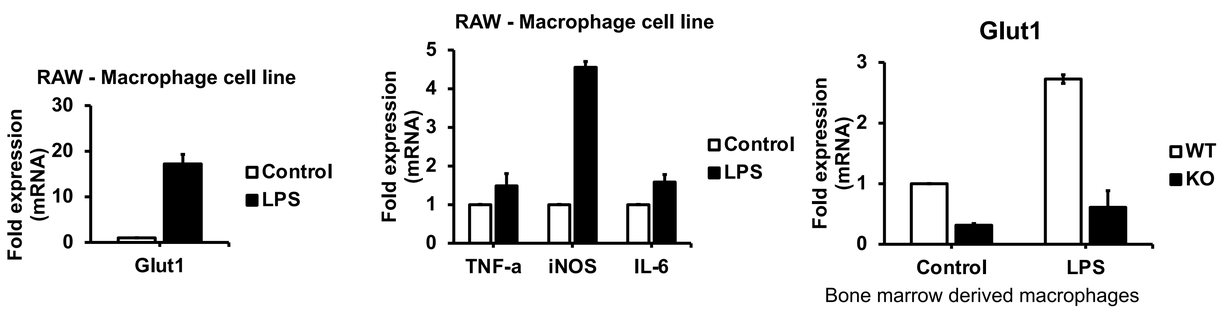
To comprehensively investigate the role of macrophage Glut1 in metabolic complications related to diet induced obesity.

Methodology

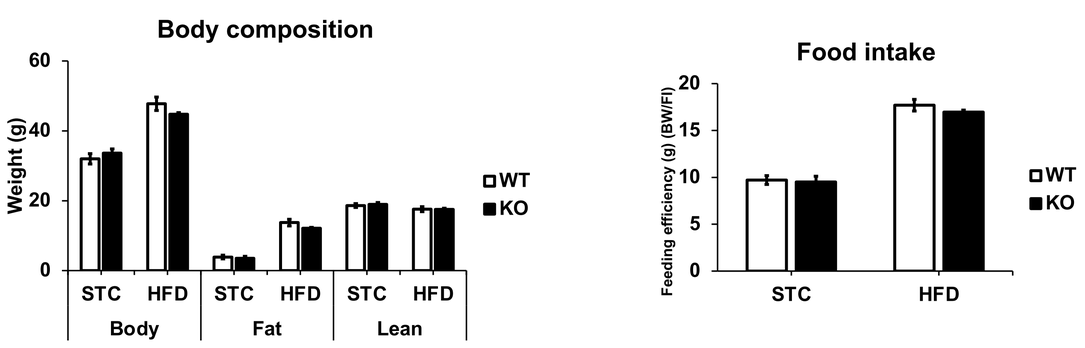
Macrophage specific Glut1 knockout (KO; Cre expression under the control of macrophage Lys2 gene) and Glut1 flox mice (wildtype; WT) were used in this study. Both WT and KO mice were fed with either standard diet (STC) or high fat diet (HFD) to model lean and obese phenotypes, respectively. Phenotypic and obesity related physiological changes were measured after 20 weeks on diet and sacrifice for tissue histology and other analysis.

Results

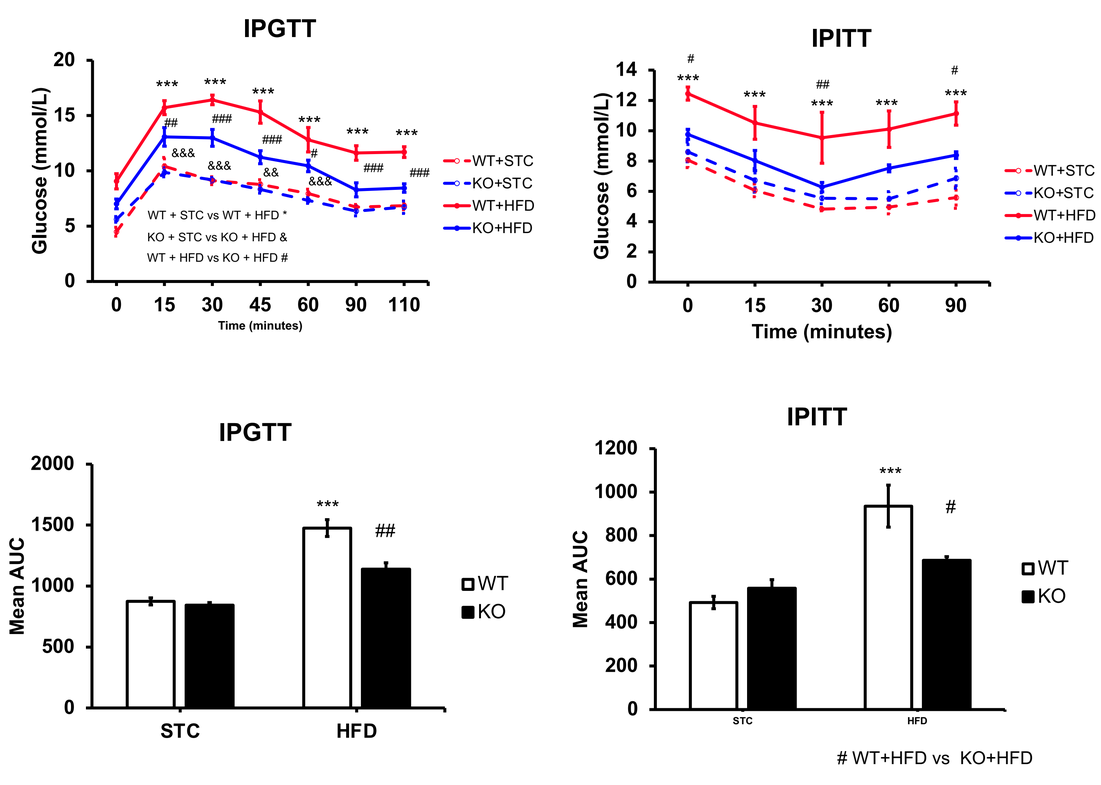
1. Macrophage inflammatory response accompany increased Glut1 expression



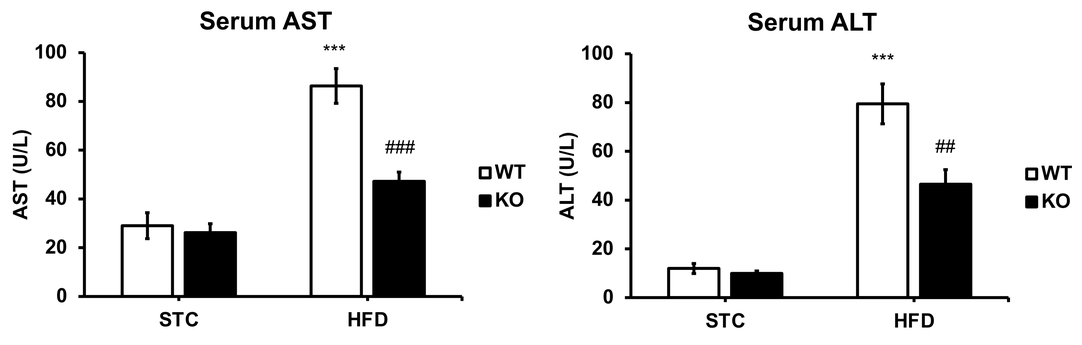
2. Macrophage specific Glut1 KO mice had no change in body composition and food intake during obesity



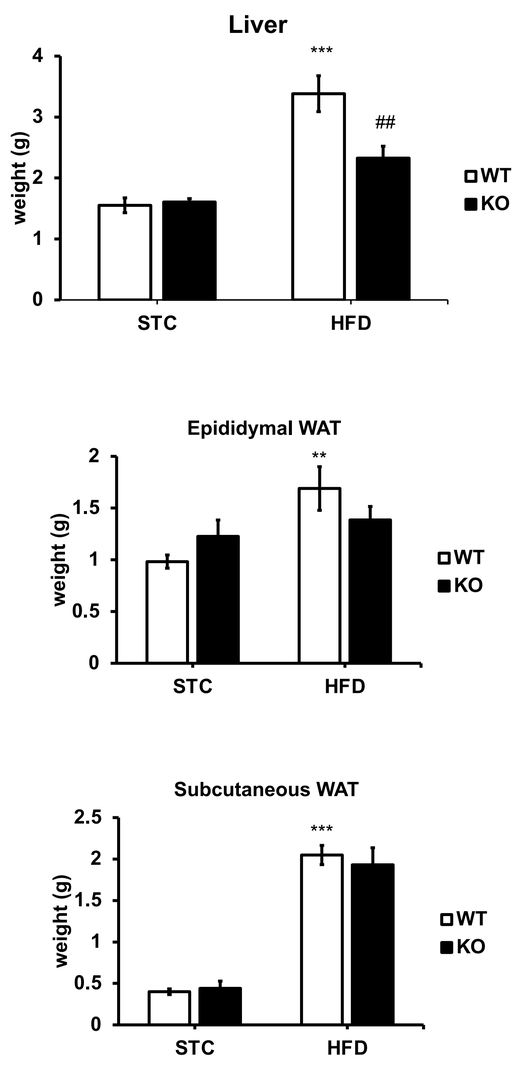
3. Macrophage specific Glut1 KO mice exhibit improved glucose tolerance and insulin sensitivity in obesity

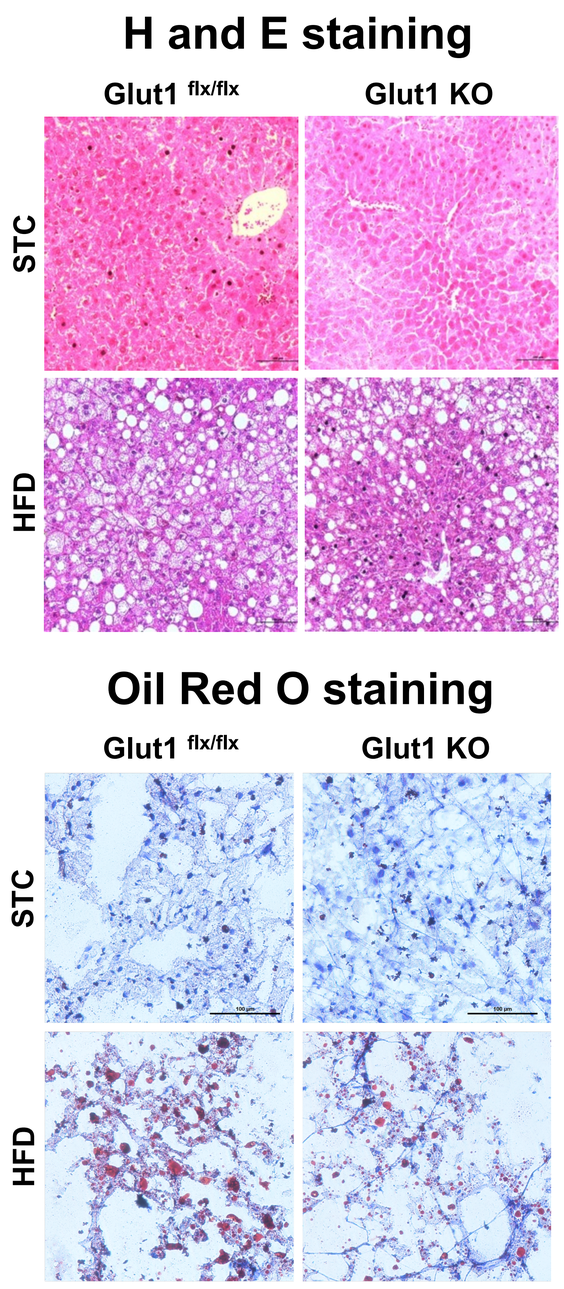


4. Macrophage specific Glut1 KO mice attenuate liver damage marker in obesity



5. Macrophage specific Glut1 KO mice reduced obesity induced liver weight and steatosis





Conclusion:

- Loss of Glut1 in macrophages ameliorate metabolic defects and improves metabolic health in obese mice.
- Pharmacological intervention of Glut1 mediated glycolytic flux may represent a promising therapeutic strategy for obesity related NAFLD

Reference:

1. Lu FB et .al., (2018) *Expert Rev Gastroentrol Hepatol* 12(5): 491-502.
2. Tacke F (2017) *J Hepatol* 66(6): 1300-1312.
3. Bossche JV (2017) *Trends Immunol* 38(6):395-406.

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