High fat-high sucrose diet induced hepatic accumulation of lipotoxic compounds without hepatic mitochondrial dysfunction

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INTRODUCTION

Excess fat and sugar in the diet promote lipid synthesis/accumulation and the deterioration of glucose metabolism likely through gluco- and lipo-toxicity, associated with impaired mitochondrial function[1, 2]. However, the effect of high fat–high sucrose (HFHS) diet on liver mitochondria lipid composition has not been fully elucidated.

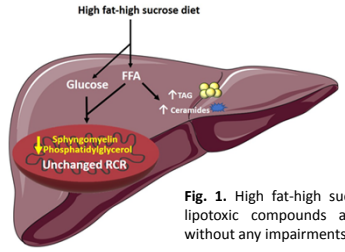


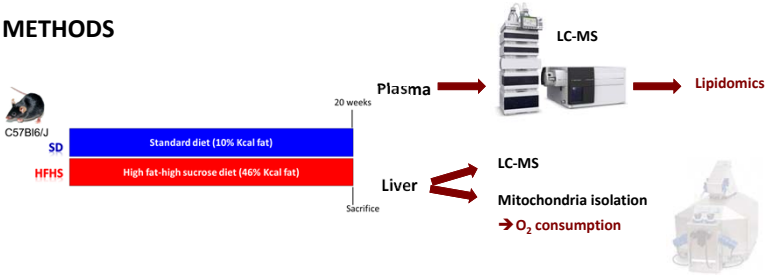
Fig. 1. High fat-high sucrose diet induces hepatic accumulation of lipotoxic compounds and variations on mitochondrial lipidome without any impairments on mitochondrial respiratory control (RCR).

AIM

LC-MS QTOF lipidomic of plasma, hepatic tissue and isolated liver mitochondria of mice fed HFHS vs standard (SD) diet and studied the relationship with hepatic mitochondrial function and lipid accumulation.

- Lipid composition – neutral lipids, phospholipids and sphingolipids
- Liver mitochondrial O2 consumption

METHODS



RESULTS

1 Phenotype characterization

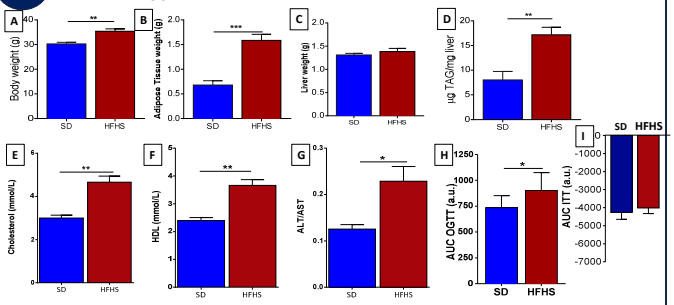


Fig. 2 –HFHS diet induced a significant increment in body (A) and adipose tissue weight (B), with no significant changes regarding liver weight (C) but incremented hepatic fat (D). HFHS feeding mice showed significant increased cholesterol (E) and HDL (F) plasma levels plus an increased ALT/AST ratio (G), suggesting liver damage. Fasting glucose was not changed with HFHS diet but 2h post OGTT glucose (H) was increased with high fat diet, showing that these animals were glucose intolerant but not insulin resistant (I). Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice); *p < 0.05, **p < 0.01 and ***p < 0.005 indicate significant differences (Mann-Whitney U test).

2 Lipidomic analysis

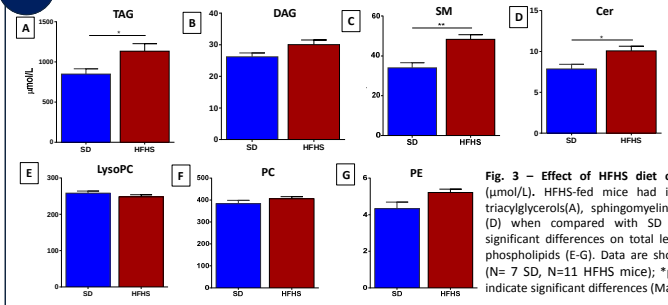


Fig. 3 – Effect of HFHS diet on circulating lipids (µmol/L). HFHS-fed mice had increased circulating triacylglycerols(A), sphingomyelin (C) and ceramides (D) when compared with SD fed mice with no significant differences on total levels of DAG (B) and phospholipids (E-G). Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice); *p < 0.05, **p < 0.01 indicate significant differences (Mann-Whitney U test).

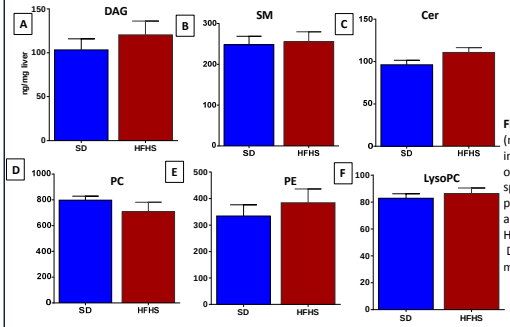


Fig. 4 – Effect of HFHS diet on hepatic lipidomics (ng/mg liver). Although HFHS diet increased intrahepatic TAG it did not cause accumulation of other lipid classes. Hepatic diacylglycerols (A), sphingomyelin (B), ceramides (C), phosphatidylcholine (D), phosphoethanolamine (E) and lysophosphatidylcholine (F) were unaltered after HFHS diet.
Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice). Significant differences (Mann-Whitney U test)

3 Liver mitochondrial lipidomics

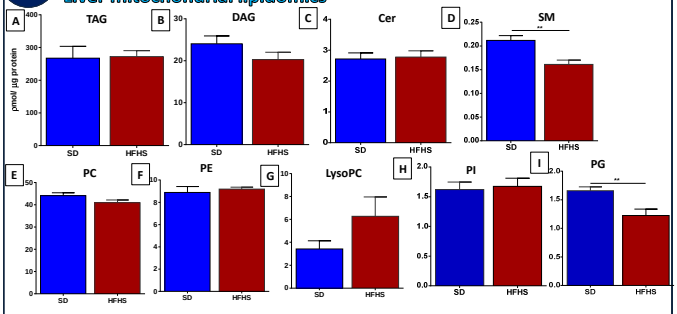


Fig. 6 – Effect of HFHS diet on mitochondrial lipids (pmol/µg protein)**.** Despite the increased circulating fat after HFHS diet, hepatic mitochondria show no lipotoxic compounds accumulation. There were no significant differences on total levels of triacylglycerol (A), diacylglycerols (B), ceramides (C), phospholipids (E-G) and phosphoinositol (H). On the other hand had decreased sphingomyelin (D) and phosphatidylglycerol (I) levels. Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice); *p < 0.05, **p < 0.01 indicate significant differences (Mann-Whitney U test).

Liver mitochondrial O_2 consumption

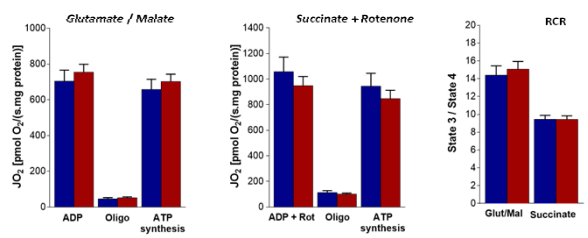


Fig. 7 - Respiration of liver mitochondria from SD, and HFHS fed mice. HFHS diet had no effect on hepatic mitochondrial function. Oxygen consumption was measured using liver mitochondria in the presence of glutamate/malate (5mM each) or succinate (7mM) plus rotenone (1µM). The respiratory control ratio (RCR) was calculated to assess the tightness of the coupling between respiration and phosphorylation. Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice). Oligo: oligomycin

Bioactive lipids

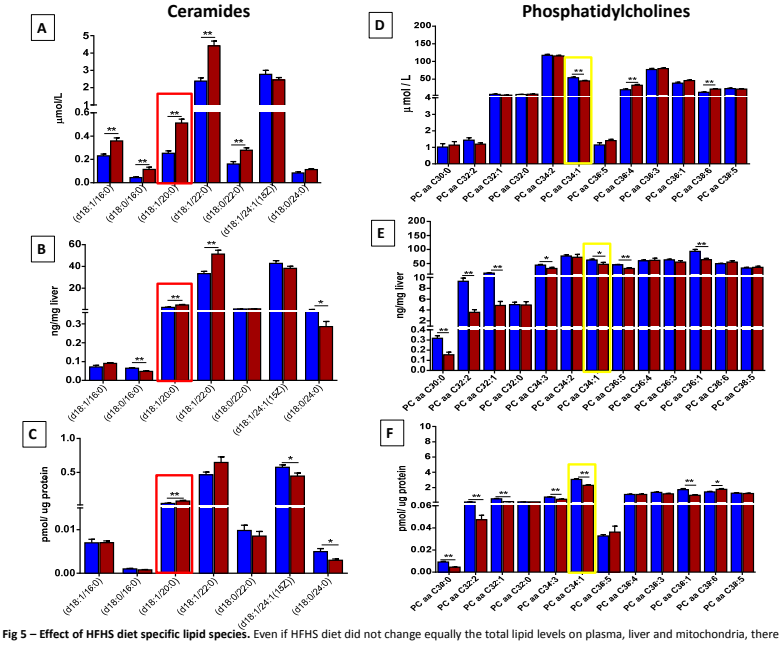


Fig 5 – Effect of HFHS diet specific lipid species. Even if HFHS diet did not change equally the total lipid levels on plasma, liver and mitochondria, there are similarities between plasma (A), liver (B) and mitochondria (C) Ceramides and also between plasma (D), liver (E) and mitochondria (F) phosphatidylcholines. Among these active lipids, is notable that CER (18:1/20:0) and PC aa 34:1 were increased and decreased, respectively, similarly in plasma, liver, and mitochondria. Data are shown as mean ± SEM (N= 7 SD, N=11 HFHS mice); *p < 0.05, **p < 0.01 indicate significant differences (Mann-Whitney U test).

CONCLUSIONS

HFHS-diet is associated to hepatic fat accumulation, increased adipose tissue and increased glucose intolerance. Despite the increased circulating fat after HFHS diet, hepatic mitochondria show no lipotoxic compound accumulation and normal oxidative capacity indicating that a lipotoxic environment is a necessary condition but not sufficient to alter mitochondrial activity.

This work was performed as part of the activities of the project FOIE GRAS funded by the European Union's Framework Programme for Research and Innovation Horizon 2020 under the Marie Sklodowska-Curie Grant Agreement N°722619 (A Gastaldelli and C Prip-Buus are FOIE GRAS project leaders, Sara Guerra and Inês Mateus scholarships were funded by the project FOIE GRAS).

1. Peng, K.Y., et al.; *Journal Lipid Research*, 2018. 59(10): p. 1977-1986.
2. Chella Krishnan, K., et al.; *Cell Systems*, 2018. 6(1): p. 103-115 e7.