2k brief Obesity
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High-resolution respirometry: Obesity and Liver

High-fat diet activates liver iPLA$_2$γ generating eicosanoids that mediate metabolic stress

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High-resolution respirometry of hepatic mitochondria isolated from wild-type and hepatic calcium-independent phospholipase A2$_\gamma$ knock out (iPLA$_2$γKO) mice after normal-chow (NC) or high-fat (HF) feeding for 12 weeks

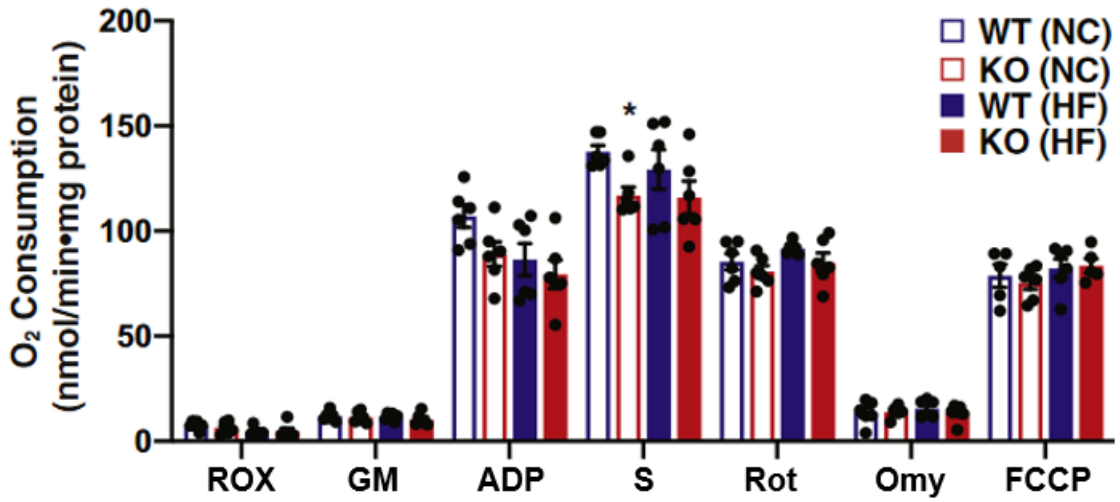

Figure 1. Mitochondrial respiration states were observed by the sequential addition of substrates and inhibitors as indicated in the figure: residual oxygen consumption - mitochondria alone (ROX), GM, ADP, succinate (S), rotenone (Rot), oligomycin (Omy), and FCCP. Antimycin A was finally added to determine oxygen consumption by nonoxidative phosphorylation reactions which was then subtracted from each prior condition measured. *p<0.05 when compared with WT on the same diet, N=6.

Mitochondrial O$_2$ consumption utilizing GM and GMS was modestly decreased in hepatic iPLA$_2$γKO liver mitochondria in comparison to their WT counterparts on a NC diet. In addition, HF-fed WT mice demonstrated a modest decrease in respiration with ADP relative to NC-fed WT controls.

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Inhibition of hepatic mitochondrial respiration by 5 µM 12-hydroxyeicosatetraenoic acid (12-HETE)

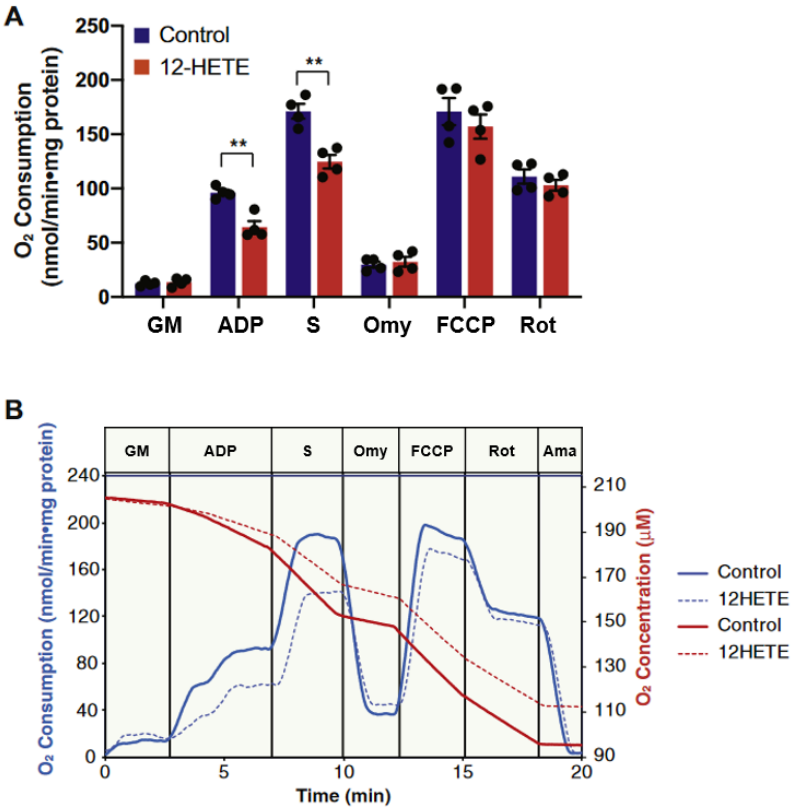

Figure 2. High-resolution mitochondrial respirometry was performed using hepatic mitochondria isolated from wild-type mice fed a normal-chow diet to examine the effects of 12-HETE on respiratory states. **(A)** Rate of oxygen consumption by mitochondria respired with glutamate & malate substrates (GM) with sequential additions of ADP, succinate (S), oligomycin (Omy), FCCP, rotenone (Rot), and antimycin A (Ama) in the absence (DMSO vehicle alone), or the presence of 5 µM 12-HETE. Net oxygen consumption rates were calculated by subtracting the respiration rate in the presence of antimycin A. The values are means ± SEM from four independent high-resolution respirometry measurements. $^{**}p<0.01$ when compared with control. **(B)** Representative tracings for oxygen consumption rate (blue lines) and oxygen concentration (red lines) in the absence (DMSO vehicle alone) or presence of 12-HETE during different respiration states are shown.

12-HETE, which can accumulate in HF-diet, inhibits GM-linked and GMS-linked respiration in the presence of ADP in liver mitochondria.

High fat diet in mice increases hepatic iPLA2γ-mediated 12-HETE production leading to mitochondrial dysfunction and hepatic cell death.

Reference: Moon SH, Dilthey BG, Liu X, Guan S, Sims HF, Gross RW (2021) High-Fat diet activates liver iPLA$_2$γ generating eicosanoids that mediate metabolic stress. J Lipid Res. 62: 100052.

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