Manipulating the Bile Acid Pool to Alter Intestinal Lipid Absorption

Alvin P Chan MD MPH
Tarling-Vallim Laboratory | Division of Pediatric Gastroenterology
David Geffen School of Medicine at UCLA
Bethan Clifford PhD, Kelsey Jarrett PhD, Leslie Sedgeman PhD, Madelaine Sholto PhD, Angela Cheng BS, Elinor Lee MD PhD, Elizabeth Tarling PhD, Thomas Vallim PhD

Background

- Bile acids are potential targets for treatment of obesity and NAFLD because of their role in lipid absorption

Objective

- Investigate whether the size and composition of the bile acid pool can be manipulated to alter lipid absorption

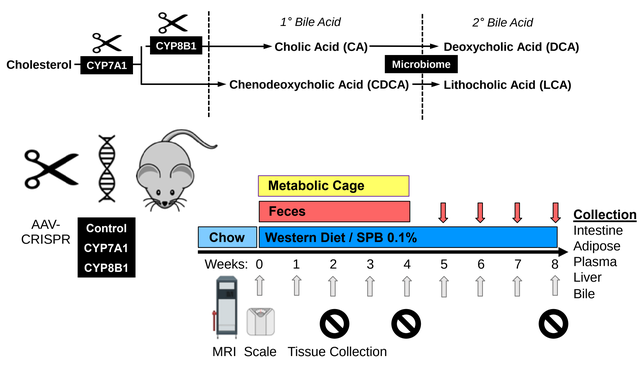
Hypotheses

- Reduction in bile acid pool size and shift in the composition towards weaker detergent bile acids decrease fatty acid (FA) absorption
- Decrease in FA absorption positively changes the lipidomes of adipose, plasma, and liver; improving body composition, insulin resistance, and hepatic steatosis

Methods

- AAV was used to deliver CRISPR targeting key hepatic bile acid synthesis enzymes (*Cyp7a1*, *Cyp8b1*) in C57Bl/6 mice to modulate the bile acid pool

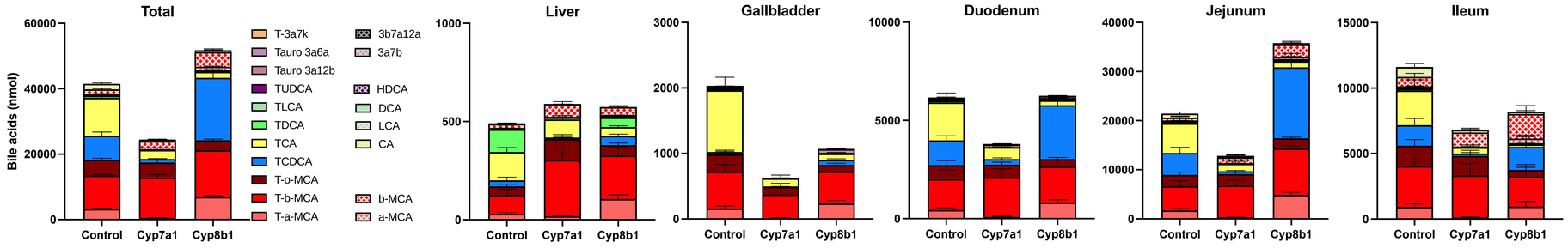
Simplified Bile Acid Synthesis Pathway



- Fecal FA was measured by GC/MS to determine FA absorption using sucrose polybehenate (C22:0) standard
- Tissues were collected at weeks 2, 4, and 8 and analyzed for bile acids (UPLC-MS/MS), plasma FAs (GC/MS), liver lipidomics, and histology

Results

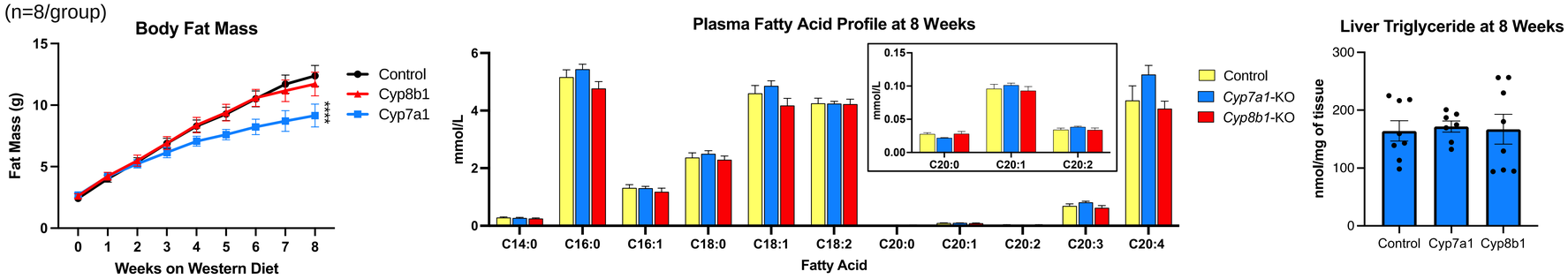
Cyp7a1-KO and _Cyp8b1_-KO alter the size and composition of the bile acid pool (n=8/group)



Bile acid changes caused by _Cyp7a1_-KO leads to _selective absorption_ of certain FAs; absorption of saturated FAs easily disrupted, while that of polyunsaturated FAs preserved (n=7-14/group)

***Cyp7a1*-KO decreases FA absorption more than *Cyp8b1*-KO and control** (n=8/group)

Reduced FA absorption by _Cyp7a1_-KO decreases body fat mass, but not plasma FAs or liver lipidomics (n=8/group)



Conclusions

- In this ongoing study, *Cyp7a1*- and *Cyp8b1*-CRISPR KO changed the size and composition of the bile acid pool, leading to differential absorption of certain FA species
- This selective FA absorption may confer certain metabolic advantages. It is possible that the increased load of unabsorbed saturated FAs activates specific free FA receptors in the intestine, driving increased fat loss. Glucagon-like peptide-1 or insulin is suspected to mediate this process.
- Future work will be replicated over longer timeframe and with hamsters due to closer similarities with human physiology

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