Branched chain amino acids exacerbate insulin resistance when supplemented with high-fat diet

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Abstract: Elevated plasma branched-chain amino acids (BCAAs) are one of the robust predictors of development of type-2 diabetes mellitus (T2DM) in humans. Also, the recent literature links BCAAs to disrupted mitochondrial metabolism during insulin resistance and Non-alcoholic fatty liver disease (NAFLD). Around 70% of obese patients are affected by NAFLD and are further predisposed to T2DM. Therefore, understanding the role of BCAAs in the setting of metabolic diseases is of significant interest. We hypothesized that BCAAs aggravate insulin resistance when supplemented with high-fat diet. Mice (C57BL/6N) were either fed a control (LF; 10%kcal from fat), high fat (HF; 60%kcal from fat) or high-fat diet supplemented with BCAA (HFBA; 60%kcal from fat and 150% BCAA) for 24 weeks. These mice were either fed or overnight fasted HFBA. Another set of mice on HF and HFBA diets were inserted with a jugular vein catheter and were subjected to hyperinsulinemic euglycemic clamps. All the mice were sacrificed for blood and tissues. Mice fed with BCAAs showed a 1-2-fold elevation in circulating BCAAs and their respective keto-acids (BCKAs). Mice on diet were associated with higher levels of blood glucose and plasma insulin compared to their HF counterparts when fasted. Furthermore, BCAA supplementation caused a lower suppression in endogenous glucose production with insulin and has higher hepatic insulin resistance index (HIRI). Overall, the data suggests that BCAA supplementation worsens the insulin resistance in mice when supplemented with high-fat diet. The data also implies that excess BCAAs supplementation during pre-existing metabolic diseases would impair hepatic insulin sensitivity.

Introduction

- Elevated plasma branched-chain amino acids (BCAAs) are one of the robust predictors of development of type-2 diabetes mellitus (T2DM) in humans [2,3]
- BCAAs are well known as precursors of protein synthesis, but their role in mitochondrial lipid metabolism and insulin resistance is still unclear
- The recent literature links BCAAs to disrupted mitochondrial metabolism during insulin resistance and Non-alcoholic fatty liver disease (NAFLD) [1]
- Around 70% of obese patients are affected by NAFLD and are further predisposed to T2DM [3,4]
- Therefore, our goal was to determine the role of BCAA supplementation in a pre-diabetic environment (or when supplemented with high fat diet)

Hypothesis:

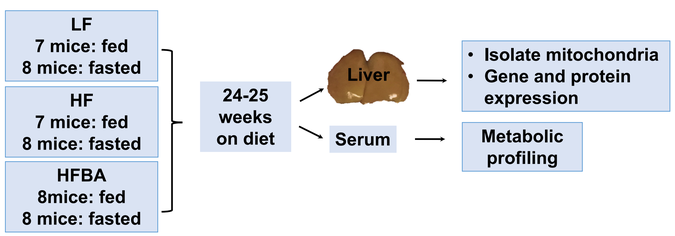
BCAAs aggravates insulin resistance when supplemented with high-fat diet

Methods

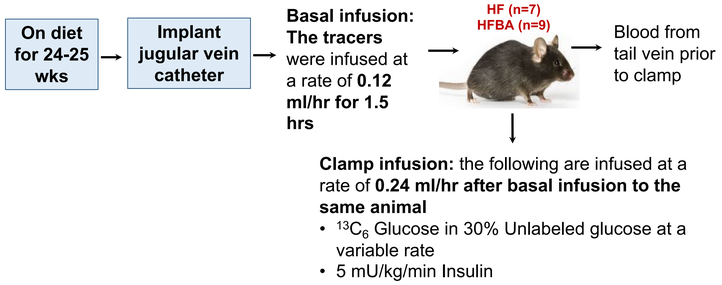
Mice (C57BL/6N) were either fed a control (LF; 10%kcal from fat), high fat (HF; 60%kcal from fat) or high-fat diet supplemented with BCAA (HFBA; 60%kcal from fat and 150% BCAA) for 24 weeks. These mice were either fed or overnight fasted. Another set of mice on HF and HFBA diets were inserted with a jugular vein catheter and were subjected to hyperinsulinemic euglycemic clamps. All the mice were sacrificed for blood and tissues.

Metabolic profiling during embryonic to post-hatch transition

Experiment 1: Metabolic profiling

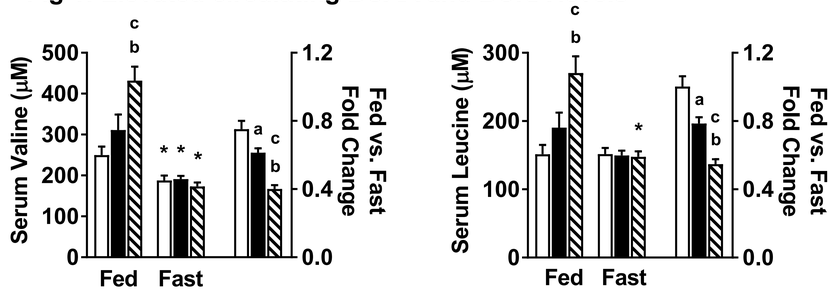


Experiment 2: Hyperinsulinemic euglycemic clamp

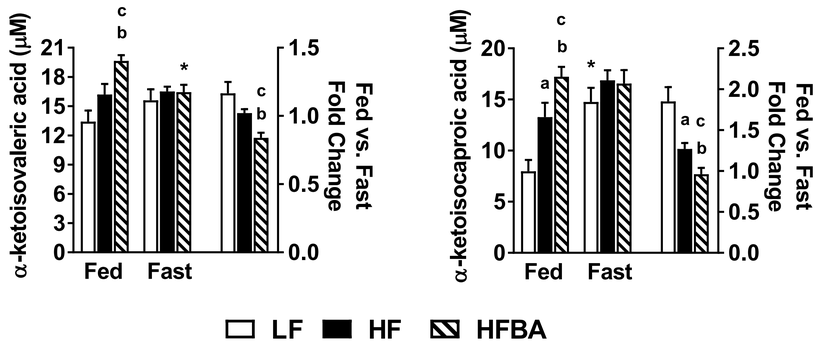


Results

Fig 1: Elevated circulating BCAA and BCKA levels

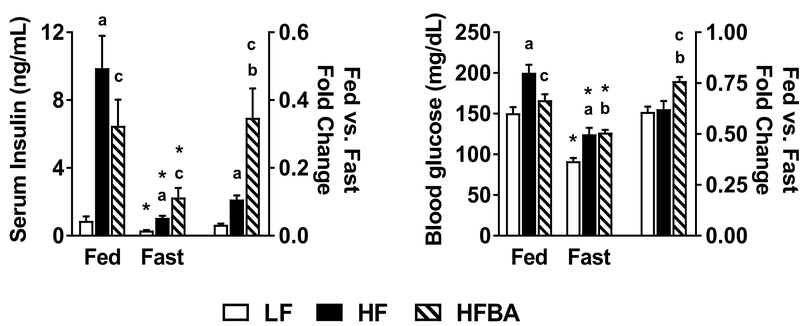


a. Concentration of plasma BCAAs



b. Concentration of plasma BCKAs

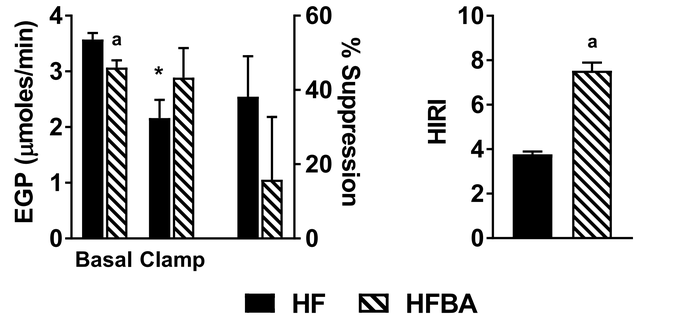
Fig 2: Loss of metabolic flexibility in HFBA mice



a. Concentration of Serum Insulin

b. Concentration of blood glucose

Fig 3: Lower suppression of EGP with insulin in HFBA mice



a. Endogenous glucose production

b. Hepatic insulin resistance index

Summary

- Plasma BCAAs and their respective ketoacids are elevated after HFBA compared to their HF counterparts
- Blood glucose and insulin are lower in fed HFBA mice, however both are high in fasted HFBA mice
- Mice fed with HFBA have lower suppression in endogenous glucose production with insulin clamp
- HFBA mice have significantly higher hepatic insulin resistance index

Conclusion

- BCAA supplementation elevates plasma BCAAs and their respective degradation products (BCKAs)
- BCAA supplementation could worsen the insulin resistance in mice in an pre-insulin resistant environment
- Excess BCAAs supplementation during pre-existing metabolic diseases such as fatty liver disease would impair hepatic insulin sensitivity.

References

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