Reduction diet branched-chain amino acids improves the metabolic health and reduces cellular senescence in the liver of male C57Bl/6j mice

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Introduction
Diet has been shown to have a profound impact on aging. Others have previously shown that protein restriction (PR) can increase lifespan and increased protein consumption leads to increased senescence gene expression in the liver of male mice. The Lamming lab has shown that the metabolic benefits of PR are partly due to decreased branched-chain amino acids (BCAAs). We have also shown that BCAA restriction improves metabolic health and extends lifespan in male mice with others showing the converse shortens lifespan. In this study, we set out to comprehensively determine the role of total protein and BCAAs in high-protein-induced senescence and its effects on metabolic health and physical fitness after 16 weeks on diet. We hypothesized that higher protein consumption will lead to increased lipid dysregulation and decreased cellular senescence in mice, which will be rescued by reducing BCAAs from the diet down to levels of a low protein diet.

Study Design

12-week-old
C57Bl/6j mice

Diet start

Weeks on Diet

ITT Blood glucose

[ITT Blood glucose (mg/dL)]

0 1 2 3 4 5 6 7 8 9 10

Figure 2. Low BCAA diets improve glucose regulation and increases energy expenditure.

(A) Liver weight at sacrifice at 16 weeks on diet; n=10 mice/group; one-way ANOVA, ****p<0.0001. (B) Gene expression differences of expression. (B) n=7 mice/group; statistics for the overall effects of time, diet, and the interaction represent the p value from a two-way ANOVA, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Data represented as mean ± SEM.

Alterations in protein and BCAA consumption does not impact physical fitness in young mice

(A) Body weight over time and final body weight shows that LP, C-BR and HP-BR fed animals do not gain weight over 16 weeks of dieting compared to the CTL and HP fed animals. (B) Fat mass over time and final fat mass suggests that this attenuation of body weight gain is primarily due to the prevention of fat mass accumulation. (C) Lean mass over time and final lean mass also support an attenuated weight gain for the LP BR and HP BR diets. (D) Oxidative stress percentage of adiposity over time and final adiposity. (E) Food consumption as measured by Kcal per mouse per day over time suggests weight loss is not due to starvation as data show in BCAAs display increased local consumption. (F) Food consumption per gram of BW suggests animals fed low BCAAs diet in BCAAs consume higher amounts of food for their body weight. (G) Kcal from BCAAS over time confirm that consumption of BCAAs is reduced in the LP, C-BR and HP-BR diets as compared to CTL and HP (A-D) one-way ANOVA, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Data represented as mean ± SEM.

Figure 3. Protein and BCAA consumption does not affect grip strength and balance, but does impact body condition frailty scoring.

(A-B) Hanging to assess grip strength was measured and normalized to body weight to account for weight as a factor via one-way ANOVA. (C-D) Rotarod was performed to measure for coordination and normalized to body weight via ANOVA. (E) Rotarod speed was measured. (F-G) Physical/muscular/skeletal scoring from frailty assays are displayed and displayed differences in body condition frailty scoring. (n=10 mice/group; one-way ANOVA, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Data represented as mean ± SEM.

Conclusion and Future Directions

- Lowering consumption of BCAAs results in lowered fat mass, improved glucose homeostasis and increased energy expenditure
- Altering protein and BCAA consumption does not impact physical performance tests, but does impact body condition-related frailty measures
- Reduced consumption of BCAAs result in decreased senescence gene expression in the liver of young male mice
- Future directions include looking at the role of the individual BCAAs as well as FGFP and mTORC1

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