The effects of branched-chain amino acid restriction on Hutchinson-Gilford Progeria Syndrome

Elizabeth Konon, Alexis Mitchell, Colin Boyle, Nicole Cummings, Dudley Lamming
Department of Medicine, University of Wisconsin, and William S. Middleton Memorial Veterans Hospital, Madison WI

Introduction

- Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disorder caused by a splicing mutation in the Lamin A/C gene that leads to the production of an abnormal, truncated Lamin A protein called progerin (Gabriel et al., 2016). Humans with HGPS usually die prematurely as a result of heart attack or stroke.
- HGPS has been associated with defective autophagy and increased signaling of mammalian Target of Rapamycin Complex 1 (mTORC1) (Cao et al., 2011), a protein kinase implicated in aging and many age-related diseases.
- Caloric restriction (CR) is the strongest nutritional intervention known to extend lifespan and improve metabolic health, but is unsustainable for the general population. Dietary regimens that mimic CR but are easier to follow are desirable.
- Our lab recently discovered that specifically reducing dietary levels of the three branched chained amino acids (BCAAs; leucine, isoleucine and valine), which are potent agonists of the mechanistic Target of Rapamycin Complex 1 (mTORC1) protein kinase, has beneficial effects on the metabolic health in mice.
- As inhibition of mTORC1 by the immunosuppressant rapamycin can extend the lifespan of some mouse models of HGPS, we hypothesized that a reduced BCAA diet might be a translatable, food-as-medicine based approach for the treatment of HGPS.

Methods

- Subjects were 36 male mice and 51 female mice at 7 weeks of age on average.
- Mice were weaned and randomly assigned to either Control diet (21% amino acids) or Low BCAA diet (21% amino acids, with BCAAs reduced by two-thirds).
- The mice were genotyped to determine whether they were wild type or heterozygous for alleles containing the specific human mutation for HGPS.
- For all tests, groups were compared using 2-way ANOVA with a 2x2 factorial. Significance was determined at α=0.05.

Decreased consumption of BCAAs improves glucose tolerance in males

Conclusions

- A reduction in BCAA consumption improves glucoregulatory control in LmnaG609G/males.
- MRI data suggests that Low BCAA diets in LmnaG609G/+ mice reduce weight gain by reducing fat gain.
- A low BCAA diet may increase muscular strength or decrease the decline in muscle strength in LmnaG609G/+ mice.
- Reducing dietary BCAAs or total AAs may improve health and longevity in mice, and may inform future therapeutic treatments for HGPS and other age-related diseases.

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