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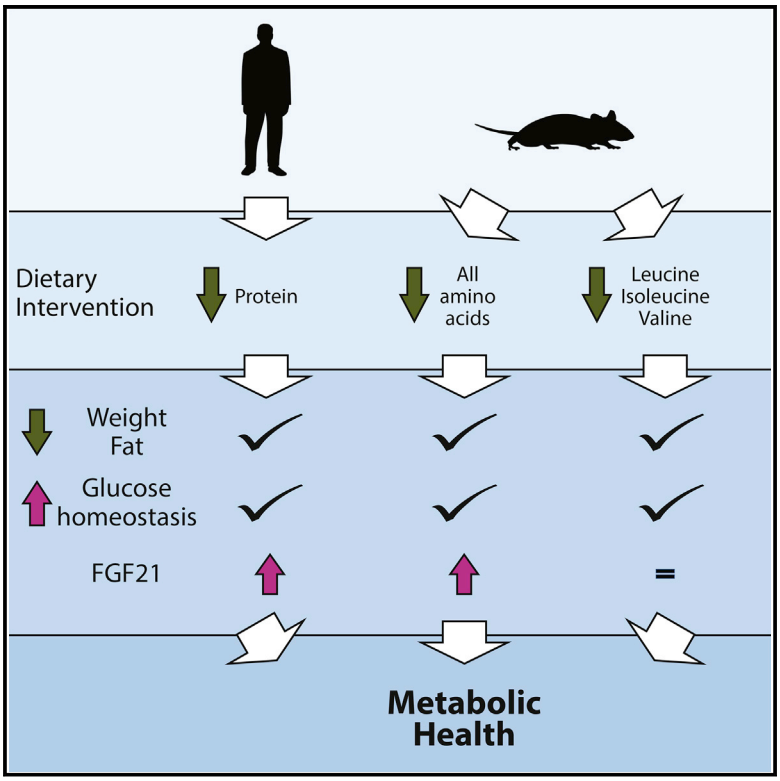
Decreased Consumption of Branched-Chain Amino Acids Improves Metabolic Health

Graphical Abstract



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In Brief

Protein-restricted (PR) diets improve metabolic health in mice. Fontana et al. find that PR diets improve metabolic health in humans and that a specific reduction in the consumption of three branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—by mice improves many aspects of glycemic control and body composition to the same extent as reducing all dietary amino acids.

Highlights

- Protein-restricted (PR) and branched-chain amino acid (BCAA)-restricted diets improve metabolic health
- Decreasing dietary BCAAs recapitulates many of the benefits of a PR diet
- Low BCAA diet improves metabolic health independently from changes in energy balance
- Dietary protein quality regulates metabolic health independently from protein quantity

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Decreased Consumption of Branched-Chain Amino Acids Improves Metabolic Health

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SUMMARY

Protein-restricted (PR), high-carbohydrate diets improve metabolic health in rodents, yet the precise dietary components that are responsible for these effects have not been identified. Furthermore, the applicability of these studies to humans is unclear. Here, we demonstrate in a randomized controlled trial that a moderate PR diet also improves markers of metabolic health in humans. Intriguingly, we find that feeding mice a diet specifically reduced in branched-chain amino acids (BCAAs) is sufficient to improve glucose tolerance and body composition equivalently to a PR diet via metabolically distinct pathways. Our results highlight a critical role for dietary quality at the level of amino acids in the maintenance of metabolic health and suggest that diets specifically reduced in BCAAs, or pharmacological interventions in this pathway, may offer a translatable way to achieve many of the metabolic benefits of a PR diet.

INTRODUCTION

A calorie-restricted (CR) diet, in which total caloric intake is reduced while maintaining adequate nutrition, promotes metabolic health and longevity in invertebrate model organisms and mammalian species ranging from mice to humans (Colman et al., 2014; Fontana et al., 2010; Lamming and Anderson, 2014; Mercken et al., 2012). Mammals, including humans, placed on a CR diet, significantly lose body weight and abdominal fat and display a robust improvement in glycemic control and insulin sensitivity (Barzilai et al., 1998; Foster et al., 2003; Weiss et al., 2006). A CR diet usually involves decreased consumption of all macronutrients, and the role of decreased protein, in particular, has received significant attention (Fontana and Partridge, 2015; Weindruch and Walford, 1988). Recently, protein-restricted (PR) diets have been shown to significantly improve the metabolic health and longevity of rodents (Ables et al., 2014; Fontana and Partridge, 2015; Solon-Biet et al., 2014, 2015).

Although in humans, high-protein, low-carbohydrate diets have recently been popular for weight loss, epidemiological studies suggest that high-protein intake correlates with increased mortality, whereas lower protein intake is associated with decreased mortality (Lagiou et al., 2007; Levine et al., 2014). Indeed, individuals consuming high-protein diets are at increased risk of developing metabolic diseases including obesity and type 2 diabetes (Halkjær et al., 2011; Sluijs et al., 2010; Vergnaud et al., 2013). Little is known about the molecular mechanisms through which PR regulates metabolic health. Moreover, many of the studies conducted thus far have utilized extremely restrictive protein diets, well below the estimated average requirement for human adults, and are therefore likely unsustainable and unhealthy (Otten et al., 2006). The impact of a moderate PR diet without CR on metabolic health in humans has not been considered.