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How low protein diets promote healthy aging

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Low protein diets help us improve health and reduce the risk of death. But, how these diets are beneficial in metabolism remains mysterious. Our study suggests that specific amino acids – the building blocks which make up dietary protein – are responsible for their effects. Surprisingly, we found that only male mice – not female mice – fed diets restricting those amino acids lived longer.

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Age-related, life-threatening diseases – including cardiovascular disease, cancer, and diabetes – are a growing problem worldwide as we increasingly live longer. As a result, there is great interest in finding ways to promote healthy aging by delaying or preventing these diseases.

Restricting calorie intake has long been the gold-standard for interventions that promote health and longevity. However, most people have trouble cutting calories over a prolonged period. A potential alternative lies in the growing realization that "a calorie is not just a calorie" – and that the source of the calories we eat matters. Studies by our laboratory and others have recently shown that, surprisingly given most popular dietary advice, low protein diets are associated with improved health and decreased risks of diabetes and death.

Several years ago, we began to wonder if reduced levels of specific amino acids – the building blocks which make up dietary protein – might be responsible for these benefits of a low protein diet. In 2016, we found that a diet with reduced levels of the three amino acids leucine, isoleucine, and valine – collectively known as the branched-chain amino acids – had similar effects to a low protein diet, and promotes health in both humans and mice.

In later studies, we turned to focus on mice as an animal model, in which we can easily and precisely control dietary intake, and importantly, mice respond to healthy and unhealthy diets in much the

same way that people do. In 2018, we showed that reducing dietary branched-chain amino acids rapidly restores normal body composition and the ability to regulate blood sugar in mice that were previously obese due to consuming a high-fat, high-sugar energy-dense "Western" diet.

We have now extended these studies to the context of aging. We set out to determine if reducing levels of dietary branched-chain amino acids affects healthy aging in mice. We evaluated a low branched-chain amino acid diet using three different mouse models. First, examining special mouse models that undergo premature aging, we found that the lifespan of these mice was significantly increased by a low branched-chain amino acid diet. Second, using normal middle-aged mice, we found that a reduced branched-chain amino acid diet improved body composition and the ability to regulate blood sugar, but did not affect longevity. Third, we examined normal mice, and fed them a reduced branched-chain amino acid diet starting when they were very young. We found that this long-term consumption of a reduced branched-chain amino acid diet extended lifespan by over 30%, comparably to a low protein diet. Interestingly, this lifespan extension was sex-specific, with only male mice living longer.

While athletes often consume protein supplements – including branched-chain amino acids – hoping to build healthy skeletal muscle, branched-chain amino acid-restricted mice did not show any defects in strength. In fact, we found that branched-chain amino acid-restricted male mice had reduced frailty (remained more robust) as they aged.

We also found that the activity of a key metabolic enzyme called mTORC1 reduced in the long-lived branched-chain amino acid-restricted male mice, but not in females. As mTORC1 regulates lifespan and healthspan in mice, the reduced mTORC1 activity might be responsible for the male-specific life extension and increased health strength.

In summary, we uncovered that a diet with a reduced level of branched-chain amino acids helps mice live healthier and longer. If humans and mice respond to this diet in the same way, such diets – or drugs that mimic the effects of a low branched-chain amino acid diet – could be an effective way to promote healthy aging, at least in men. Notably, the mice in our studies could eat as much as they wanted yet remained lean, and thus reduced branched-chain amino acid diets may be easier to adhere to than diets in which calories have to be carefully tracked and limited each day. We are currently working to understand the physiological and molecular mechanisms behind the beneficial effects of reduced branched-chain amino acid diets, and to translate these findings to the clinic.