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Low-protein diet enhances glucose metabolism

Scientists at the German Cancer Research Center (DKFZ) have shown in mice that a low-protein diet increases fat and carbohydrate burning, thus raising energy expenditure. Changing the animals' diet to low-protein intake even led to the regression of insulin resistance – independent of their body weight and total energy intake. A temporary low-protein diet also lowered insulin and glucose levels in young human volunteers. This effect is regulated by a central stress response by liver cells.

Only four decades ago, there were twice as many underweight people than there were obese people in the world. However, this situation has changed dramatically over this short period. Today, there are considerably more people worldwide who are obese than people who are underweight. Gross overweight, or obesity, can lead to a number of severe conditions including cardiovascular diseases, cancer, type 2 diabetes and metabolic syndrome.

The main causes for the worldwide rise in body weight are considered to be changes in dietary habits and lack of physical activity. However, scientists have suspected further factors to be responsible for the rapid rise in body weight. They have focused their attention particularly on changes in the composition of food in terms of fat, carbohydrates and protein.

"Particularly when it comes to protein there is contradictory evidence," said Adam Rose, a scientist at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg. "On the one hand, scientists have observed that people on a low-protein diet tend to eat more in total in order to cover their protein needs. On the other hand, epidemiological studies have revealed that a high share of protein in the diet is associated with high diabetes rates."

In order to investigate the effects of a low-protein diet at the molecular level, the investigators fed mice with a diet that was low in protein (5 % of total calories vs. 20 % in normal diet) Allthough they ate slightly more in total, these animals gained weight more slowly than control animals on a normal diet. The researchers determined that the efficiency of food conversion was 40 percent lower in these animals. They burned more fat and carbohydrates and thus expended more energy. Metabolic indicators that were measured in blood samples were found to have improved substantially: The animals had lower insulin, lipid and glucose levels. By contrast, levels of a protein called FGF21 (fibroblast growth factor 21) rose.

When the scientists fed obese mice a low-protein diet, this did not lead to any changes in their body weight. However, their blood glucose levels improved and even prior insulin resistance regressed.

Central stress response by hepatic cells involved

The researchers proved that FGF21 plays a crucial role in the improvement of glucose metabolism. They did so by using mice whose hepatic cells lacked the respective gene. In these animals, a low-protein diet did not have any positive impact on metabolism.
The rise in blood levels of FGF21 was particularly steep when mice acutely consumed the low protein diet. This was mediated by an increase in a stress signaling pathway in the liver. Thus, the low protein diet acts as a physiological stress factor with apparently positive outcomes.

The scientists discovered that not all protein building blocks are equally responsible for the positive effects of a low-protein diet: Particularly lack of so-called nonessential amino acids, which the body can sufficiently synthesize, led to a rise in the liver stress pathway and FGF21 levels.

Rose and his team were curious to find out whether the favorable effects of a low-protein diet that they had observed in mice are also relevant in humans. In collaboration with Bente Kiens from the University of Copenhagen, Denmark they recruited five young men as volunteers who followed a low-protein diet for seven days. After that period, the researchers detected high FGF21 levels in the participants, while they found lower blood glucose and insulin levels despite increased intake of carbohydrates.

“These are very promising results, which we plan to verify in larger numbers of participants soon,” said Kiens who led the human study. Rose added “This may provide a simple and feasible method to manage disrupted glucose metabolism in particular populations.”

In addition, the researchers want to find out whether the positive metabolic effects of the low-protein diet can be confirmed in humans at the molecular level. Rose surmised “The results that we obtained in mice build upon the emerging concept that this kind of nutritional ‘stress’ may have positive effects on metabolic health.”

Adriano Maida, Annika Zota, Kim A. Sjøberg, Jonas Schumacher, Tjeerd P. Sijmonsma, Anja Pfenninger, Marie M. Christensen, Thomas Gantert, Jessica Fuhrmeister, Ulrike Rothermel, Dieter Schmoll, Mathias Heikenwälder, Juan L. Iovanna, Kerstin Stemmer, Bente Kiens, Stephan Herzig, Adam J. Rose: A liver stress-endocrine nexus promotes metabolic integrity upon dietary protein dilution. Journal of Clinical Investigation 2016, DOI: 10.1172/JCI85946

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