Mice can eat 'junk' and not get fat

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A study in the September 4th issue of the journal *Cell* identifies a gene that springs into action in response to a high fat diet. Mice that lack the gene become essentially immune to growing obese, regardless of their eating habits.

The protein encoded by the gene known as I{kappa}B kinase e (IKKe) belongs to a class of enzymes, the kinases, which typically make for good drug targets because they are relatively easy to block, according to the researchers. Even better in terms of its therapeutic promise, IKKe loss seems to have many beneficial effects. Mice without the gene are protected against weight gain, chronic inflammation, fatty liver and insulin resistance.

"Perhaps most interestingly, the mice burn more calories even though they aren't eating any less or exercising more," said Alan Saltiel of the University of Michigan, Ann Arbor. They apparently keep the weight off on a diet loaded with fat by "producing a little heat."

Loss of the gene seems to release the "brakes" on energy expenditure, Saltiel adds.

In the beginning, his team did not expect IKKe to have such far-reaching effects on obesity. Growing evidence has linked the insulin resistance in obesity to a state of chronic, low-grade inflammation. Saltiel's group suspected that IKKe had a role in eliciting that inflammatory state.

Earlier studies have found that if you stop the inflammatory chain of

events in obesity, you can break the link between obesity and diabetes, Saltiel said. In the current study, "we expected to disrupt that link, but instead we stopped the onset of obesity."

Further analysis of gene activity within mice lacking IKKe offered more clues to its influence. Loss of the gene reduces the expression of inflammatory cytokines, along with certain regulatory proteins and enzymes involved in glucose and lipid metabolism.

The researchers suspect that IKKe's effects involve the interplay between the liver, fat and immune response in obesity. It may not play a role in the initial inflammatory response to a high-fat diet, but might be required for sustaining that state, they say.

Although an earlier study has shown mice lacking IKKe to be increasingly susceptible to lethal viral infections, "the specificity of the apparent actions of IKKe, the nature of the enzyme, and the profound resistance of knockout mice to high fat diet, make it an especially appealing drug target for the treatment of metabolic disease," the researchers write.

Future work is needed to determine whether IKKe has the same impact on obesity in humans. In the meantime, Saltiel said his team is already looking for IKKe inhibitors, and they expect others will do the same.

Source: Cell Press (news : web)