Making metabolism more inefficient can reduce obesity

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In a discovery that counters prevailing thought, a study in mice has found that inactivating a pair of key genes involved in "fat-burning" can actually increase energy expenditure and help lower diet-induced obesity. These unusual findings, appearing this week in the *JBC,* might lead to some new roads in weight-loss therapy.

Humans and other warm-blooded animals need to continually "burn fat" in order to maintain body temperature, and it's currently believed that an individual's fat-burning capacity, or thermogenic potential, is connected with obesity risk; that is, people with more thermogenic potential are less likely to become obese. In fact, bodybuilders and dieters looking to burn fat commonly use thermogenic supplements like ephedra.

In theory, lowering thermogenesis should increase the chances of obesity, but Leslie Kozak and colleagues at Pennington Biomedical Research Center found that this may not be the case. They knocked-out two thermogenic genes in mice, Ucp1 (mitochondrial uncoupling protein) and Gdm (glycerol 3-phosphate dehydrogenase) and then fed the mice a high-fat diet while rearing them at a cool 20 °C (68 °F).

Surprisingly, these mice were actually quite resistant to obesity, which resulted from the mice turning on backup heat generators, so to speak. Lacking Ucp1 and Gdm, genes that have been designed for the efficient production of heat, mouse white fat cells activated alternate, and more inefficient, fat burning pathways. In this case, though, inefficiency is beneficial, as the mice had to burn more fat than normal to stay warm

(by analogy you burn more wood by warming your house with an open fire then with a well designed wood stove).

Importantly, after spending 10 weeks at 20 °C the mice retained these alternate pathways even after transferring to 28 °C (82 °F), suggesting their bodies had adapted to the change. Thus, Kozak and colleagues note, fat burning does not necessarily require making thermogenesis easier; by making it harder and forcing the body to use inefficient methods to stay warm, the same goals can be reached.

Source: American Society for Biochemistry and Molecular Biology