Scientists discover switch that turns white fat brown

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Scientists have discovered a biological switch that gives energy-storing white fat the characteristics of energy-burning brown fat. The findings could lead to new strategies for treating obesity.

The animal study by researchers at The Ohio State University Medical Center shows that the change is due to the activation of a nerve and biochemical pathway that begins in the hypothalamus, an area of the brain involved in energy balance, and ends in white fat cells. This pathway, called the hypothalamic-adipocyte axis, also induces brown-fat-like cells within masses of white fat.

The white-to-brown fat transformation occurs when animals are placed in an enriched environment, one with a variety of social and physical challenges.

The findings are published in the September issue of the journal Cell Metabolism.

"One of the holy grails of obesity therapy is to understand how to switch white fat to brown fat, and this study describes a new way to do exactly that," says study leader and researcher Dr. Matthew J. During, professor of neuroscience, of neurological surgery and of molecular virology, immunology and medical genetics. "Our findings suggest that we can potentially induce this transformation by modifying our lifestyle or by pharmacologically activating this brain-fat pathway."

Lead and corresponding author Dr. Lei Cao, assistant professor of molecular virology, immunology and medical genetics, notes that obesity is caused by a chronic energy surplus that is stored as lipid in white fat. "Increasing the output of energy is always attractive for obesity treatment, which is why the discovery of brown fat in adult humans caused much excitement a few years ago," she says.

"However, up to now the only known approach to inducing brown fat has been through exposure to chronic cold. Our research reveals a novel way of doing this without cold exposure. We show that animals living in an enriched environment become lean and resistant to diet-induced obesity, even in the presence of unlimited food." In 2010, During, Cao and their colleagues showed in a paper published in the journal Cell that this enrichment effect by itself curbed cancer growth in animals.

The current study used a similarly designed environment, with 15-20 mice housed in large containers equipped with running wheels, tunnels, huts, wood toys, a maze, and nesting material, in addition to unlimited food and water. Control mice were housed in groups of five in smaller, standard laboratory containers without toys but with unlimited food and water.

Key findings include the following:

- Enriched animals showed a significant reduction in abdominal white fat mass (49 percent less than controls).
- Exercise (running in a wheel) alone did not account for the changes in body composition and metabolism of enriched animals.
- Fed a high fat diet (45 percent fat), enriched animals gained 29 percent less weight than control mice and remained lean, with no change in food intake. Enriched animals also had a higher body

temperature, suggesting that greater energy output, not suppressed appetite, led to the resistance to obesity.

In brief, During and Cao explained that the enriched environment stimulates production of a protein called brain-derived neurotrophic factor (BDNF) in the hypothalamus. The normal function of BDNF includes helping control food intake and energy balance.

The increased BDNF triggers sympathetic nervous signals to white fat masses in the body. These signals activate genes specific for brown fat such as Prdm16 and Ucp1, and suppress white-fat genes such as Resn. Blocking BDNF, on the other hand, inhibits or reverses the browning effect.

Overall, the study shows that environmental enrichment has an anti-obesity effect that involves the transformation of white fat to brown fat. That happens through a central mechanism called the hypothalamic-sympathoneural-adipocyte axis - environmental enrichment stimulates the hypothalamus to produce the protein BDNF, increasing sympathetic nerve output to white fat, causing the "browning" of white fat and the burning of stored energy.

Next, During, Cao and their colleagues plan to identify which components of environmental enrichment - sensory, cognitive, motor or social stimulation - are essential for the browning effect.

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