Brown fat holds promise for addressing obesity and a host of related ills

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Obesity is a scourge on the American public, contributing to a multitude of ailments. “Burning” fat has become the obsession of millions. But not all fat is created equal. Activating a particular kind of fat could reduce harms related to high blood pressure, type 2 diabetes, and excess cholesterol, according to some researchers. Although researchers have long known that this so-called “brown fat” generates heat, recent findings, so far mostly in mice, have offered a greater appreciation of its potential role in improving health and wellness. “In mice, in genetic models and interventional models, activation of brown fat can protect against obesity and the ablation of brown fat can promote obesity,” says Paul Cohen, who studies metabolism and obesity at Rockefeller University in New York.

White adipose tissue clusters around our bellies and under the skin, storing extra caloric energy that we don’t expend during daily activities. The result: lots of overweight and obese people—42% of adults in the United States according to the Centers for Disease Control and Prevention (1). Mitochondria in brown fat, which is primarily located near the neck, kidneys, collarbone, and spinal cord, breaks down blood sugar and fat molecules to produce heat that regulates body temperature. We also have “beige” fat cells within white fat depots, which can

Researchers are exploring how to convert abundant white fat into scarce brown fat—seen here surrounded by capillaries in a colored scanning electron micrograph—in hopes of capitalizing on brown fat’s protective effects. Image credit: ScienceSource/Prof S. Cinti.

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behave like brown fat in cold situations. The advent of central home heating, or the mere act of putting on a sweater, negates the natural activity of brown fat.

Cohen says that researchers initially thought that activating brown fat would primarily help people lose weight, as it does in mice. More recently, though, some researchers have come to believe that targeting brown fat could help improve metabolic health—even if a person’s weight remains unchanged.

But skeptics note that brown fat’s benefits remain unproven and that work in humans to date is mostly associative, not causal. There are no large-scale prospective clinical trials that trace the effects of brown fat activation over long periods of time, only smaller trials that explore the effects of activating brown fat for brief periods. “I see the statements made in the abstracts or the discussion about the enormous therapeutic potential” of brown fat, says Daniel Drucker, an endocrinologist and professor of medicine at Mount Sinai Hospital in Toronto, Canada. So far, he adds, these claims haven’t been substantiated.

Activating the Fat

Researchers who are enthused about the potential of brown fat study what happens when people are in environments colder than their usual; they explore how to convert abundant white fat into scarce brown fat and are keen to capitalize on the protective effects of brown fat. The approaches may vary, but all hope to harness brown fat to capitalize on the protective effects of brown fat. The more active brown fat had broken metabolic health.

In another part of the experiment, researchers genetically engineered mice to have defective brown fat and compared them with mice with normal brown fat. Just as with humans, mice with higher brown fat activity had reduced amounts of the circulating BCAAs. According to Kajimura, the results suggest that brown fat can be harnessed to protect metabolic health.

Key Transformation

Because we have a scarcity of brown fat relative to white adipose tissue, other researchers are trying to turn white fat brown using, for example, CRISPR gene editing techniques. “The idea is really simple,” says Yu-Hua Tseng, a cell and molecular biologist at Harvard’s Joslin Diabetes Center in Cambridge, MA. Converting white fat into brown fat provides a “really exciting opportunity” for treating obesity and related ills, says Tseng.

In 2020, Tseng and colleagues used CRISPR to add a gene expressed in brown fat, called UCP1, to cell cultures containing white fat (3). The edited compound developed brown fat properties in cell culture, as measured by a 6,000-fold increase in UCP1 mRNA, a 20-fold increase in UCP1 protein, and enhanced mitochondrial activity that indicated these cells are now better equipped to burn energy.

These cells maintained their brown-like state after being transplanted into mice. Tseng and colleagues fed these mice a high-fat diet and compared their weight gain with that of other mice who were infused with unaltered white fat cells. The mice with brown-like cells gained significantly less weight—an average of 3% weight gain 4 weeks after transplantation—compared with mice with the white cells (8% weight gain on average).

Beyond fighting obesity writ large, one could envision specific uses for brown fat—for example, as an infusion that protects heart attack victims from frequent after-effects that include developing type 2 diabetes or impaired heart functioning. A 2021 study found that mice fed a high-fat diet and then induced to have a heart attack had a better ability to process glucose and to exercise strenuously if they had received a prophylactic brown fat infusion soon after the heart attack (4). What’s more, compared with control mice, those who had received brown fat did not experience a common warning sign of coronary artery disease: an increase in the mass of the heart’s left ventricle.

The data are there to support the benefits of brown fat, according to study lead author Kristin Stanford, a physiologist and cell biologist at the Ohio State University Wexner Medical Center in Columbus. “Now we just need to figure out how to turn it up, to increase brown fat’s beneficial effects,” she says.

Human Potential

Although most of the research has been in mice, there are hints that approaches associated with brown fat could work in humans. Cohen and colleagues, as part of research published last year, reported an association between greater brown fat activity and lower risk of developing conditions such as high blood pressure and coronary artery disease, with particularly beneficial effects in obese people (5).

Quick, direct measurement of brown fat activity is not yet possible. Studies like Cohen’s use the standard approach: He and his group correlated a proxy measurement of brown fat activity such as high blood pressure and coronary artery disease, with particularly beneficial effects in obese people (5).

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Kajimura led a 2019 study of 33 healthy young men (with an average age of 23 years) who had varying amounts of brown fat activity as measured on PET/CT scans (2). First, the researchers measured brown fat activity at normal room temperature. Based on these measures, they classified 17 of the study subjects as having high brown fat activity and the other 16 as having low brown fat activity. They then exposed everyone to colder temperatures (19°C or 66 °F) for two hours, to activate their brown fat further.

Serum tests after the cold exposure showed that people with higher levels of brown fat activity had reduced amounts of branched chain amino acids (BCAAs) in their bloodstream; BCAAs are linked to greater incidence of obesity and type 2 diabetes. The more active brown fat had broken down a greater amount of BCAAs before they could circulate in the body and cause harm.

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Cohen and colleagues analyzed more than 100,000 PET and CT scans that had been collected at the Memorial Sloan Kettering Cancer Center in New York to detect whether and where cancer had spread among patients. These scans measured glucose activity throughout the body to seek out cancer cells, which consume more glucose than other cells. The researchers then isolated glucose activity within the body’s brown fat regions (generally speaking, in the upper body around the neck) by using the CT scans.

The 10% of patients who exhibited activated brown fat had significantly lower odds than the others of developing high cholesterol, type 2 diabetes, coronary artery disease, or cerebrovascular disease. Patients with activated brown fat and a body mass index (BMI) greater than 30 were less likely to develop these conditions than were people with a lower BMI who also had activated brown fat. For Cohen, the implication is that, although anyone of any weight could benefit from activated brown fat, heavier people could experience the greatest benefits in metabolic health.

If such findings could safely be translated to humans, the potential benefits are clear. But the techniques that researchers use on mice, such as force-feeding them a high-fat diet, obviously cannot be done on people. And that might not be the only hurdle. “The small animal biology for brown fat is profoundly different than, so far, the human biology both in terms of its physiological importance and the ability to pharmacologically and safely activate it,” Mount Sinai’s Drucker says.

An attempt at using medication to harness the benefits of brown fat offers important caveats and raises potential safety concerns. In 2020, in an off-label use, researchers at the National Institutes of Health reported that the drug mirabegron (Myrbetriq), which is used to build bladder capacity in people who urinate frequently, also increases brown fat activity (6). This drug, which binds to bladder cells to force the bladder muscles to relax and expand, binds to a protein that stimulates brown fat known as a β3-AR receptor.

Researchers recruited 14 women of various ethnicities who took 100 mg of mirabegron—double the FDA-approved dose for bladder control—every day for four weeks. The women demonstrated greater brown fat activity and better blood sugar control. But their blood pressure rose significantly and remained elevated for the four weeks—a known risk for drugs such as mirabegron. Even if a perfectly safe drug for activating brown fat entered the market, Drucker notes, it would have to compete with other effective therapies for type 2 diabetes.

**Careful Caveats**

Besides the translational challenge from mice to humans and drug safety concerns, the very act of measuring brown fat activity remains imprecise. Studies to date have relied on PET/CT images of glucose uptake in brown fat tissue, a proxy measurement. But as Kajimura’s 2019 study showed, brown fat also uses other fuels, such as BCAAs, which is why fewer of these amino acids are left in the bloodstream in people with robust brown fat activity. This means that if someone’s PET scan showed no glucose uptake, the official reading might falsely indicate no brown fat activity when in fact their brown fat is using different fuels.

Even a more accurate imaging test would expose people to radiation. In a perfect world, a simple blood test could accurately detail someone’s brown fat activity. Early preclinical work along these lines suggests that serum RNA levels fluctuate based on brown fat activity (7). But no widely adopted brown fat biomarker exists. A 2021 review by Cohen and Kajimura notes that there’s limited information, so far anyway, about how genetic mutations or someone’s ancestry might influence their brown fat activity (8).

This cluster of challenges continues to fuel Drucker’s skepticism. But he acknowledges that these roadblocks are not insurmountable. “Scientists have to be prepared to just go with the data,” Drucker says. “I’ll be the first person to stand up on the rooftops or go on Twitter and say, ‘Wow, look how far we’ve come.’”

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