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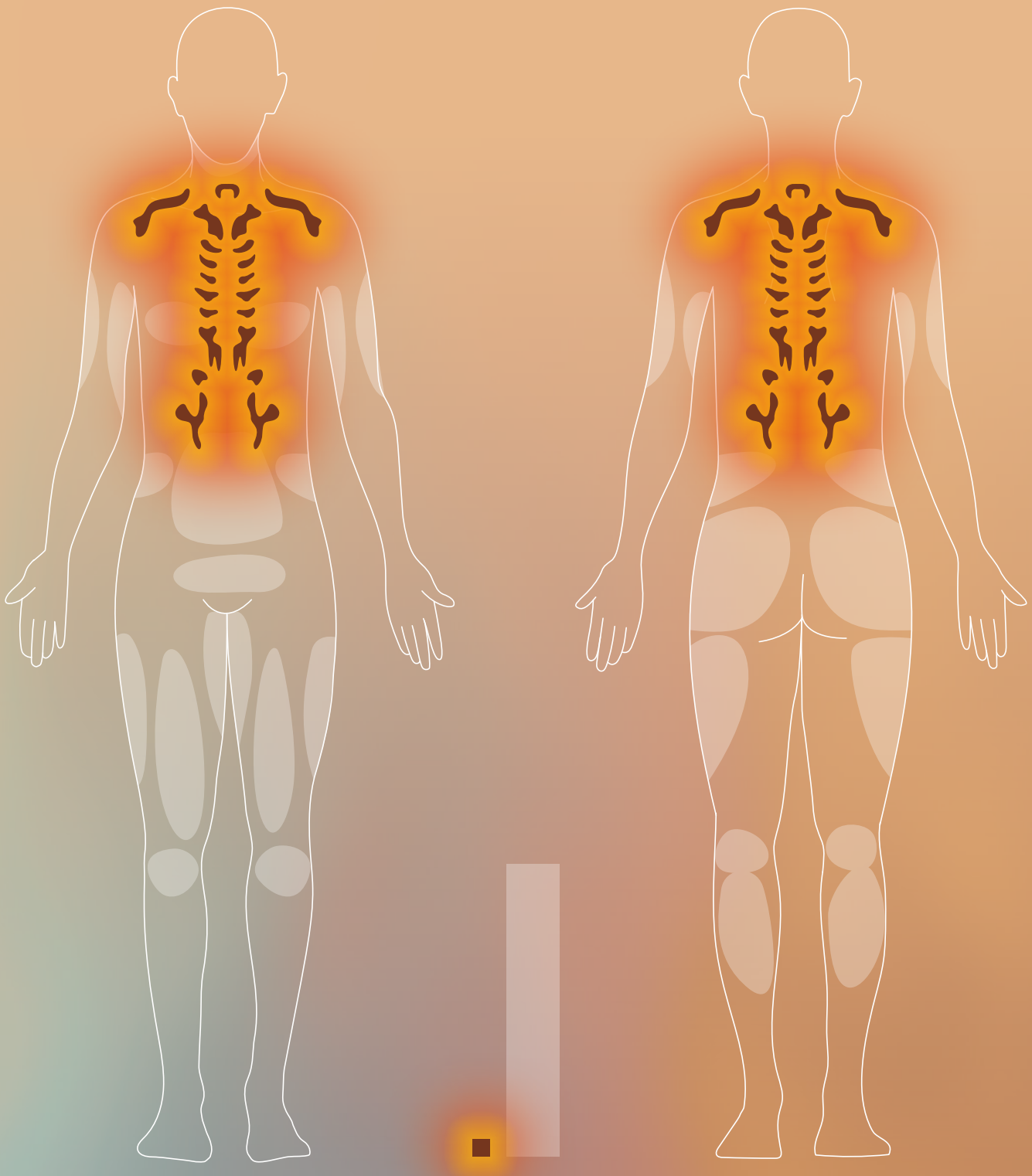
The fat that makes you slim?

Brown adipose tissue can produce heat without making our teeth chatter. But this natural “thermal jacket” has a further use: It tells the brain when we’ve had enough to eat. Does this offer a new approach to the treatment of overweight and obesity?



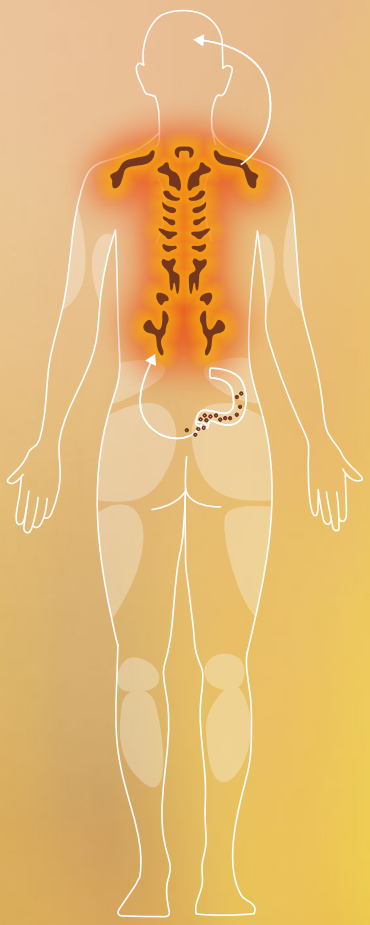
Humans have an average of 300 grams of brown adipose tissue. This tissue is to be found on the neck, collar bones, along the spine and near the kidneys. In contrast to white fat, of which a normal male adult has around 15 kilos, this brown tissue makes an active contribution towards generating heat.

Picture credits: Magdalena Jooss; Graphics: ediundsepp (source: TUM)

After feasting comes the hot flush. When the pork roast has been polished off, the last drops of sauce licked from the spoon and the final crumbs of cake consumed, most people start to feel warm. Because eating also means work for our bodies. But that is apparently not the only reason. The second seems to be our brown adipose tissue. This special type of fat can heat up the organism without making our teeth chatter. With this function, it acts like a thermal jacket. It's thanks to brown fat, for example, that small rodents foray out in search of food even when temperatures are far below zero and still maintain their body temperature. For a long time, scientists assumed that only babies and small mammals possess this special kind of fat. But that is not the case. "Almost 20 years ago, it was discovered that adults also still have small deposits of brown adipose tissue," explains Prof. Martin Klingenspor from the Chair for Molecular Nutritional Medicine at TUM's Else Kröner-Fresenius Center.

Initially, the decisive clues did not come from researchers studying the human metabolism, but oncologists looking for metastases in their patients. In this nuclear medicine process, radioactively marked glucose molecules are injected into the bloodstream. As cancer cells have a special predilection for sugar, they consume particularly large amounts of these energy-rich compounds. This can be detected with so-called PET-CT scans.

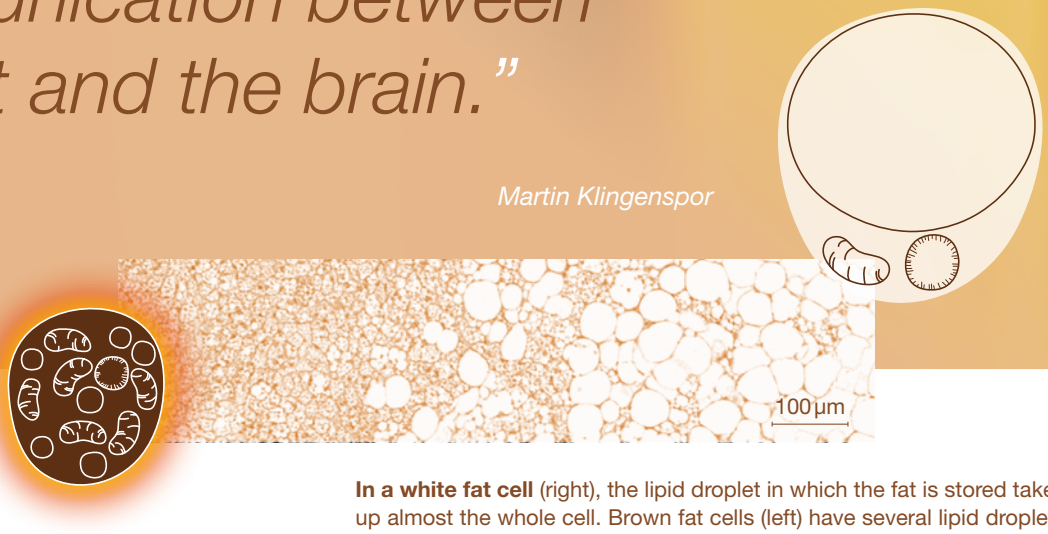
Doctors noticed that it was always the same regions which lit up in their images even with very different patients. In the neck area, above the collar bones and along the spine, occasionally around the kidneys. Could so many patients really have developed tumors in exactly the same places? That seemed unlikely. In 2009, three studies established beyond doubt that these tissues were active brown adipose tissue.



What Martin Klingenspor and his team discovered: During a meal, the cells of the duodenum produce the hormone secretin. It circulates through the bloodstream, docks onto receptors on brown fat cells and activates them: the tissue heats up. Special nerve cells in the brain register this rise in temperature, and trigger a feeling of satiety.

"The brown adipose tissue plays a central role in the communication between the gut and the brain."

Martin Klingenspor



In a white fat cell (right), the lipid droplet in which the fat is stored takes up almost the whole cell. Brown fat cells (left) have several lipid droplets that store less fat and also many mitochondria which are responsible for the high metabolic activity of these cells.

Overweight individuals have scarcely any brown adipose tissue

Older people or individuals suffering from diabetes or obesity had less or even no more brown adipose tissue that could be activated. It hasn't been clarified yet whether there is a causal connection or the loss is only a side effect of the disease. But since this discovery, there have been an increasing number of clues indicating that this thermal jacket also plays a very important role in our energy metabolism. Martin Klingenspor is driven by the following question: Can brown fat perhaps help to treat diabetes or obesity?

To understand how that might be possible, we first have to know that brown adipose tissue not only looks different but also has different tasks to white adipose tissue. Our body stores energy in this white adipose tissue for times when food is scarce. An average adult man carries about 15 kilos of white adipose tissue around with him, mainly in the abdomen, legs and hips.

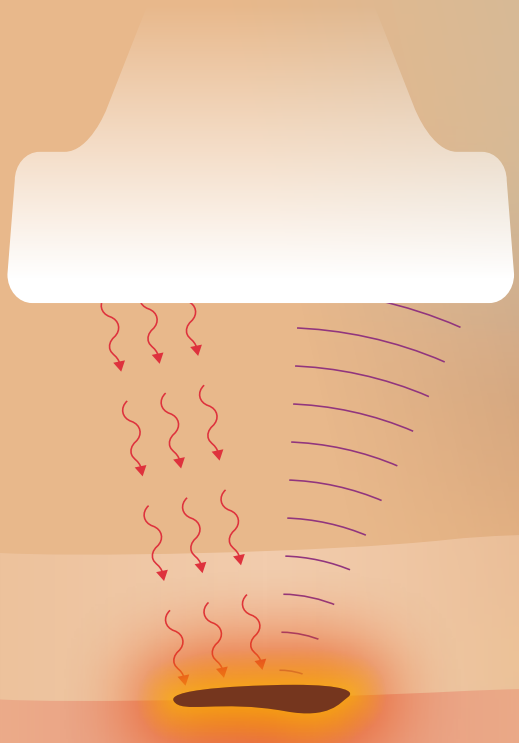
Brown fat, on the other hand, is much rarer, as every one of us has no more than an estimated 300 grams of such tissue. It is activated by cold when neural pathways in the brown adipose tissue leading from the brain release increasing quantities of the neurotransmitter noradrenalin. As a result of this stimulus, the cells begin to absorb and break down fatty acids and glucose as fuel from the blood. In contrast to all other tissues, however, the mitochondria, our cellular power plants, do not produce the molecule adenosine triphosphate (ATP), the universal source of energy. Instead, the energy is released directly in the form of heat. The blood heats up as a result and with it the whole body. Scientists refer to this process as thermogenesis, a specialist discipline of brown adipose tissue. If we spend time in a cold environment, our energy metabolism rises considerably as a result. Slender and slim from freezing? Possibly. But not pleasant. ▷

Picture credit: Magdalena Jooss; Graphics: ediundsepp (source: TUM)

Thanks to an invention by Prof. Vasilis Ntziachristos, researchers can now more easily make brown adipose tissue visible.

Laser and ultrasound in a single device

In “multispectral, optoacoustic tomography” developed by Ntziachristos, infrared laser pulses are beamed into the tissue. They heat it up locally, thereby generating ultrasonic waves that are shown on the computer as images.



This handheld device, placed on the skin, can measure the oxygen content in the underlying veins, thereby detecting increased activity.

Brown fat signals: satiated

Martin Klingenspor has discovered a further path by which brown adipose tissue can be activated: food intake itself. At a molecular level, this works as follows: Shortly after the beginning of a meal, the cells of the duodenum produce the hormone secretin. This stimulates the pancreas to change the pH level in the gut in such a way that the digestive enzymes can work to optimal effect. But that's not all.

Secretin circulates through the bloodstream, docks onto receptors on brown fat cells and activates them. The mitochondria work to their fullest capacity, and the tissue heats up. Special nerve cells in the brain register this rise in temperature, thereby prompting a feeling of satiation. "The brown adipose tissue plays a central role in the communication between the gut and the brain," Martin Klingenspor explains.

Exactly how the brain registers the activation of the brown adipose tissue is still to be researched. "Our pet hypothesis is that its activation first heats up the blood and then directly warms the brain," states the metabolism researcher. Two further approaches, however, are also conceivable, he concedes. On the one hand, it is possible that after activation, the brown adipose tissue releases its own neurotransmitters, called batokines, into the blood which reach the brain through the bloodstream. On the other, so-called afferent nerve fibers could transmit the information from the brown adipose tissue to the brain. "We're conducting our first experiments in the lab right now in order to confirm or disprove this theory," the scientist reports.

Through his discovery, the biologist has somewhat shifted the discussion of the significance of brown adipose tissue. Previously, everything had revolved around the question of whether the small amount of this tissue could in any way be sufficient to significantly alter the energy management of an organism by its activation. But since it has become known that it is involved in triggering feelings of satiation, it is now clear that large amounts may not even be needed. ▷

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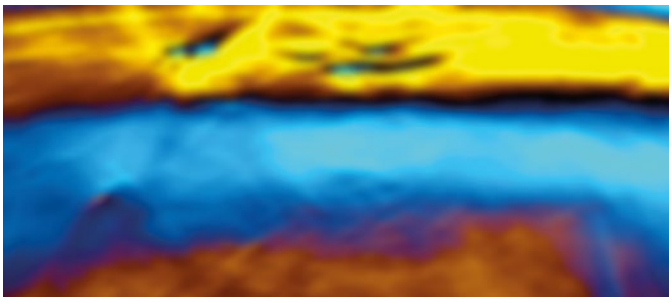
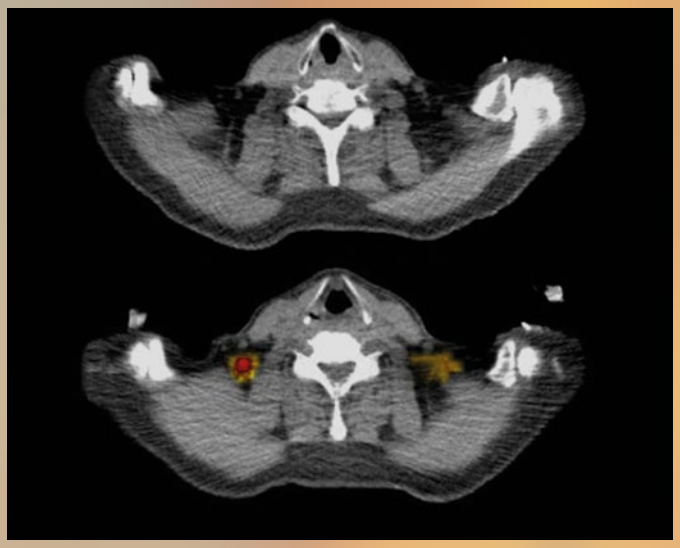


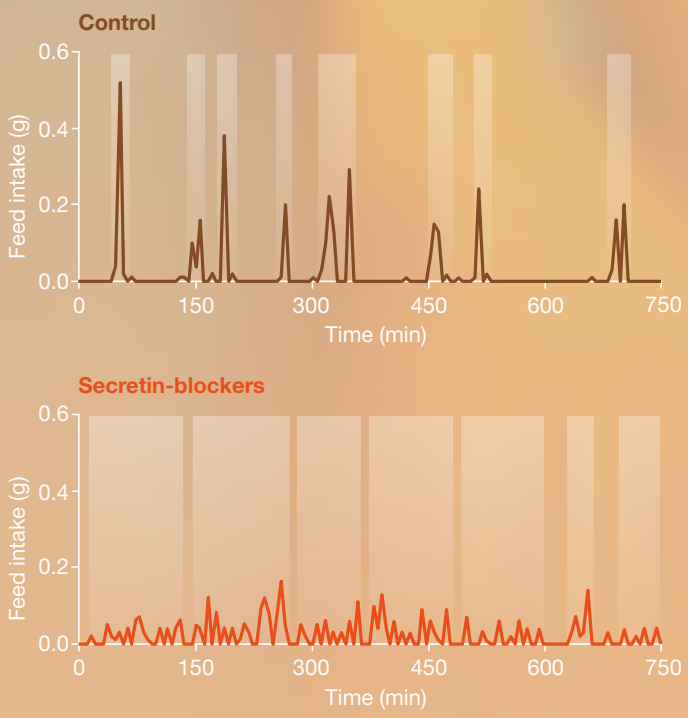
The ultrasonic images thereby created, shown here in false colors, indicate the brown fat layer.

Picture credits: Magdalena Jooss; Graphics: ediundsepp (source: TUM)

The effect of secretin on the cellular respiration of brown fat cells is examined in a respirometer.



The increased absorption of glucose by the brown adipose tissue, stimulated by secretin, can be shown by modern imaging technologies (above without, below with).



Mice did not become slimmer

In mice, secretin affects the number, size and length of meals. The total energy intake, however, remains the same. If the effect of the secretin is blocked by an antibody, the mice eat significantly larger portions but in fewer meals. These are marked here by the lightly shaded areas. We can see that the rodents take in exactly the same level of energy as they did before.

Could a secretin pill that makes you feel satiated soon be on the market as a new slimming aid? No, it's not that simple. Nocturnally active, mice eat around ten times per night. Secretin certainly affects the number, size and length of these "meals". The long-term energy intake remains unchanged, however. When the effect of secretin was blocked by means of an antibody, the eating habits of the mice changed. They ate significantly larger portions in altogether fewer sessions. The result, however, was that in the course of the whole day, their energy intake was exactly the same as before.

The reason is that from an evolutionary perspective, the regulation of our energy reserves has a major impact on our survival. "That is why there's more than one mechanism controlling the balance between energy intake and consumption," Martin Klingenspor explains. "There are multiple

Prof. Martin Klingenspor

Klingenspor studied biology at the Philipps University in Marburg. In 1994, the scientist obtained his doctorate in the field of animal physiology. After a research stay at the Lipid Research Laboratory in Los Angeles, USA, Martin Klingenspor returned to Marburg and became Assistant Professor for Animal Physiology. His habilitation followed in the same discipline in 2001. Klingenspor remained in Marburg for a further five years before moving on to TUM as Professor of Molecular Nutritional Medicine in 2007. The aim of his research is to find out how the body establishes a balance between food intake and energy consumption.

back-up systems just as with any technical system. And we have to expect our body to resist any intervention." That means if we consume more energy by activating our brown adipose tissue, we may also feel hungrier and eat more.

This research may also be advanced thanks to an invention by Vasilis Ntziachristos, Professor for Biological Imaging at TUM. He has developed so-called multispectral, optoacoustic tomography, a kind of ultrasound with laser light. Thanks to this method, researchers can now make brown adipose tissue visible without relying on a biopsy or radioactively labeled substances. Initial tests on mice and humans have shown promising results.

Martin Klingenspor now wants to find out what happens when secretin receptors in the brown adipose tissue are deactivated. This can quite easily be accomplished in mice by genetic engineering. "The metabolic activities in mice and humans are very similar, and we can derive genuinely good information from the mouse model for humans and make faster progress," the biologist explains. In such a mouse, you would not expect secretin to trigger any further feeling of satiation.

A miracle pill is still a distant prospect

He is also tracking down further activators of the brown adipose tissue. For example, Klingenspor intends to investigate the influence of the adrenocorticotropic hormone ACTH. So far, ACTH is known to stimulate the release of the stress hormone cortisol. But brown fat cells also have numerous ACTH receptors. What's their purpose? Hopefully, that will be revealed in the next few years.

In spite of all the groundbreaking innovations, we cannot expect a miracle pill for metabolic diseases anytime soon. "So far there have only been a few pharmacological therapies for obesity, and none of them relies solely on one drug," Martin Klingenspor says. People should still change their lifestyle, eat more healthily and play more sport in order to keep their weight in check. But it looks as if brown adipose tissue may be able to support this process.

Claudia Doyle

Picture credits: Magdalena Jooss; Graphics: ediundsepp (source: TUM; Li et al., 2018, Cell 175, 1570)