Brown fat cells in adult humans

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Brown fat is a thermogenic organ in mammals, which is activated by cold exposure. Brown fat cells use lipids as fuel in the mitochondria to produce heat. In humans, brown adipose tissue is present in infants and children playing an important role in thermoregulation. Recently, the presence of brown fat was discovered in human adults raising promises for understanding its role in health and disease. The first challenge is how to detect and measure activation of brown fat cells. Next, to describe the physiological role of brown fat during life in young and old individuals. Third, to investigate the brown adipose tissue in pathological conditions like obesity.

A fat cell that consumes energy sounds contradictive. It is nevertheless true for the heat-producing, mitochondria-rich brown fat cell. A sympathetic response to cold stimulates brown fat cells to burn stored lipids as fuel in the mitochondria, which uncouple through uncoupling protein 1 (UCP1), allowing the energy to dissipate as heat. This activation is associated with a simultaneous uptake of glucose and lipids from the blood stream to rebuild the lost lipid storages (Figure 1).

Thus, whereas brown fat primarily evolved as a thermogenic organ in mammals, it has the potential for counteracting obesity and its associated diseases. The discovery of cold-responsive brown fat cells in adult humans a decade ago further raised the expectations on identifying factors that could enhance brown fat cell activity in humans (1). Since then, research on human brown fat function and physiological relevance, as well as tools for investigating brown fat activity has exploded.

How to study brown fat in humans

A challenge in brown fat research in adult humans is the difficulty of obtaining brown fat needle biopsies. The reason for this is that the most accessible brown fat in adult humans appears in the neck region, and biopsies are thus associated with risks of accidentally injuring major blood vessels or even puncturing a lung. Another problem is that the fat tissue in this region is heterogeneous and only partly contains cold-responsive brown adipose tissue (BAT). Therefore, some laboratories have developed methods to perform PET/CT-scanning following cooling of the subjects, to find the areas of cold-responsive BAT prior to obtaining a needle biopsy in the neck region. This kind of approach is still risky and resource demanding and not possible for most laboratories. An alternative approach is to collect the tissue biopsies during unrelated neck surgery, for example during removal of a dysfunctional thyroid gland. With surgical approaches, it is also possible to access the deeper brown fat depots, including the tissue around the kidney, called perirenal fat.

Active brown fat cells can be visualized in humans by injecting a radioactive glucose tracer, cooling down the subject and subsequently performing a PET/CT or a PET/MRI scan. The cooling initiates a sympathetic response, which activates heat production in the brown fat cells, leading to lipid and glucose uptake. The fat tissue including the glucose tracer therefore represents the active brown fat cells.

An alternative technique is infrared thermography. This is simply a camera, which is sensitive for infrared radiation, and therefore detects fluctuations in heat. The camera images the skin temperature and is therefore only useful for studying the more superficial brown fat depots, including the one in the neck region. The advantages with this technique are that it is completely non-invasive and that it allows for measurements of brown fat heat production to acute stimuli in real-time. Using both techniques is so far preferable as the PET/CT or PET/MRI scans allows for a more precise quantification of the amount of active brown fat compared to infrared thermography.

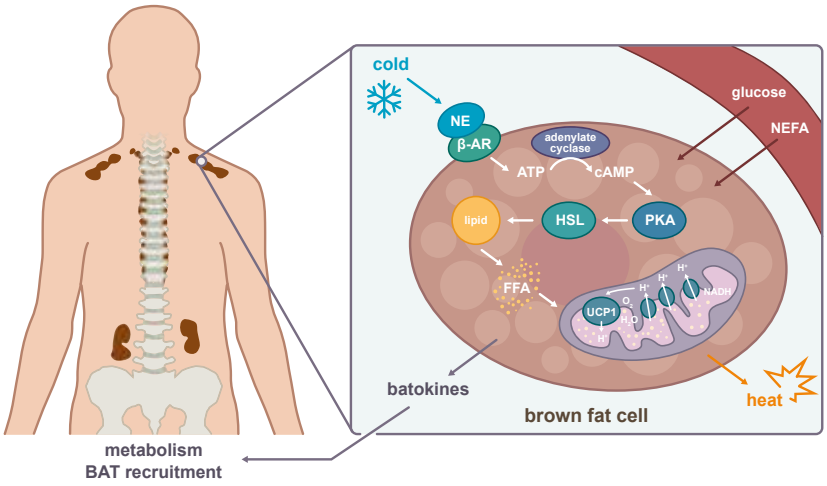

Figure 1. *Active Brown Fat. β-adrenergic signaling is induced by cold, and the released norepinephrine (NE) binds to β-adrenergic receptors at the brown fat cell surface. This induces a lipolysis signaling cascade including activation of adenylyl cyclase to catalyze the conversion of ATP into cyclic adenosine monophosphate (cAMP). The increased intracellular concentration of cAMP results in the activation of protein kinase A (PKA). PKA initiates lipolysis for example through activation of hormone sensitive lipase (HSL), resulting in the release of free fatty acids (FFA). These intracellular FFA constitute the main substrate for the active brown fat and allow for acceleration of the mitochondrial electron transport chain, building up a membrane potential in the mitochondria. The mitochondria are then uncoupled through mitochondrial brown fat uncoupling protein 1 (UCP1), resulting in the dissipation of energy as heat. Active brown fat has an increased plasma uptake of glucose and NEFA, and might thus serve as a "metabolic sink". There are some reports in the literature that active brown fat also secretes brown fat specific adipokines, known as "batokines" that could influence metabolism and/or induce recruitment of brown fat precursor cells. Reproduced from Scheele and Nielsen (1).*

Brown fat is reduced in aging and obesity

Brown fat is abundant and important in infants where it like a "thermogenic jacket" covers the back and the neck region as well as part of the arms. Brown fat activity decreases with age and although morphological traces of brown fat have been observed at high ages (2), the acute response to cold is decreased (3). Why do we get less active brown fat with age? An early hypothesis was that thermogenic regulation is immature in children while it gradually stabilizes with age. This could be beneficial for adaptation to the environmental conditions of a growing child. Today, most of us live our lives at thermoneutrality. We have central heating and warm clothes to protect us from cold. This could be a simple explanation to why brown fat activity declines in adult humans.

In obesity, brown fat responsiveness is even more reduced and the increased lipid storage is mainly handled by white fat cells. Interestingly, when obese people were subjected to daily cold treatments for a few weeks, their brown fat became more responsive to acute cold (4), suggesting a flexibility between an inactive, i.e. dormant, brown fat cell type, and an active brown fat cell type, which directly responds to cold by producing heat. This observation is supported by studies in mice. Here, housing mice at thermoneutrality results in a more white-like cell type in the brown fat depot.

Dormant brown fat in adult humans

We wanted to investigate the brown fat following the decline in activity in adults. We therefore performed a study on perirenal fat i.e. the fat tissue surrounding the kidney (5). The perirenal fat is interesting due to its asymmetric access to local sympathetic activity. The upper pole of the kidney is close to the adrenal gland, producing norepinephrine and epinephrine. By comparing different sites of the perirenal fat, we discovered

a more active BAT phenotype close to the adrenal gland, but also found that the rest of the perirenal fat were morphologically similar to white fat (WAT), yet contained brown preadipocytes and expressed some of the brown fat markers. We concluded that rather than disappearing with age, the brown fat surrounding the kidney becomes dormant and this is associated with local sources of sympathetic activity. This finding is important as it means that adult humans actually could increase their amounts of cold-responsive BAT by reactivation of dormant BAT depots.

Future perspectives

If we can identify regulators of brown fat cell recruitment by targeting brown fat progenitor cells or by switching the phenotype of white fat cells into brown-like cells with energy consuming properties, we would have a novel strategy to counteract obesity in humans.

Currently, researchers are putting much effort into investigating factors secreted from brown fat cells, called batokines. Some of these factors might be important for priming brown fat cell differentiation and for providing a reactivation of dormant brown fat cells. Other batokines could be important regulators of appetite and energy expenditure. Importantly, by studying the cross-talk between batokines and brain, novel pathways controlling appetite regulation could be identified. Indeed, efforts should focus on identification and neutralisation of brown fat induced energy-saving negative feedback circuits. Allowing the brown fat to be active for a longer time would increase the anti-obesity effect.

Another approach for understanding the regulation of fat cell properties can be provided by studying fat cell progenitor cells at single cell level. By comparing the gene expression between fat cell precursor cells derived from multiple brown and white fat depots, we hope to identify key regulators of brown versus white fat cell types, which then can be used to manipulate white fat progenitors into brown.

In conclusion, the last decade of brown fat research has leveraged our understanding of human brown fat biology and has thereby provided us with new tools and ideas on how to search for alternative anti-obesity strategies.

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