

## **Can your fat make you thin?**

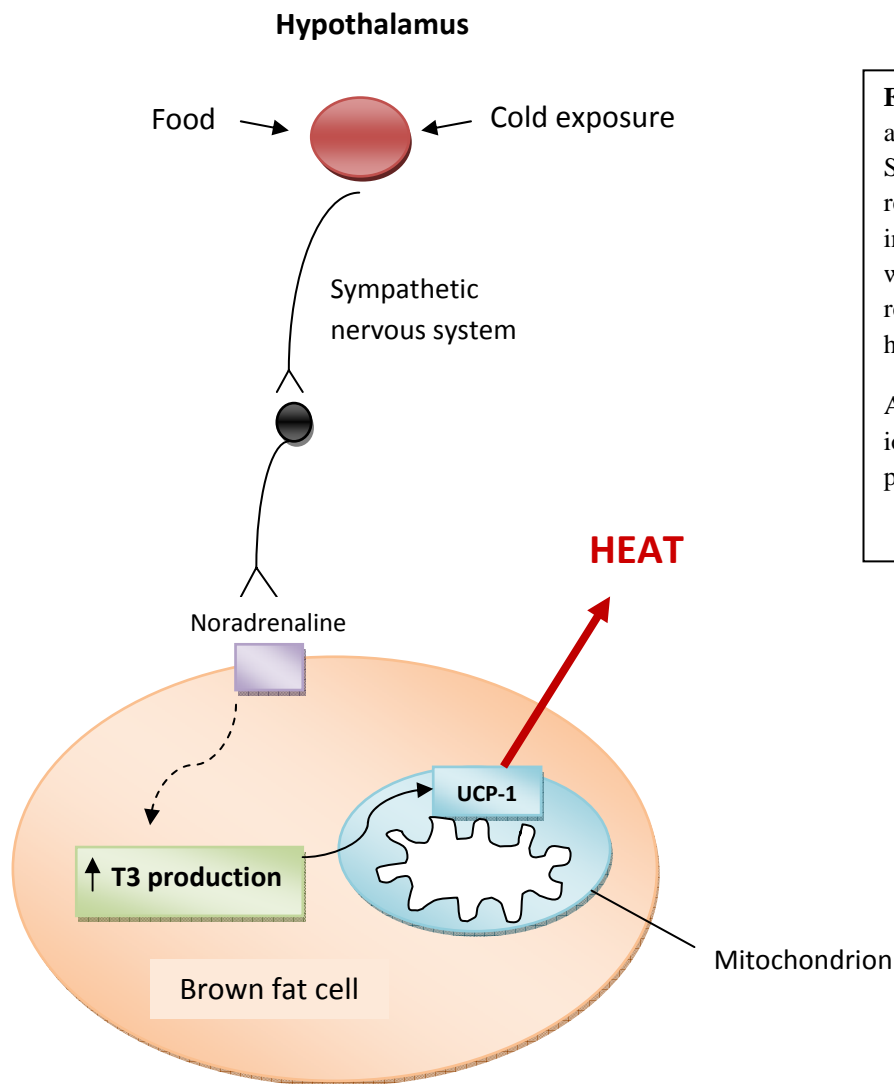
Hoping to shift a few pounds? You could subject yourself to a gruelling exercise regime, try the latest fad diet (anyone for cabbage soup?), take the newest blockbuster weight-loss pill or...simply chill out in the fridge for a couple of hours a day. Recent findings have suggested that specialised fat stores known as brown adipose tissue (BAT), which are activated by the cold, can help control body weight and may be a target for new anti-obesity therapies.

Obesity really *is* a big problem – currently in the UK almost two-thirds of adults and one-third of children are overweight or obese. The treatment of obesity and its co-morbidities is estimated to cost the NHS £4.2 billion per year. Obesity is defined as a surplus of body fat which is detrimental to health. This fat, or white adipose tissue (WAT), is located underneath the skin and around the internal organs and stores excess energy in the form of triglycerides. WAT located around the abdomen (giving rise to the ‘apple’ body shape) is considered more dangerous than fat stored around the hips and thighs as it is strongly correlated with type 2 diabetes, heart disease and certain types of cancer.

### **So, if fat is such a bad thing, is it really possible for your existing stores to help you burn calories and become a potential anti-obesity drug target?**

In mammals the other, less well known type of fat is BAT. Brown adipocytes (fat cells) are structurally very different to white fat cells. Although they still contain lipid, it is stored in many small droplets rather than in one big one. Brown fat cells contain large numbers of mitochondria (the energy-producing organelles within cells) which are packed with a specialised protein: uncoupling protein 1 (UCP-1). Usually, adenosine tri-phosphate (ATP), the main energy substrate in living organisms, is produced by the chemical process respiration which takes place in mitochondria. UCP-1 disrupts respiration and prevents the production of ATP. Hence, energy acquired from the uptake of free fatty acids and glucose from the circulation is burned off as heat, rather than being stored. UCP-1 is almost exclusively expressed in BAT.

BAT is activated by the sympathetic nervous system (SNS) and thyroid hormones. The release of noradrenaline by the SNS stimulates brown adipocyte proliferation and local production of tri-iodothyronine (T3, the active form of thyroid hormone) within BAT which stimulates the production of UCP-1. The SNS is activated by exposure to cold temperatures and the ingestion of high-calorie foods; hence, BAT is able to regulate both core body temperature and body weight by increasing energy expenditure (1) (Figure 1).



**Figure 1:** Diagram to represent the activation of brown adipose tissue. Stimulation of the SNS results in the release of noradrenaline, which increases the production of T3 within BAT. T3 stimulates UCP-1, resulting in the loss of energy as heat. Adapted from (2).  
Abbreviations: T3, tri-iodothyronine; UCP-1, uncoupling protein 1.

BAT is commonly found between the shoulder blades and around the internal organs and blood vessels. It is present in most small mammals and the newborns of larger animals, including humans. It is particularly important for babies to be able to produce heat via BAT as they have a large body surface area and therefore lose heat more easily. They are also unable to shiver, which is the normal mechanism of generating body heat.

It was previously thought that in humans BAT regresses by approximately one year of age and loses its heat-generating properties, except in very rare circumstances. For example in the 1980s it was

demonstrated that people who work outdoors in extremely cold conditions (in this case lumberjacks in Norway) have deposits of BAT around their neck arteries which were thought to warm blood flowing to the head. The size of these BAT ‘nests’ correlated with the length of time the participants worked in the cold (3).

Recent advances in imaging have challenged the view that BAT is neither present nor functional in most adult humans. In a specialised type of positron emission tomography (PET) scanning patients are injected with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), a radioactive form of glucose which is taken up by metabolically active tissues. Unlike glucose, once inside cells  $^{18}\text{F}$ -FDG only undergoes the first step of metabolism and becomes ‘trapped’; its emissions can then be detected. This type of scan is usually used to detect tumours as cancer cells take up large quantities of glucose to fuel their growth. From an oncologist’s perspective this technique is hampered by the fact that other metabolically active tissues such as the brain and heart, which also absorb large amounts of glucose, are labelled in addition to the tumour. However, this led to an unexpected discovery when a symmetrical area of glucose uptake commonly seen on scans around the neck and shoulders, originally thought to be muscle, turned out to be BAT (4).

Three studies published recently used the technique of  $^{18}\text{F}$ -FDG PET to determine the physiological relevance of BAT in adult humans (5, 6, 7). All demonstrated that BAT is present in adults (shown by  $^{18}\text{F}$ -FDG uptake), predominantly above the collar bones and around the neck. This distribution is different to that seen in rodents, where BAT stores are mainly located between the shoulder blades. Interestingly on average lean participants had more active BAT than overweight and obese participants, suggesting BAT may help protect against obesity (5, 6). As expected, exposure to cold temperatures (in this case dipping your foot in icy water) increased BAT activity (7). The probability of detecting BAT depended on the outdoor temperature at the time of scanning; detection rates were higher in the colder winter months than in the summer. Additionally, BAT was identified more readily in young women than older men, suggesting there may be age and sex differences (5).

### **So if BAT is present and active in adult humans, can it be targeted to help people lose weight?**

Body weight is determined by the fine balance between calories consumed and energy expended – if you burn more calories than you eat, you lose weight. Numerous attempts have been made to find a wonder drug which increases energy expenditure and burns fat. In the past, very high levels of thyroid hormones or drugs which stimulate the SNS were administered in an attempt to stimulate BAT but

both had unpleasant side effects. Dinitrophenol (DNP), a highly toxic industrial chemical, became popular in the 1930s when it was reported to cause dramatic weight loss by increasing metabolism by up to 50%. By affecting respiration in a similar way to UCP-1, DNP caused energy generated in mitochondria to be lost as heat rather than being stored as fat. DNP was banned in 1938 when thousands of people reported side effects such as blindness, blood disorders and death due to uncontrollable heat production. A less dangerous potential alternative was highlighted in 2005 when researchers found that fucoxanthin, the compound which gives seaweed its brown colour, increased the expression of UCP-1 in WAT and reduced the amount of abdominal fat in rodents (8). Although fucoxanthin is available to buy online as a slimming aid, no studies in humans have yet been carried out.

The recent identification of BAT in humans suggests that it is a potential target tissue for anti-obesity therapies. However, it might be of limited use in obese people who have smaller BAT stores to begin with. It would be useful if these stores could be increased and new BAT tissue formed, to boost calorie-burning capacity.

PRDM16 is a protein which is thought to control the development of brown adipocytes. It is expressed at much higher levels in BAT compared to WAT and 'knocking out' PRDM16 in BAT causes abnormal tissue development and a loss of heat-producing capacity (9). When PRDM16 is artificially over-expressed in the precursors of white fat cells it changes their fate and induces them to become brown fat cells instead. This causes the cells to express markers of BAT such as UCP-1. This phenomenon was demonstrated in mice engineered to express high levels of PRDM16 protein in their white fat stores, which resulted in BAT formation (9).

Although brown and white adipocytes are very different, it was commonly assumed that they originate from the same precursor. However, it was recently discovered that brown fat cells arise from the same progenitor as muscle cells, whereas white adipocytes emerge from an independent source. Like in white fat cell precursors, increasing the expression of PRDM16 in muscle cells causes them to differentiate into brown adipocytes (10). Therefore a drug which increases PRDM16 in either white fat cell precursors or muscle cells could be a potential future anti-obesity therapy – it may increase BAT stores, leading to increased energy expenditure and weight loss. Alternatively, PRDM16 could be used to transform stem cells into brown fat cells in a test tube, which could then be transplanted

into humans. However, it must be noted that the effectiveness of any weight loss therapy is limited as the body has many compensatory mechanisms in place to ensure your weight stays constant.

In conclusion, recent findings have shown that BAT is active and present in adult humans and demonstrated that it may be a target for future anti-obesity treatments. So, this winter try turning down the central heating and embracing the cold weather and maybe the pounds will fall off!

Words: 1497.

### Reference list

1. Celi FS 2009 Brown Adipose Tissue – When It Pays To Be Inefficient. *N Engl J Med* 360:1553-1556
2. Jia JJ, Tian YB, Cao ZH, Tao LL, Zhang X, Gao SZ, Ge CR, Lin QY, Jois M 2009 The polymorphisms of UCP-1 genes associated with fat metabolism, obesity and diabetes. *Mol Biol Rep*
3. Huttunen P, Hirvonen J, Kinnula V 1981 The occurrence of brown adipose tissue in outdoor workers. *Eur J Appl Physiol Occup Physiol* 46:339-345
4. Nedergaard J, Bengtsson T, Cannon B 2007 Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 293:E444-E452
5. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR 2009 Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 360:1509-1517
6. Van Marken Lichtenbelt WD, Vanhommelrig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ 2009 Cold activated brown adipose tissue in healthy men. *N Engl J Med* 360:1500-1508
7. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P 2009 Functional brown adipose tissue in healthy adults. *N Engl J Med* 360:1518-1525
8. Maeda H, Hosokawa M, Sashima T, Funayama K, Miyashita K 2005 Fucoxanthin from edible seaweed, *Undaria pinnatifida*, shows antiobesity effect through UCP1 expression in white adipose tissues. *Biochem Biophys Res Commun* 332:392-397
9. Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, Spiegelman BM 2007 Transcriptional control of brown fat determination by PRDM16. *Cell Metab* 6:38-54
10. Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scime A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM 2008 PRDM16 controls a brown fat/skeletal muscle switch. *Nature* 454:961-967