Joseph Robertson

New research by scientists investigating how our bodies store and convert fat into energy has begun to raise hopes for a new weapon in the fight against fat

Imagine we could lose weight by simply taking a drug. No strict exercise regimes, no fad diets. We could gorge on our favourite foods without having to worry about our waistlines. It could also help us to tackle the substantial obesity and diabetes problems that face us today (see pp. 27–31).

Key words

Adipocyte
Diabetes
Glucose
Metabolism
Obesity
Triglycerides

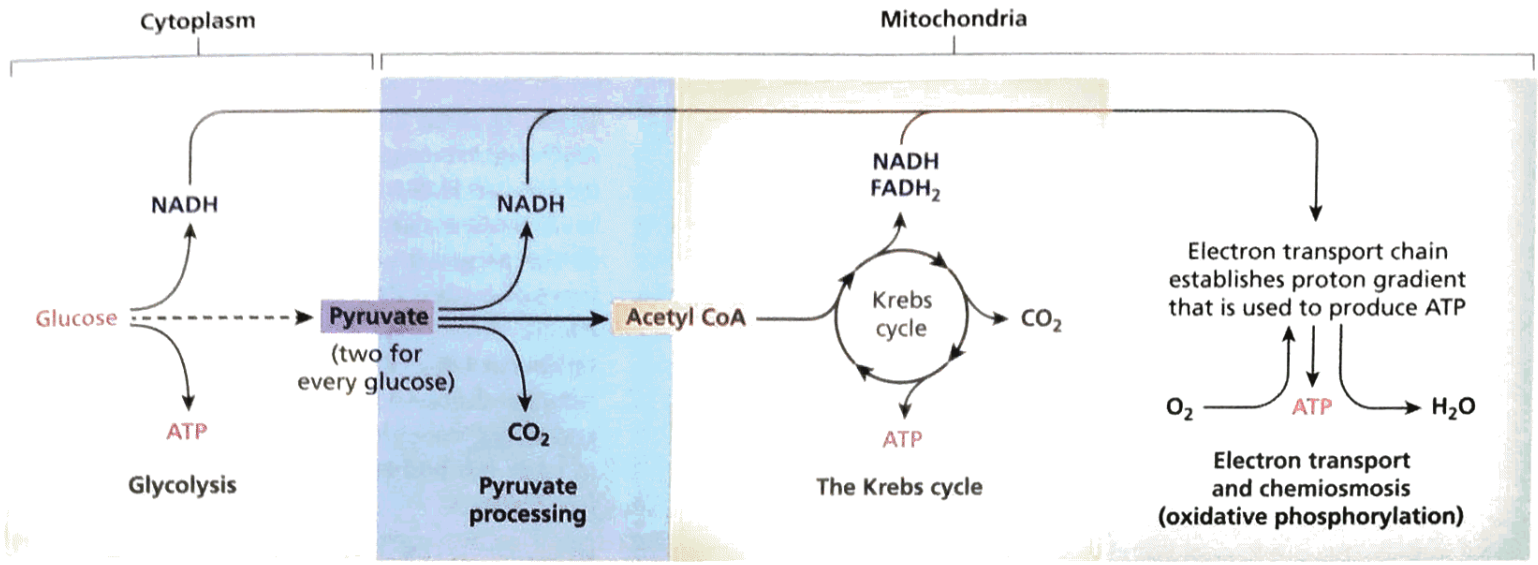


Figure 1 Energy-releasing reactions in our cells

Eating to live

The food and drink we consume on a daily basis supplies us with the energy that our cells need to function properly and to stay healthy. First and foremost, this energy comes from the carbohydrates in our diet. Carbohydrates provide us with the molecule that every cell in our body needs to use energy — glucose. The breakdown of carbohydrates by enzymes in our digestive system releases single molecules of glucose, which are absorbed into the bloodstream and transported around the body. In healthy, non-diabetic individuals, increased levels of glucose in the blood trigger the release of the hormone insulin from the pancreas and, consequently, the uptake of glucose by our cells. Here, glucose forms the starting material for the production of adenosine triphosphate (ATP) — the 'energy currency' of our cells (see Box 1 and Figure 1).

Our cells quickly use up a lot of the ATP produced from glucose. This is especially the case if we are physically active, because the muscle cells that go into overdrive during exercise need all the energy they can get to power their contraction. However, when there is enough ATP to fulfil our cells' requirements, glucose can instead be stored in different forms and locations around our bodies.

Storing energy

For short-term storage, glucose is converted into glycogen via a process called glycogenesis. Glycogen is stored in muscle and liver cells, and can be quickly converted back into glucose via a process called glycogenolysis when ATP is needed again. For longer-term storage, our bodies convert glucose into fat molecules called triglycerides (see Figure 2). These triglycerides are stored in fat cells called adipocytes (Latin, *adip* — fat; *cyte* — cell). As with glycogen, triglycerides can later be broken down and used for energy via a process called lipolysis when required.

Of course, excess glucose isn't the only source of fat that ends up in our adipocytes. A healthy diet should contain a decent proportion of fat, which gets broken down by lipases in our digestive system into its two major components — fatty acids and glycerol. These molecules, when absorbed into the bloodstream, are reassembled into triglycerides.

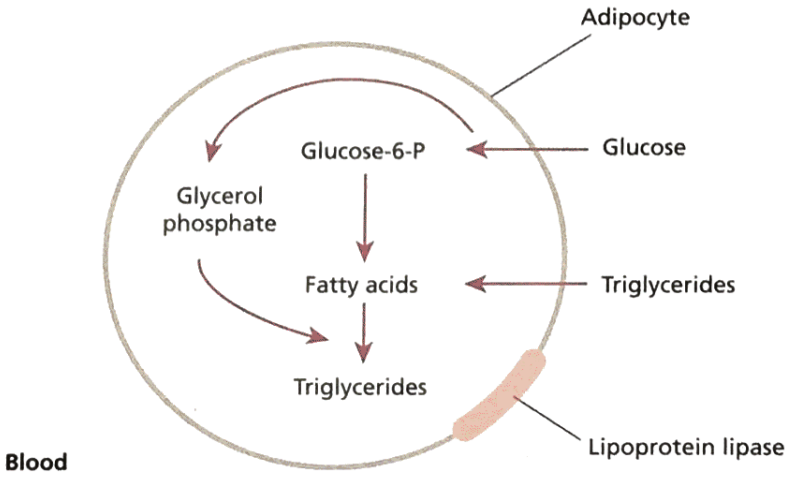


Figure 2 Fat storage and conversion of glucose to triglycerides in adipocytes

Box 1 Cellular respiration

Once inside our cells, glucose is processed by a set of exothermic (energy-releasing) reactions, including glycolysis, the Krebs cycle and oxidative phosphorylation. These processes lead to the production of ATP (which provides the energy our cells need to function and survive) and carbon dioxide (a waste product that gets transported back to the lungs via the bloodstream and exhaled) (see Figure 1 and **http://tinyurl.com/yayelo9** for some helpful videos explaining the Krebs cycle and oxidative phosphorylation).

If required, the triglycerides, like glucose, can be taken up by muscle cells to produce energy. Alternatively, they are taken up and stored by our adipocytes.

Stored fat can be good...

This stored fat plays numerous important roles in keeping us healthy. It provides us with a great alternative to carbohydrates as a source of energy — per gram, fats contain more than twice as much energy as carbohydrates. Adipocytes sit just beneath our skin and line our internal organs. The areas of the body in which triglycerides tend to get deposited vary slightly between women and men. In women more goes to the buttocks, thighs and hips, while in men more is stored in the belly. This is how fat provides us with insulation, protection and cushioning. In addition, several essential vitamins are soluble only in fat. Without fat, we would not be able to absorb and circulate these vitamins.

...or bad

Clearly, having enough fat is important. Most of us are aware, however, that there is such a thing as too much fat. Eating lots of food — especially food that is high in fat — and doing little exercise will make us overweight. All the energy that doesn't get used up by our cells has to be stored in our adipocytes. There are many health risks associated with being overweight or obese, including high blood pressure (which can lead to heart attack, see pp. 27–31) and an increased risk of developing type 2 diabetes. Obese people are more likely to develop certain types of cancer. This is not to mention the adverse effects obesity has on quality of life and mental wellbeing. Ultimately, we must get the balance right between eating the things we need, want and enjoy and doing enough exercise to ensure the amount of fat in our bodies is maintained at a healthy level (see Figure 3).

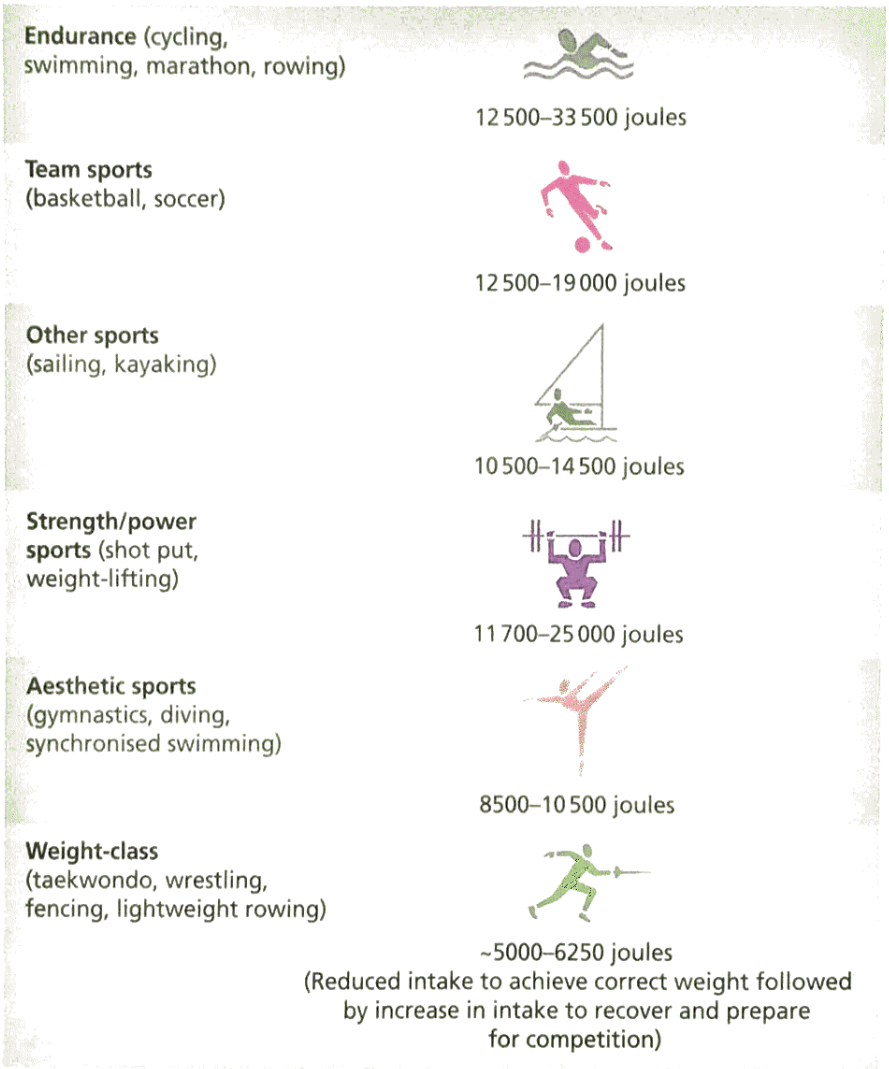


Figure 3 Rough estimates of energy consumed per day by different types of Olympic athlete (see **http://tinyurl.com/cehlv4u**)

White fat vs brown fat

There are two different types of fat. The type that stores energy as triglycerides is made up of white adipocytes, so the more white adipocytes we have, the fatter we get, and the more likely we are to develop heart disease and diabetes. A second type of fat, made up of brown adipocytes, does not store so many of the triglycerides. Instead, brown adipocytes burn up the triglycerides to release the energy contained in them, and release that energy as heat.

In humans, brown adipocytes were originally thought to be present only in newborn infants, where the heat they generate helps to protect from the cold conditions to which newborns are particularly susceptible. However, it is now known that brown adipocytes are also present in adults — roughly 60 g in the neck region of the average adult. These cells are thought to switch their activity on and off throughout the day in response to food intake, exercise or exposure to different temperatures. In mice, it has been shown that brown adipocytes help protect against diet-induced obesity and type 2 diabetes by preventing the build-up of triglycerides in other cell types, such as those in the liver and muscle.

So what is so different about brown adipocytes that allows them to burn up, rather than store, energy? One striking difference is that brown adipocytes have an abnormally high number of

Terms explained

Receptor A protein present in either the plasma membrane or nuclear membrane of cells that can 'sense' chemical signals and make the cell respond to these signals.

Transcription factor A protein present in the nucleus of cells that can bind to DNA to switch certain genes 'on' or 'off'. When a transcription factor switches a gene 'on', the cell starts to produce the protein encoded by that gene.

mitochondria (see pp. 20–21) — they have more mitochondria than any other cell type in the human body. Mitochondria are the energy factories of the cell — most of the ATP made by a cell is produced in its mitochondria. Brown adipocytes use their mitochondria to process triglycerides for energy, using exothermic reactions similar to those used by other cells to process glucose. However, rather than using the released energy to make lots of ATP, mitochondria in brown adipocytes switch off oxidative phosphorylation (the major producer of ATP in normal cells). Instead, the energy is released as heat.

Turning white fat brown

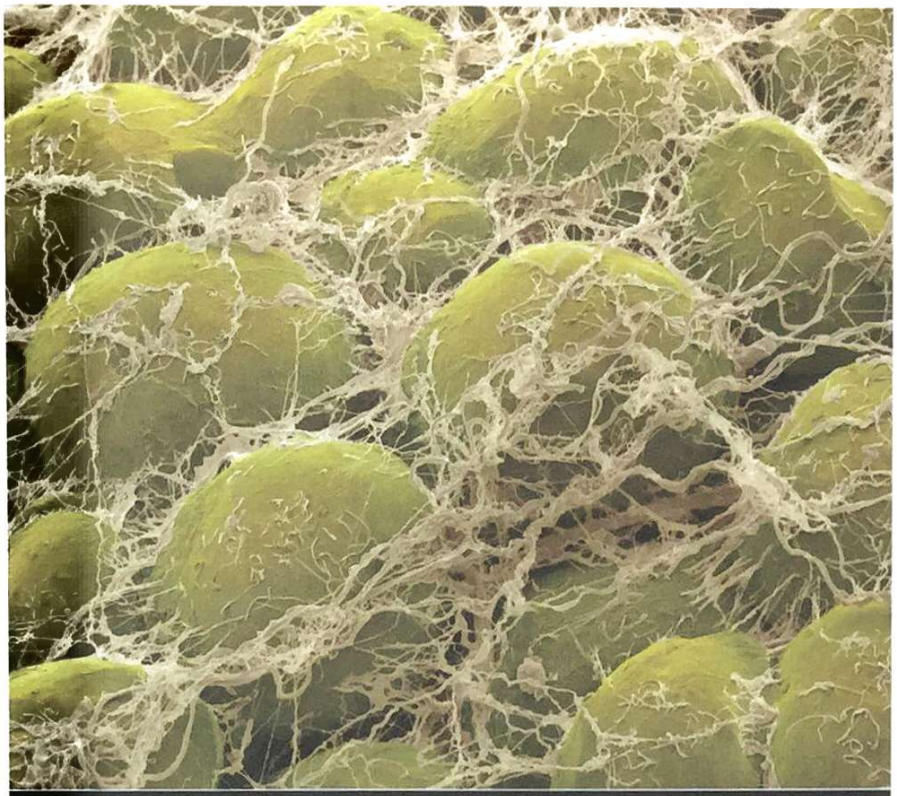
What if we could turn the energy-storing white fat into energy-burning brown fat? New research by scientists attempting to achieve this goal has produced some encouraging results. The scientists investigated a molecule found in fat cells called sirtuin, which is known to become activated when we exercise or reduce the number of joules (or calories — 1 calorie = ~4.2 joules) we consume. Interestingly, sirtuin has also been associated with the life extension that is caused by dramatically decreasing the number of calories consumed over long periods of time (so-called 'caloric restriction' — for example, see Box 2).

Could it be that sirtuin stimulates brown adipocytes to burn up triglycerides under energy-requiring conditions, and therefore that stimulating sirtuin in white fat cells could make them burn up fat instead of storing it?

It appears so. By investigating what happens in mice in which sirtuin activity was increased, scientists noticed that the mouse white adipocytes started to switch on some of the genes that are normally only switched on in brown adipocytes. The same white adipocytes also started to switch off some of their own genes, which aren't usually switched on in brown adipocytes. In short, the white adipocytes were turning into brown adipocytes.

The scientists were able to show that sirtuin does this by targeting and modifying a **receptor** on the nucleus of white adipocytes called PPARgamma. This receptor is involved in switching on a 'signal of plenty' when there is a lot of glucose and ATP present, triggering the storage of energy. However, when modified by sirtuin, PPARgamma activates a **transcription** factor called Prdm16 that switches on a set of genes necessary for using up chemical energy to produce heat instead of storing it as fat. In short, PPARgamma switches off the signal of plenty, favouring energy expenditure instead of storage (see Figure 5).

The scientists also showed that the 'browning' of white adipocytes in diabetic mice helped to restore their sensitivity to insulin, the hormone that tells



Steve Gschmeissner/SPL

Coloured scanning electron micrograph of adipocytes surrounded by fine strands of connective tissue (×400)

Box 2 Eat less, live longer

Scientists have performed research on many different species that suggests that reducing the amount of calories consumed can extend lifespan. Figure 4 shows the results of experiments using mice fed on either a normal diet (non-CR) or a diet in which the amount of calories the mice consumed was reduced by 25%, 55% or 65%. The more the number of calories the mice consumed was reduced (CR), the longer (on average) the mice survived. Such studies have led some humans to believe they will see similar results in themselves and live longer lives if they reduce the number of calories they eat on a daily basis (see **www.crsociety.org/about**).

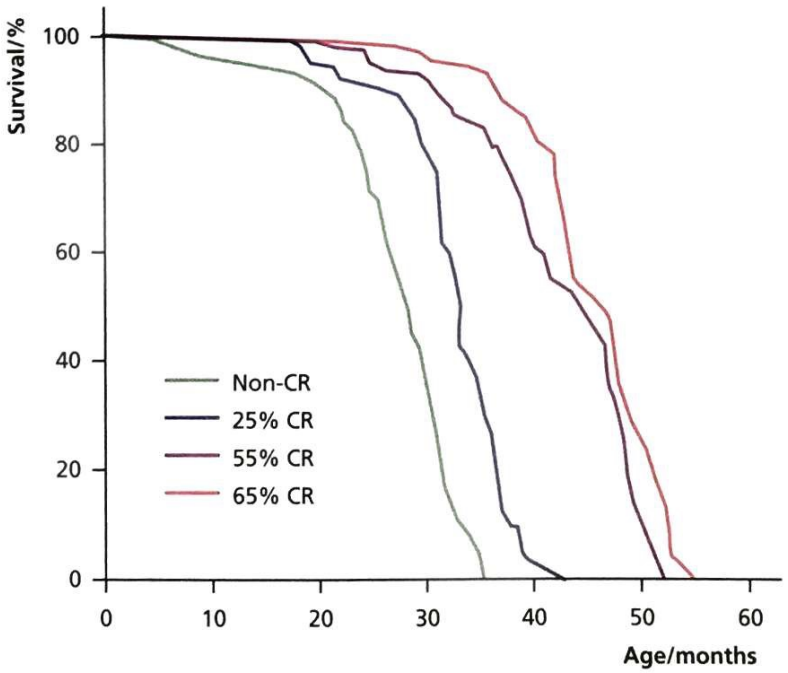


Figure 4 Lifespan of CR mice and non-CR mice

cells to absorb glucose from the blood (this process stops working in people with diabetes).

Activating sirtuin in humans

Scientists hope these findings will help develop drugs that promote sirtuin activity in white fat cells, making them less useful at storing energy as fat. If the same encouraging results are seen in humans, targeting sirtuin could prove a valuable therapy in treating type 2 diabetes and other conditions associated with being overweight or obese.

However, before we all scoff some cake in celebration, it is worth mentioning that the development of drugs targeting sirtuin is no trivial task. Sirtuin is known to play important roles in numerous different cellular processes in a diverse range of cell and tissue types. So activating sirtuin would likely affect more than just the storage of fat in our white adipocytes. It has even been suggested that sirtuin plays a role in cancer cells, making them more resistant to radiotherapy. Scientists will need to learn more about the way sirtuin works in different cells before they can consider testing drugs that target it in human trials.

The complications don't stop there. Even if we got as far as switching on sirtuin in white adipocytes without any nasty side effects, it would be important to do so in a controlled manner. After all, brown adipocytes are highly energy inefficient — they throw away energy as heat instead of putting it to good use. Over-stimulating our white adipocytes to behave like brown adipocytes might have the undesired effect of making us too thin, not to mention too hot.

Clearly, activating sirtuin to help us lose weight needs to be approached with some caution.

Fortunately, we already know the best way to avoid the health risks associated with being overweight: stick to a balanced diet and do plenty of exercise. This will always prove the most powerful weapon in the fight against fat.

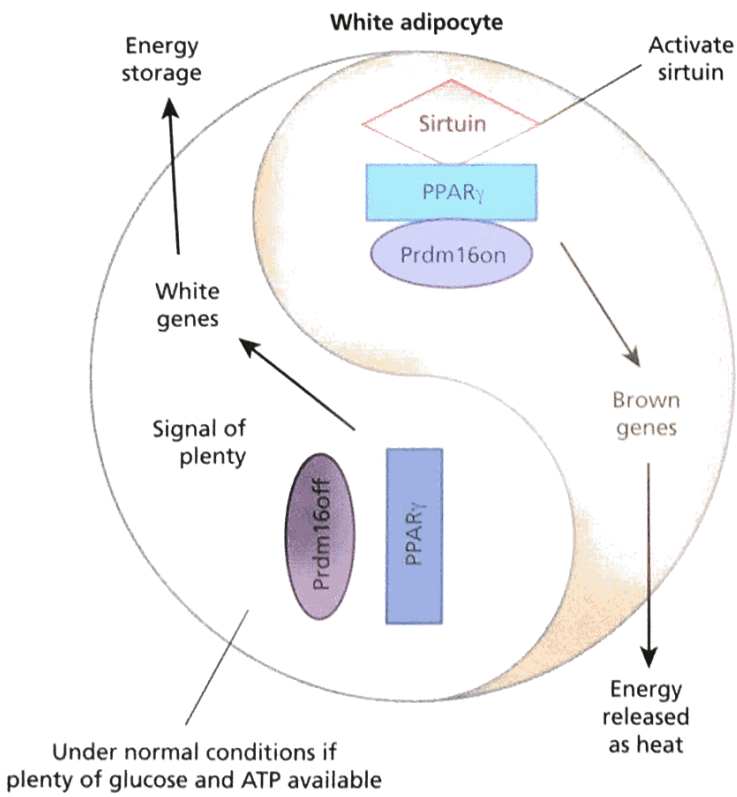


Figure 5 The role of sirtuin in switching off fat storage in white adipocytes

Points for discussion

- If there was an experimental sirtuin pill you could take, would you volunteer for trials?
- What would the economic/ethical consequences be if we were able to consume as many calories as we like and not get fat?

Joseph Robertson is a final year PhD student in the Faculty of Life Sciences at the University of Manchester. His research investigates cell adhesion. This article was based on a paper published in August 2012 by Qiang et al. (see Further reading).

Key points

- Excess energy is converted into fat molecules (triglycerides) and stored in cells called adipocytes.
- There are two types of adipocyte: white and brown.
- White adipocytes store energy as fat molecules, whereas brown adipocytes burn energy to release heat.
- Sirtuin promotes browning of white adipocytes, making them burn energy instead of storing it.
- Activated sirtuin modifies a nuclear receptor, making it switch on the genes necessary for burning energy.
- Drugs that activate sirtuin have potential as a therapy for obesity.

Further reading

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