Uncoupling mitochondria turns up the heat

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In eukaryotes, including animals and plants, the production of adenosine triphosphate (ATP) largely reflects the actions of mitochondria and chloroplasts. The energy usually transferred into the phosphate bonds of ATP can, alternatively, lead to the production of heat. This is accomplished through the actions of special proteins called uncouplers. Senior teaching fellow Katrine Wallis explains this remarkable process

Exam links

AQA Photosynthesis; Respiration
Edexcel A Light-dependent reactions of photosynthesis; Respiration
Edexcel B Respiration; Photosynthesis
OCR A Photosynthesis; Respiration
OCR B Cellular respiration; Photosynthesis
WJEC Eduqas The importance of ATP; Photosynthesis; Respiration

Key words

Mitochondria
Chloroplast
Electron transport
Uncoupling
Hibernation

In early spring, from Nova Scotia to the foothills of Minnesota, USA, winter is still apparent. Nonetheless, the eastern skunk cabbage (*Symplocarpus foetidus*) is melting the snow. Despite the temperature being only just above freezing, parts of the plant can maintain a temperature of around 15°C. This elevated temperature allows the plant to emerge and flower early (see Figure 1). It also allows the flowers to release chemicals that attract pollinators. These smelly chemicals are what gives the plant its specific name — *foetidus* (from the Latin for foul-smelling).

In northern America, groundhogs and other small mammals are still hibernating in their burrows. Their body temperature can be as low as 3°C, and while it regularly spikes to normal mammalian levels (37°C) it cools down again. These physiological events are the result of mitochondrial function (see Figure 2), inside both the skunk cabbage and in the hibernating mammals.

Mitochondria are found in cells of all eukaryotes. Their main function is not to release heat but to produce ATP. Producing ATP and releasing heat are biochemically related processes. Unlike animals, plants have another organelle that can produce ATP. In chloroplasts (see Figure 2), the **light-dependent reactions** of photosynthesis trap energy from light and couple it to ATP production. Here we will compare the heat release and ATP production from these organelles.

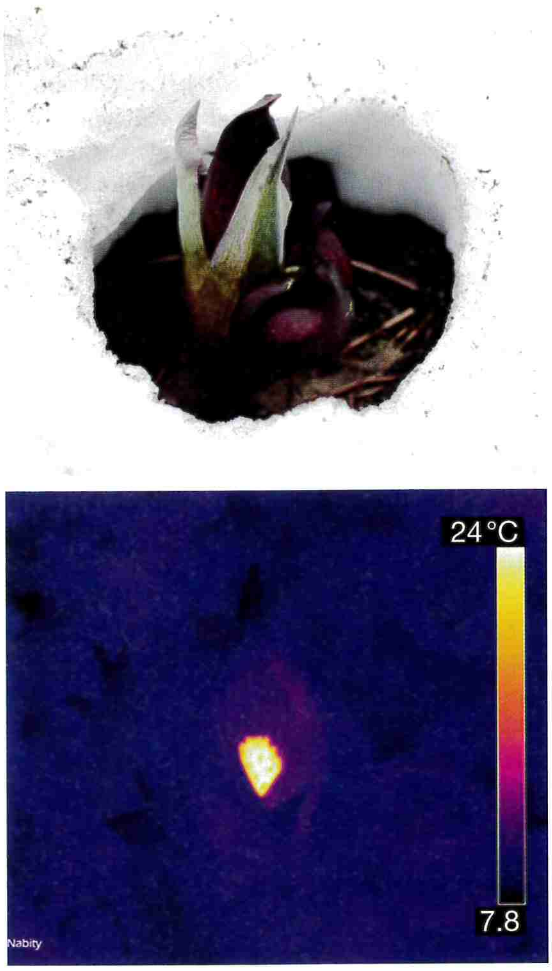


Figure 1 (Top) Skunk cabbage melting the snow. (Bottom) Thermal imaging of the plant shows that the **spadix** is some 16°C warmer than other plant tissues

Terms explained

Aerobic respiration The process of transferring cellular energy into ATP by involving oxygen.

Electron carrier A molecule capable of accepting an electron(s) before donating to another molecule.

Light-dependent reactions In photosynthesis, the creation of ATP and reduced NADP.

Light-independent reactions In plants, the use of carbon dioxide by the Calvin cycle to produce triose phosphate, some of which is then used to make glucose and other compounds.

Redox A change in reduction/oxidation state of a molecule.

Spadix A spike of small flowers packed tightly together on a small stem.

Thylakoid A membrane-bound compartment inside chloroplasts.

Uncoupling proteins allow hibernating groundhogs to warm up

Mitochondria and respiration

The energy needed to make ATP or to release heat comes from a series of reactions that make up **aerobic respiration**. The energy released from this process is linked to adding phosphate groups (P_i) to ADP molecules, creating ATP:

$$\text{glucose} + \text{oxygen} + P_i + \text{ADP} \rightarrow \text{carbon dioxide} + \text{water} + \text{ATP}$$

As part of this process, glucose is oxidised to carbon dioxide and some of its electrons are transferred to oxygen, which is reduced to water. This transfer of electrons is the key energy-transfer step, resulting in production of ATP. The electrons are not transferred directly from glucose to oxygen, but instead are transferred via a series of **electron carriers**, resulting in a gradual, controlled release of energy. Much of this process takes place in mitochondria (see Box 1). The energy released in this process is used to move protons (H^+) from the matrix of the mitochondrion to the inter-membrane space (IMS) resulting in a proton gradient building up, with a high concentration of protons in the IMS and a low concentration in the matrix (see Box 1).

Glucose has now been fully oxidised to carbon dioxide and the electrons have been transferred to their final destination, which is oxygen, but not much ATP has been made yet. Instead there is a proton gradient across the inner mitochondrial membrane (see Box 2). Just like a dam prevents water from flowing down the river, the membrane prevents the protons flowing back into the matrix. In the same way that dammed water can be used to release energy by passing the water through a turbine, the protons can flow through a membrane protein called ATP synthase. The ATP synthase acts like a turbine, as the flow of protons is used to spin part of the protein inside the membrane. This spinning results in the production of ATP (see Box 2).

The generation of a proton gradient used to drive the formation of ATP was termed the chemiosmosis theory by Peter Mitchell from the University of Oxford in 1969. We call this process **oxidative phosphorylation** because the oxidative process of moving electrons and building a proton gradient is coupled to addition of inorganic phosphate to ADP forming ATP.

Uncoupling

The coupling of the proton gradient with ATP production creates the vast majority of ATP that cells need. Sometimes the two are uncoupled to allow release of heat. This is equivalent to releasing some water from a dammed river without flowing it through the turbine. It is carried out by uncoupling proteins (UCP) in the inner mitochondrial membrane (see Box 2). In this case the energy from the proton gradient is released as heat.

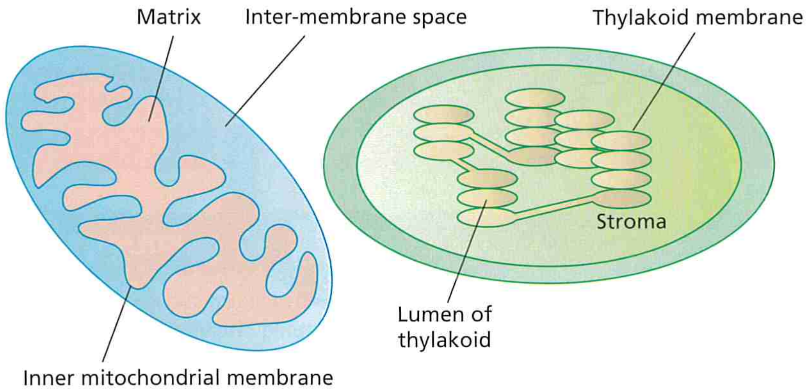
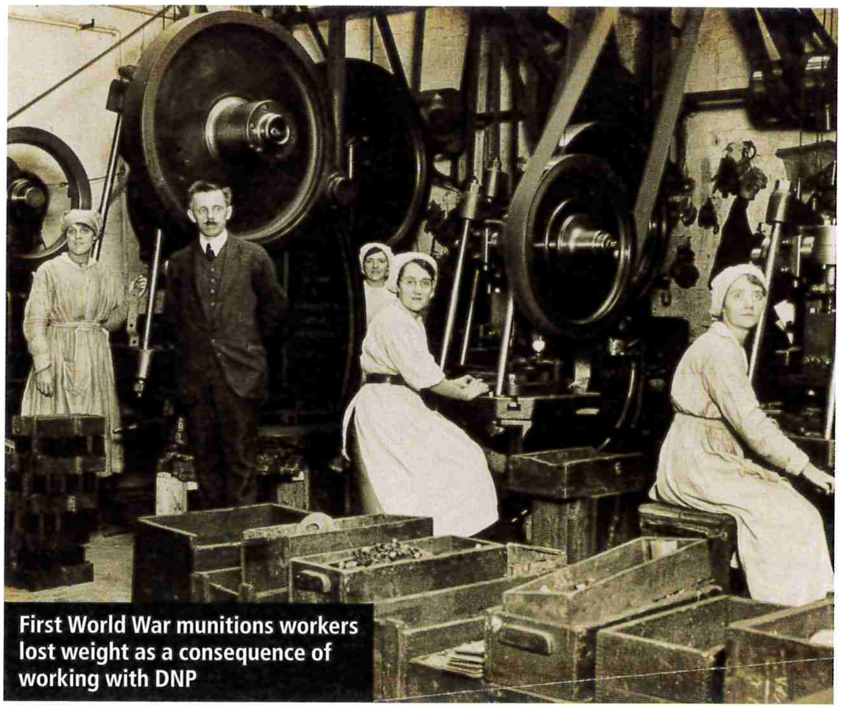


Figure 2 Structure of mitochondrion (left) and chloroplast (right)



First World War munitions workers lost weight as a consequence of working with DNP

In mammals this heat generating process mainly happens in specialised fat tissue known as brown fat owing to its large number of mitochondria and rich blood supply (which give it a brown shade). It is this uncoupling process that allows hibernating animals, such as groundhogs, to warm up their bodies to normal temperature. Other mammals can also generate heat through uncoupling. The process is particularly common in young animals that can struggle to keep warm. Uncoupling proteins are found in all known mammals that have been investigated except the pig.

Photosynthesis

Just like animals, plants use aerobic respiration to produce ATP. Unlike animals they can make it by photosynthesis. Photosynthesis happens in two stages. First, in the light-dependent reactions, light is harvested to make ATP. Then, in the **light-independent reactions**, the ATP is used to convert carbon dioxide into organic compounds. If we look at the energy-harvesting parts — the

Box 1 Electron transport

Mitochondrial electron transport

The electrons taken from glucose during its oxidation in glycolysis and the Krebs cycle are carried by reduced NAD (NADH). Electrons from NADH are transported along a series of electron carriers until they reach oxygen (see Figure 1.1, red arrows). The oxygen is then reduced to water. The carriers of electrons consist of three big protein complexes (I, III and IV) embedded in the membrane, and smaller carriers that ferry the electrons from one complex to the next. A carrier is in the reduced state when it is carrying electrons and in its oxidised state when it gives up the electrons. This process of transporting electrons releases energy, a little in each step, which is linked to transporting protons from the matrix, across the inner mitochondrial membrane to the IMS (green arrows). This results in a high concentration of protons in the IMS.

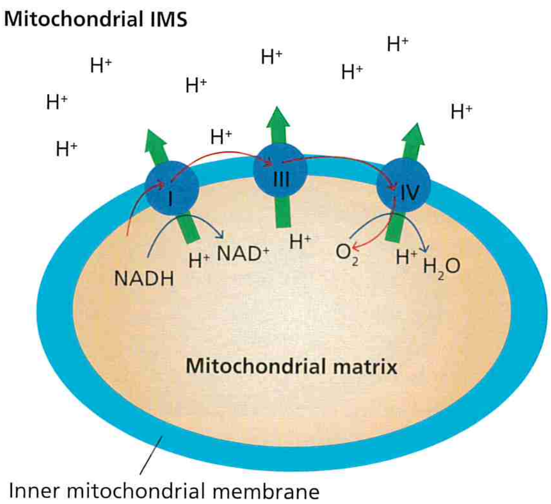


Figure 1.1

Light-dependent reactions of photosynthesis

The electron transport process is similar to the mitochondrial electron transport. Again, there are three large protein complexes in the membrane — photosystem 2 (PS2), cytochrome bf and photosystem 1 (PS1) (see Figure 1.2) and smaller carriers that ferry the electrons from one to the next (red arrows). As the electrons are transported from one carrier to the next, energy release is linked to transporting protons across the thylakoid membrane from the stroma into the lumen of the **thylakoid** (green arrows). However, unlike respiration, regular inputs of energy are needed during this process of electron transport. They are provided by light, which is harvested by photosynthetic pigments associated with PS2 and PS1. The final destination is oxidised NADP ($NADP^+$), which becomes reduced NADP (NADPH). PS2 replaces the electrons it lost by taking electrons from water in a process called photolysis, resulting in the release of oxygen.

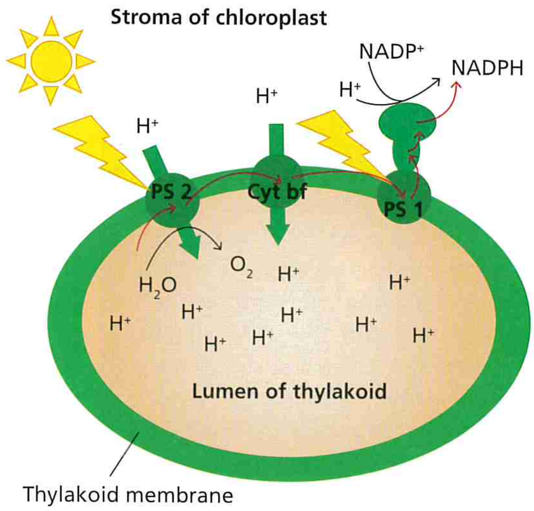


Figure 1.2

Further reading

'Toxic chemical DNP in weight loss products causes several deaths in Australia: NSW Health': **https://tinyurl.com/yyfnweee**

light-dependent reactions — they are similar to oxidative phosphorylation, used to generate ATP during aerobic respiration. Electrons are transported along a series of carriers and the energy released in these **redox** processes results in a proton gradient (see Box 1). Just like in respiration, this proton gradient is used to make ATP, except that this process happens in chloroplasts rather than mitochondria.

Uncoupling in plants

Most plants are less able than animals to move away if their environment becomes unfavourable. Most cannot move into the shade if there is too much sunlight. Plants have several mechanisms for dealing with too much light, including ways to uncouple the electron transport chain from the production of ATP.

Excess sunlight results in production of too much reduced NADP (see Box 1). This reduced NADP can be removed from the chloroplasts and converted into NADH, which is then transferred to the mitochondria. Plant mitochondria have mechanisms for releasing energy from NADH without creating ATP. They can bypass the electron transport chain by oxidising NADH without generating a proton gradient, simply releasing the energy as heat. They can also use uncoupling proteins, like those in mammalian mitochondria, to get rid of the proton gradient, releasing heat. Unlike animals, only a few plants, like the skunk cabbage, are adapted to use these mechanisms in physiological processes.

Pharmacological uncoupling

During the First World War it was noticed that some munitions workers were inexplicably losing weight. The cause was dinitrophenol (DNP) — a chemical used in the production of ammunition. Shortly thereafter, DNP was on the market as a weight loss drug. DNP can move protons through the inner mitochondrial membrane, hence it is an uncoupler. However, it quickly became apparent that far from being a wonder drug, its use can lead to liver damage and in many cases death, due to dangerous increases in body temperature. The drug was withdrawn from the market, but it is still sold illegally via the internet to people desperate to lose weight, often with tragic consequences.

Despite these poor results, it remains a hope that in the future we can make drugs that can uncouple electron transport and ATP production sufficiently to cause weight loss but not so much that it becomes life threatening. It is hoped that such drugs could help combat obesity.

In summary, mitochondria and chloroplasts function as power stations of the cells by using electron transport chains to generate a proton gradient across key membranes. This proton gradient is then coupled to ATP production, exploiting the energy released by allowing protons to cross the membranes. Disrupting this process through uncoupling can serve important physiological processes, such as generating heat or, in plants, helping to deal with excess sunlight. However, if this is not tightly regulated it can have disastrous consequences for the organism, as has been seen when drugs have been used to cause uncoupling.

Box 2 How can protons cross back over the membrane?

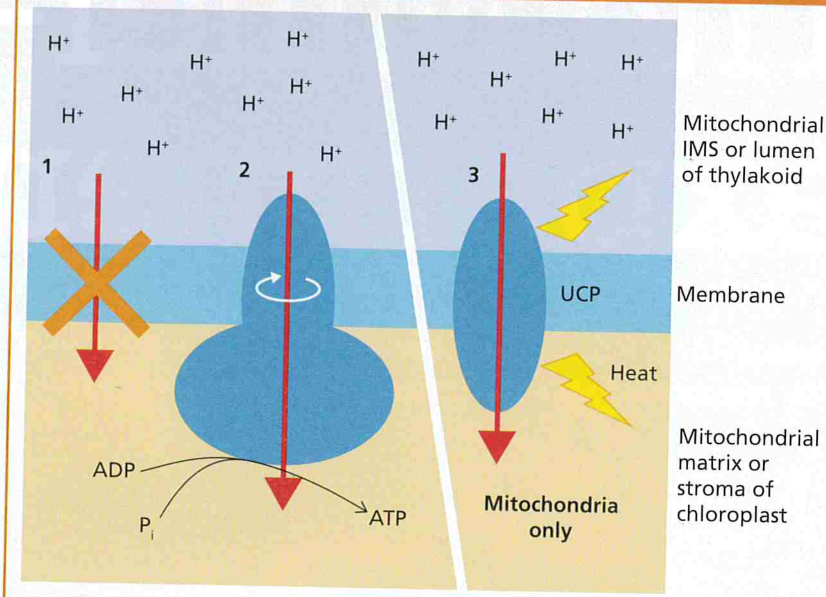


Figure 2.1

Electron transport, whether in the chloroplast or mitochondria, results in a high concentration of protons on one side of a membrane and a low concentration on the other side. Such a concentration gradient has potential energy, which can be released by letting the protons back to the side of the membrane where there are fewer protons. The protons, however, cannot pass freely through either the inner mitochondrial membrane or the thylakoid membrane (1) so must pass through the ATP synthase (2). The ATP synthase uses the energy released to spin part of its structure. The energy obtained from the spinning allows the production of ATP. In the mitochondria, uncoupling proteins (UCP) allow protons to go back into the matrix bypassing the ATP synthase under controlled conditions (3).

Dr Katrine Wallis has spent her research career as a biochemist studying the molecular mechanisms of protein disulfide isomerase. She is currently a senior teaching fellow in the School of Life Sciences at The University of Warwick.

Key points

- Mitochondria can uncouple oxidative phosphorylation in both plants and animals.
- Uncoupling of oxidative phosphorylation in mitochondria transfers energy into heat as an alternative to creating ATP.
- Ecological adaptations can be achieved by some animals and plants by using biochemical uncoupling.