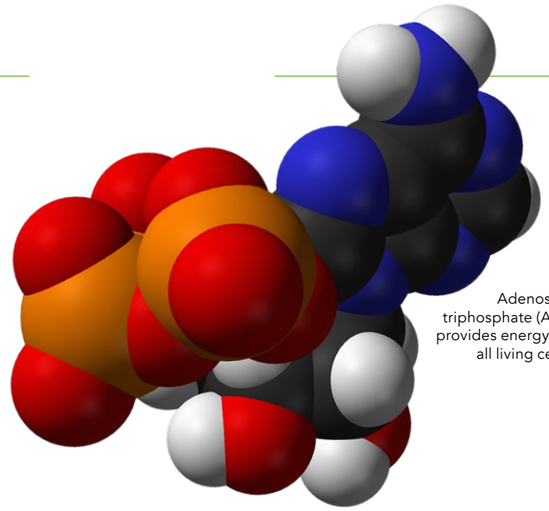
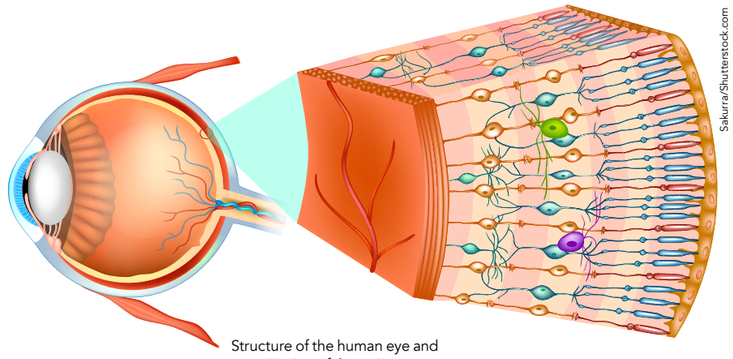
A new way of understanding bioenergetics



Adenosine triphosphate (ATP) provides energy for all living cells.



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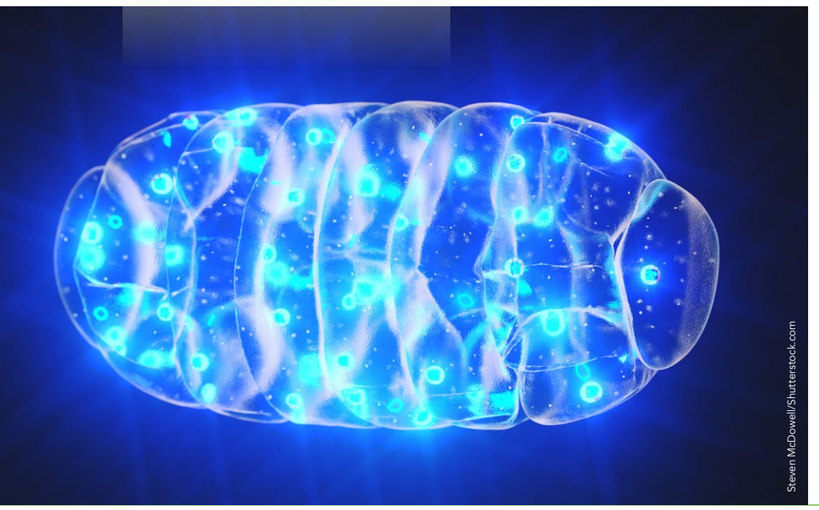
Structure of the human eye and organisation of the retina.

Extra-mitochondrial oxidative phosphorylation that leads to the production of energy, in the form of ATP, has been shown to occur in the rod outer segments in the retina. This supplies energy for the process whereby light is converted to an electrical impulse and carried by the optic nerve to the brain. Professor Alessandro Maria Morelli and Professor Isabella Panfoli, from the University of Genoa, Italy, show that extra-mitochondrial oxidative phosphorylation also occurs in the myelin sheath surrounding nerves, and suggest that it is a vital energy supply for the nerve.

Modern biology has taken a tumultuous turn since April 1953 with Watson and Crick's *Nature* paper describing the structure of DNA and the subsequent progress of molecular biology methods. This has translated into concrete results such as the mapping of the human genome, the advent of personalised medicine and, more recently, development of RNA vaccines against COVID-19. The same cannot be said for bioenergetics. For example, despite the clear energetic deficits documented for Alzheimer's disease and other neurodegenerative diseases, there have been no major advances in this field that have helped us to identify the exact molecular mechanisms that underpin the phenomenon of neurodegeneration.

Alessandro Maria Morelli from the University of Genoa, Italy, proposes a new way of understanding bioenergetics.



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It all started in 2008 with a discovery made by Isabella Panfoli, principal investigator in Morelli's laboratory. Panfoli demonstrated that the outer segments of rods – the photoreceptive cells within the eye – produce large quantities of ATP (the 'energy currency' of all biological systems). Yet outer segments of rods are completely devoid of mitochondria, the so-called 'powerhouse of the cell' – thought to be responsible for all energy production within cells. Morelli and Panfoli have made several groundbreaking contributions that are shaking up the traditional view that energy production (oxidative phosphorylation) occurs solely within mitochondria.

Morelli and Panfoli show that extra-mitochondrial oxidative phosphorylation occurs in the rod outer segments in the retina, where it converts light into an electrical signal. In addition, the researchers demonstrate that myelin – the sheath covering nerve fibres – plays an important role: supplying energy to the nerves.

EVIDENCE OF ATP PRODUCTION OUTSIDE THE MITOCHONDRIA

In 2020, Morelli, Panfoli, and their collaborators reviewed studies investigating the role of the myelin sheath around neurons in the central nervous system (CNS). There is a dramatic increase in conduction speed of the nervous signal in myelinated neurons, compared to unmyelinated neurons. This has traditionally been attributed to the 'electrical insulating properties' of myelin, thought to prevent electric current from dissipating as it travels along neurons. According to Morelli's group, this model does not explain the different conductive patterns seen in unmyelinated versus myelinated nerves. In a 2020 review, the researchers put forward the idea that myelin actively supplies ATP, essentially powering the signal conduction along the length of the nerve. In their model, Morelli and colleagues propose that the thickness of the myelin sheath is responsible for a directly proportional increase in ATP delivery, which in turn fuels the energy demand for high-speed nerve conduction.

Myelin actively supplies ATP, the molecule acting as the 'energy currency' of all biological systems, to power the conduction in the axons.

Morelli and colleagues propose a novel function for myelin based on bioenergetic considerations, ruling out physical mechanisms such as electrical insulation properties. Their hypothesis is that myelin directly synthesises ATP, which is transferred to the axons – the long projections of nerve cells that transfer signals away from the nerve cell body. In this model, the mechanisms of nerve conduction do not change between non-myelinated and myelinated nerves. The only change is the efficient flux of ATP that increases the speed of nerve impulses because the ATP feeds the sodium/potassium pump, restoring the correct ionic distribution, allowing propagation of electrical activity along the nerve (the 'action potential').

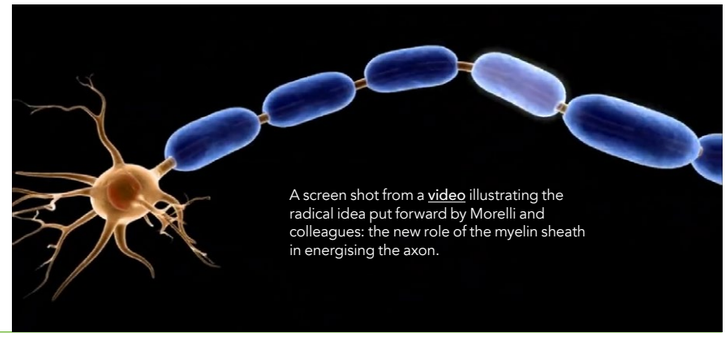
The authors point out that it has been demonstrated that ATP externally applied to unmyelinated neurons alters the membrane potential of the nerve cells. In addition, in 2008 Panfoli discovered that cells within the retina that are responsible for vision at low light levels: the rods (very long cylindrical photoreceptors), contain a large number of proteins that are typically associated with mitochondria. This came as a surprise, since rod outer segments were previously thought to be virtually free of mitochondria. Morelli and Panfoli conducted more investigations and in 2009 published functional measurements of rod outer segments, demonstrating that they are an extra-mitochondrial site responsible for oxidative phosphorylation with an ATP synthesis rate that is 50 times larger than that typically observed in mitochondria.

REVISITING THE MECHANISM OF ATP SYNTHESIS

As a result of their observations, Morelli and Panfoli published an article in 2020 demonstrating that ATP synthesis and cellular energy production can be sustained by other membranous structures besides mitochondria. Indeed, these structures were sometimes found to produce a higher level of ATP than mitochondria, as is the case for the rod outer segments in the retina. The authors outline that ATP synthesis has also been observed in diverse cellular systems, such as exosomes, microvesicles, cell plasma membranes, and platelets.

While the current chemiosmotic theory holds that ATP synthesis only occurs in systems equipped with double membranes (such as the mitochondria), Morelli and Panfoli suggest that extra-mitochondrial synthesis of ATP can take place on any single membrane.

Morelli and Panfoli put forward the idea that the mitochondria can export the machinery for aerobically synthesising ATP in extra-mitochondrial regions of the cell, primarily within the endoplasmic reticulum (ER). The mitochondria possess, via mitochondrial



A screen shot from a video illustrating the radical idea put forward by Morelli and colleagues: the new role of the myelin sheath in energising the axon.

Morelli shows that extra-mitochondrial oxidative phosphorylation occurs in the myelin sheath surrounding nerves, and is important for energy supply to the nerve.

Morelli and colleagues envisage that the myelin sheath acts as a capacitor, accumulating positive charge within the membrane during sleep.

DNA, the exclusive ability to assemble proteins for the cellular respiration apparatus, including the enzyme ATP synthase (the nanomachine that synthesises ATP). Thus, this vesicular transfer generates lipid structures in the ER, with the cellular respiration machinery operative in the ER itself.

Careful imaging experiments in cells shows that mitochondria and the ER are tightly associated, indicating that the two function together in healthy cells. When this relationship is lost, the aerobic capacity of the cell is affected. This could help to explain the impact of diminished cellular respiration observed in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.

The mitochondria could act in tandem with the endoplasmic reticulum to export the synthesis of ATP in extra-mitochondrial districts.

AN EXAMPLE OF CONVERGING EVOLUTION

In 2021, Morelli and collaborators contributed to the Royal Society's *Open Biology* with an article that aimed to systematically address the question: What is the role of the myelin sheath in nerve axons? The researchers offer compelling evidence that myelin sheaths with concentric multi-lamellar structures (membranous folds) possess similar bioenergetics to sheet-like membrane structures of cyanobacteria (known as thylakoids) that are responsible for the light-dependent reactions in photosynthesis.

Cyanobacteria are very ancient photosynthetic organisms, believed to have been responsible for the appearance of oxygen in the Earth's atmosphere. While the 2021 article does not claim that myelin itself was derived from cyanobacterial thylakoids, it brings to our attention that both structures share the function of feeding nutrients, potentially including ATP-synthase-derived ATP, into the central heart of a complex multi-lamellar structure. In the same way that cyanobacteria feed ATP, NADPH and bicarbonate to the carboxysome (for sustaining photosynthesis), myelin sheaths feed nerve axons with ATP.

In this way, the thylakoids and myelin sheaths can be seen as an example of 'convergent evolution'. Furthermore, the multi-lamellar thylakoids of cyanobacteria absorb/release CO_2 and oxygen respectively; conversely, myelin absorbs oxygen and releases CO_2. These crucial functions are possible due to the high lipid content of thylakoids and myelin, which have an affinity for gases that are approximately four times higher than water. In cyanobacteria it is worth noting that absorption of gases cannot make use of haem-proteins (such as haemoglobin), which appeared in more recent evolutionary time; whereas oxygen absorption carried out by lipids benefits combustion, and occurs in myelin with no blood supply.

A ROLE FOR MYELIN IN ENERGY REGULATION DURING SLEEP

With its newly identified role in ATP synthesis, the myelin sheath appears essential for the normal metabolic needs of the axons in the CNS and could explain how myelin loss in diseases like multiple sclerosis (MS) causes axonal tissue damage. Other researchers have described sleep problems and fatigue in MS patients.

During sleep, the demand for glucose in the brain is very similar to that observed in wakefulness, even though the energetic demand is low. Morelli and colleagues envisage that the myelin sheath acts as a capacitor, in other words: a store of positive charge that accumulates within the membrane during sleep. The energy accumulated by the 'proton capacitor' would then be transferred from myelin to the axon to make it active during periods of wakefulness. In this model, the authors provide a theoretical framework for the common assertion that during sleep we recharge our batteries. This, if proven, will constitute a milestone in the history of biology, solving one of the greatest mysteries of biology – sleep.

Behind the Research

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Research Objectives

Professor Alessandro Maria Morelli discovered the energetic function of myelin, which hosts the extramitochondrial synthesis of ATP. A revolution in neurobiology, it offers new insights for the study of neurodegenerative diseases and to understand the mysteries of sleep.

Detail

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Bio
Alessandro Maria Morelli retired from University of Genoa, Italy. His biochemical research has focused on the enzyme glucose-6-P-dehydrogenase and its molecular mechanism of senescence, on the phototransduction molecular events in photoreceptor cells of vertebrate retina. He discovered the protein FX, a NADP dependent enzyme, catalysing synthesis of GDP-L-fucose, and worked on the effects of electromagnetic fields on biosystems. Morelli discovered the energetic function of brain myelin and the ATP extramitochondrial synthesis operating in it, involving new paradigms for neurobiology, with applications in multiple sclerosis and other neurodegenerative diseases.

References

Morelli, AM, Chiantore, M, Ravera, S, et al (2021) Myelin sheath and cyanobacterial thylakoids as concentric multilamellar structures with similar bioenergetic properties. *Open Biology*, 11(12), 210177. doi.org/10.1098/rsob.210177

Morelli, AM, Ravera, S, Panfoli, I, (2020) The aerobic mitochondrial ATP synthesis from a comprehensive point of view. *Open Biology*, 10(10), 200224. doi.org/10.1098/rsob.200224

Ravera, S, Morelli, AM, Panfoli, I, (2020) Myelination increases chemical energy support to the axon without modifying the basic physicochemical mechanism of nerve conduction. *Neurochemistry International*, 141, 104883. doi.org/10.1016/j.neuint.2020.104883

Morelli, A, Ravera, S, Panfoli, I, (2011) Myelin sheath: a new possible role in sleep mechanism. *Sleep Medicine*, 12(2), 199. doi.org/10.1016/j.sleep.2010.06.010

Panfoli, I, Calzia, D, Bianchini, P, et al (2009) Evidence for aerobic metabolism in retinal rod outer segment disks. *Int J Biochem & Cell Biol*, 41(12), 2555–65. doi.org/10.1016/j.biocel.2009.08.013

Panfoli, I, Musante, L, Bachi, A, et al (2008) Proteomic analysis of the retinal rod outer segment disks. *Journal of Proteome Research*, 7(7), 2654–69. doi.org/10.1021/pr7006939

Personal Response

Do you plan to conduct experiment to investigate the role of myelin in the bioenergetics of neurodegenerative diseases?

There is evidence that neurodegenerative diseases such as multiple sclerosis (MS) and Alzheimer's can be triggered by impaired myelin lipid metabolism. First, it is necessary to clarify the biosynthesis of myelin lipids, where it is thought that galactose sugar favours construction of the myelin sheath. This role would be in line with the large amount of galactose – not free but condensed with glucose in the abundant lactose disaccharide – present in mammalian milk which is essential for the manufacture of myelin, which in many mammals is practically absent at birth. The preliminary results obtained with a regular intake of galactose have proved to be beneficial in counteracting the advancement of the disease both in patients with MS and Alzheimer's disease.

What experiments would you like to carry out to better understand the role of myelin?

I would like to investigate the mechanism of action of general anesthetics, a mechanism that still remains unknown today, despite being very effective, enabling the extraordinary advances that we all know of surgery. Preliminary data indicates that general anesthetics end up in myelin. Since it is known that they are decouplers of oxidative phosphorylation, they would prevent ATP production by myelin with consequent blocking of nerve conduction no longer supported by ATP. The similarities are remarkable between the state of unconsciousness due to the effect of general anesthetics and sleep. In effect, general anesthetics block the gap junctions and therefore block sending ATP to the axon by myelin, just as would happen during sleep. On the other hand, the sympathetic nervous system that controls the function of vital organs (such as the heart and lung) is not myelinated and therefore does not respond to the action of general anesthetics. Indeed, if anesthetics also acted on this nervous system it would be lethal. It is clear that knowledge of the mechanism of action of general anesthetics would pave the way for their improvement.