

# On your bike: how muscles respond to exercise

We all know that exercise makes us fitter and healthier – but what changes take place in our cells to make this happen?

By **Maléne Lindholm and Susanna Wallman Appel**

**N**ext time you are working out in the gym, or pounding the streets running or jogging, ponder this: the idea of ‘muscle memory’ – that today’s exercise has effects on our muscles years from now – has never been demonstrated scientifically. Does it really exist, and if so, how does it work? These are some of the questions we hope to answer in our on-going research, which aims to pin down the changes that occur in muscles when we exercise, and how our muscles ‘know’ to respond differently to, say, endurance training as opposed to strength training.

Helping us to investigate these questions is a large team of volunteers. Not only must they cycle to exhaustion in our gym, but before and after a strenuous exercise regime lasting several weeks, we take a tiny sample of their leg muscle under local anaesthetic (figure 1). The aim of our research is to help people optimise their training programmes for maximal fitness, and potentially to help develop new treatments for people who cannot exercise because they are paralysed or have joint diseases.

We assess the fitness of our volunteers before and after participation in the studies by measuring their maximal oxygen uptake. They cycle on an exercise bike against increasing resistance until exhausted, while wearing a

Image courtesy of Maléne Lindholm and Susanna Wallman Appel

**Figure 1:** A biopsy needle is used to take a fragment of muscle from the leg of a study participant. This tissue can reveal what changes occur in muscle fibres in response to different types of exercise



Image courtesy of Maléne Lindholm and Susanna Wallman Appel

**Figure 2:** Prior to the exercise studies, participants perform a test in which all their exhaled air is collected and the amount of oxygen taken up by the body is measured. This provides information on the fitness level of each participant’s heart and working muscles



Image courtesy of Maléne Lindholm and Susanna Wallman Appel

**Figure 3:** A microscope is used to visualise changes that occur within the muscle fibres in response to exercise. Different types of staining can reveal different structures within the cell. Here, one specific histone modification is stained in red, with the nuclei in blue and the cell membrane in green. To find out if a change has occurred, we would compare it with an image taken before training

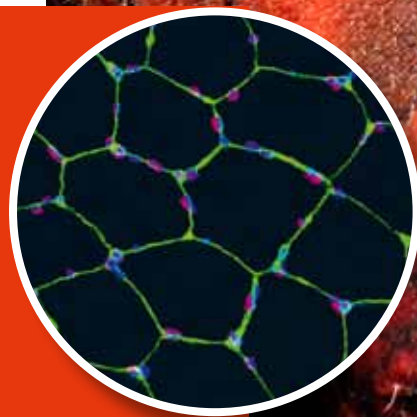


Image courtesy of Mariana Ruiz Villarreal; image source: Wikimedia Commons



Artist's impression of a cross-section of a mitochondrion, showing its inner folded membrane structure

mask to analyse their oxygen consumption (figure 2). This gives us information about the pumping capacity of the heart and metabolism of the working muscles – both factors associated with a person's fitness level.

Then we study the muscle tissue from the biopsies either by slicing and staining the tissue, then viewing it under a microscope (figure 3), or by breaking up the tissue and measuring the levels of particular molecules.

Of course, we already know that regular exercise produces health benefits. Physically active individuals have a lower risk of developing cardiovascular diseases, type II diabetes and certain types of cancer. Even a moderate amount of daily physical activity, for example 30 minutes of brisk walking, is enough to confer many of the benefits. And the more exercise we take, the greater the benefits. It's not just a question of how much exercise we take, though, but also what sort and how intense it is: different types of exercise produce different effects on the body. Heavy resistance training, such as weight lifting, causes skeletal muscles to grow, providing enhanced strength, whereas regular endurance exercise, for example long-distance running, cycling or aerobics, improves fitness and reduces fatigue.

How does regular endurance exercise lead to these effects? Over time, the heart gains the ability to pump larger strokes and after a couple of months of training, new tiny blood vessels (capillaries) form around muscle cells to ensure a good oxygen supply. Also, the number of mitochondria – the cell's 'power plants' – increases. Inside the mitochondria, enzymes use oxygen to turn digested sugar and fat into usable energy.



- ✓ Biology
- ✓ Genetics
- ✓ Ages 16+

Exercising is an activity that relates (or should relate) to every human on the planet; as such, it has received a lot of attention for decades. Although the potential benefits of exercise are well known, the cause of these benefits is largely unknown. This article gives an overview of some of the genetic factors that might be involved in the positive outcomes observed in the physical state of an individual who exercises.

Biologists and other persons with at least a modest understanding of genetics, including advanced secondary-school biology students, will probably find the information provided in this article highly interesting. They might even be motivated to think of alternative ways in which exercising can lead to health benefits.

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REVIEW

The more mitochondria the muscles have, the more fat and sugar they can metabolise and the more energy they can release.

But what we don't yet understand is exactly how exercise causes such changes. We are pursuing this question along two lines: first, how does exercise lead to more mitochondria in skeletal muscle cells? And second, how does exercise change the way in which the cell's DNA is used?

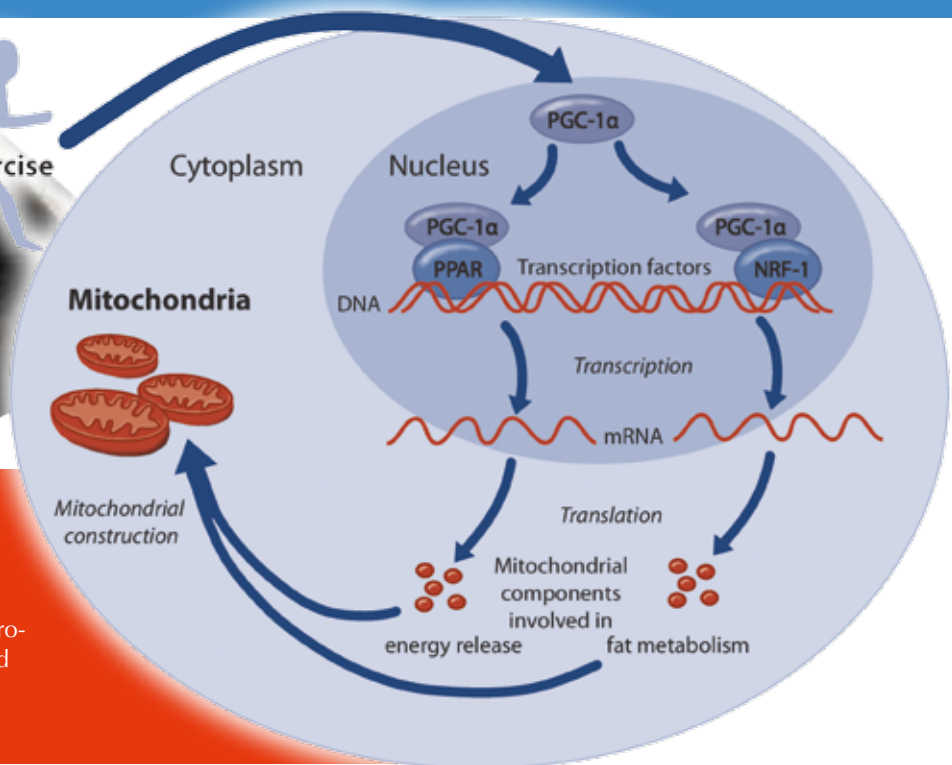


Image courtesy of Susanne Mikusch

**Figure 4:** PGC-1 $\alpha$  is one factor known to regulate the number of mitochondria in skeletal muscle fibres, thereby affecting endurance. Changes occurring during exercise stimulate the production of this protein, which acts in concert with specialised transcription factors (PPAR and NRF-1) to produce mitochondrial components

### Building mitochondria

Mitochondria are constructed from protein molecules, so factors that boost the production of mitochondrial proteins can increase the number of mitochondria in a cell. One factor that acts as a key regulator of the production of mitochondrial proteins is a molecule called PGC-1 $\alpha$  (figure 4).

For a gene to be *expressed* – that is, used to make a protein – the DNA information held in the nucleus must first be copied, or *transcribed*, onto an mRNA molecule. The mRNA molecules then move out of the nucleus to sites in the cell where protein molecules are constructed.

The transcription process is controlled by DNA-binding molecules called transcription factors. These attach to the DNA strand at very specific points, either blocking or promoting the transcription process. PGC-1 $\alpha$  acts in concert with transcription factors to promote the expression of many genes coding for mitochondrial proteins.

We have recently discovered that one variant of PGC-1 $\alpha$  is not present at all before exercise, but high levels of it can be found after only one hour of cycling. This suggests that certain genes are turned on exclusively by exercise, and this may be a clue to the

effects of exercise training on health. We are now investigating possible protein modulators of PGC-1 $\alpha$ , which may attach to this protein to increase or decrease its activity in boosting mitochondrial protein production.

### Epigenetic factors

We are also exploring the possible impact of exercise on *epigenetics*. Epigenetic changes affect how the DNA is used, without affecting the genetic information encoded within it. In our cells, DNA is wrapped around coin-shaped proteins called histones. Attaching small chemical molecules to the DNA strand or to histones affects the ability of transcription factors to reach their target genes. For example, adding a methyl (CH<sub>3</sub>) molecule to DNA generally makes the adjacent genes less accessible and thus less active, whereas attaching an acetyl (COCH<sub>3</sub>) group to histones usually relaxes that part of the DNA strand, making it more accessible for transcription (figure 5).

Using the biopsy material from our volunteers, we aim to see if such epigenetic effects remain after a prolonged period without physical training, and whether they influence how an individual responds to a

later period of training. Based on the results of these experiments, we will be able to investigate whether ‘muscle memory’ truly exists and, if so, how it works.

### Resources

To learn more about the role of exercise in the prevention and treatment of different diseases, see:

Henriksson J, Sundberg CJ (2008) General effects of physical activity. In Ståhle A (ed) *Physical Activity in the Prevention and Treatment of Disease* pp 11-37. Stockholm, Sweden: Professional Associations for Physical Activity. ISBN: 9789172577152. [www.fyss.se/wp-content/uploads/2011/02/fyss\\_2010\\_english.pdf](http://www.fyss.se/wp-content/uploads/2011/02/fyss_2010_english.pdf)

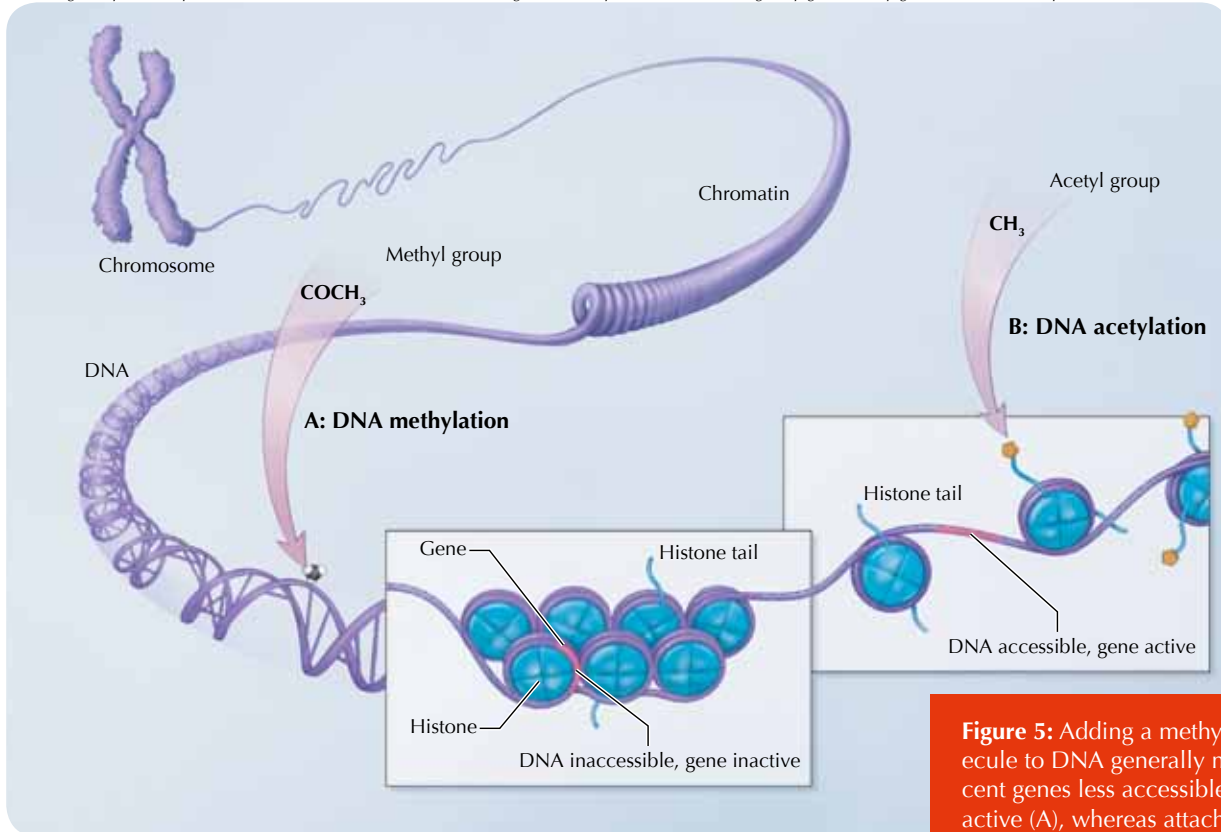
WHO (2010) Global recommendations on physical activity for health. ISBN: 9789241599979. [www.who.int/dietphysicalactivity/factsheet\\_recommendations](http://www.who.int/dietphysicalactivity/factsheet_recommendations)

The publication is currently available in English, Chinese, French, Russian and Spanish.

For more information about the physiological effects of exercise, see:

Wilmore JH, Costill DL, Kenney WL (2007) *Physiology of Sport and*

Image adapted with permission from the NIH Common Fund (for original, see: <http://commonfund.nih.gov/Epigenomics/epigeneticmechanisms.aspx>)



**Figure 5:** Adding a methyl ( $\text{CH}_3$ ) molecule to DNA generally makes the adjacent genes less accessible and thus less active (A), whereas attaching an acetyl ( $\text{COCH}_3$ ) group to histones usually relaxes that part of the DNA strand, making it more accessible for transcription (B)

Exercise 4<sup>th</sup> edition. Champaign, IL, USA: Human Kinetics. ISBN: 9780736055833

Information aimed at 14- to 16-year-old school students, with an online activity. See the BBC's GCSE Bitesize website ([www.bbc.co.uk/schools/gcsebitesize](http://www.bbc.co.uk/schools/gcsebitesize); search for 'effects of training and exercise') or use the direct link: <http://tinyurl.com/8xfk6l6>

'How the body responds to exercise' video on the US Teachers' Domain website ([www.teachersdomain.org](http://www.teachersdomain.org)) or via the direct link: <http://tinyurl.com/chvndus>

'Where do you get your energy' video on the US Teachers' Domain website ([www.teachersdomain.org](http://www.teachersdomain.org)) or via the direct link: <http://tinyurl.com/cfwct6g>

The following research articles provide more information about the scientific details:

Booth FW, Gordon SE, Carlson CJ, Hamilton MT (2000) Waging war on modern chronic diseases: primary

prevention through exercise biology. *Journal of Applied Physiology* **88(2)**: 774-787

Gollnick PD et al. (1973) Effect of training on enzyme activity and fiber composition of human skeletal muscle. *Journal of Applied Physiology* **34(1)**: 107-111

Norrbom J et al. (2011) Alternative splice variant PGC-1 $\alpha$ -b is strongly induced by exercise in human skeletal muscle. *American Journal of Physiology – Endocrinology and Metabolism* **301(6)**: E1092-1098. doi: 10.1152/ajpendo.00119.2011

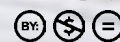
Norrbom J et al. (2010) Training response of mitochondrial transcription factors in human skeletal muscle. *Acta Physiologica* **198(1)**: 71-79. doi: 10.1111/j.1748-1716.2009.02030.x

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Maléne Lindholm and Susanna Wallman Appel are carrying out doctoral research on the effects of exercise on human skeletal muscle function and the concurrent health benefits. They both hold masters degrees in biomedicine from the Karolinska Institutet in Stockholm, Sweden, where they also teach physiology.



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