

# Exercise in a bottle

Elucidating how exercise conveys health benefits might lead to new therapeutic options for a range of diseases from cancer to metabolic syndrome

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There is no doubt that physical exercise is mostly good for your health and the list of benefits it provides grows with ever more studies being published. It is also helpful for the funding of research to understand the health benefits of exercise in detail, namely the molecules and metabolic and regulatory pathways that translate a workout into a healthier body. A major aim of this research was to identify key elements that could be manipulated using drugs to mimic the health benefits of physical activity: “exercise in a bottle”. Such a replacement for the “real thing” might sound rather frivolous, but it would actually offer a therapeutic option for people who are unable to engage in sufficient physical activity, for whatever reason. It could, for instance, kick-start a recovery programme for morbidly obese people, or for patients with severe injuries, at least until they are able to start exercising on their own.

Most research has focused on the impact of exercise on the metabolism of glucose and lipids for energy, along with insulin production and sensitivity, as these directly affect body weight, muscle and fat tissue and blood sugar levels. But physical activity also has a demonstrated positive effect on bone density and cognitive function. It can improve the outcome of cancer treatment and therapies for some autoimmune disorders, such as rheumatoid arthritis, as it dampens inflammatory reactions in the body. Lastly, exercise of course benefits the whole body, for example by strengthening the cardiovascular and skeletomuscular system.

Yet, the molecular details of how muscle action affects all these organs have proven rather elusive, as multiple molecules, pathways and organs are

involved. Research has therefore focused on a few key compounds that might elicit major benefits and therefore become candidates for manipulation with drugs. One of these molecules is irisin, which was discovered in 2002 as the circulating form of a transmembrane protein otherwise known as FNDC5 [1]. In mice models, irisin causes some of the metabolic benefits of exercise, such as reducing weight and offsetting the negative effects of a high-fat diet.

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Bruce Spiegelman at Harvard Medical School and colleagues further showed that irisin stimulates conversion of white fat cells to brown fat cells both in culture and *in vivo* [2]. While both cell types form adipose tissue in mammals, they have very different metabolic properties, which explains the significance of irisin. White fat primarily stores energy and remains relatively inert, whereas brown fat cells have many iron-containing mitochondria, which actively consume energy. Brown fat cells derive from the same stem cells as skeletal muscle and their primary function is to produce heat by short circuiting the proton gradient in mitochondrial membranes. By converting the sugars in lipids into heat, which is important, for example, in hibernating mammals and newborns to maintain their body temperature, brown fat cells can also cause

weight loss and have become research targets for treating morbid obesity.

Yet, it remained unclear whether irisin was also exerting the same effect in humans. In order to resolve this issue, Spiegelman and colleagues conducted a new study demonstrating that human irisin circulates at a level of 3.6 ng/ml in sedentary individuals, but increases to 4.3 ng/ml when those people undertake aerobic interval training [3]. “The methods we used are a version of mass spectrometry that is considered definitive, or as close as science has come, in the area of protein measurements”, Spiegelman said.

But as Mark Febbraio, Head of the Division of Diabetes & Metabolism at the Garvan Institute of Medical Research in Sydney, Australia, pointed out, it is still not clear whether the irisin circulating in humans is definitely produced by muscle tissue. “If you do a PubMed search on that, you will find as many papers saying that it is produced by muscle as that it isn’t”, he said, but pointed out that of course absence of evidence is not necessarily evidence of absence. In general, Febbraio gives more credence to the many papers that associate irisin with muscle contraction than to those that do not. Spiegelman himself conceded that while his study proves the existence of irisin, it does not conclusively prove it is associated with muscle contraction, because the sample was too small. “As noted in the paper, this method is very low input, so we were limited in the size of the exercise cohort. We certainly know that more data in many different populations is needed”, he said.

Notwithstanding these ongoing investigations, irisin cannot be considered a candidate for therapies until its mode of action is

fully elucidated. It is still possible that irisin might help to cope with the demands of exercise rather than having a direct effect on metabolism. “There are other schools of thought about the real meaning of cytokine release from the muscle, focusing on a response to muscular stress and/or muscular damage, or to a metabolic effect aimed to provide a greater energetic support to the muscle during the effort”, Domenico Di Raimondo, at the University of Palermo in Italy, said. “But these alternative points of view need further research themselves to be confirmed”. And even if irisin does have a direct bearing on metabolism, Febbraio pointed out that it will be only one among many candidates for therapies. “To suggest that irisin is a magic bullet is very naïve”, he said.

Another likely candidate for an exercise mimetic is a molecule called MOTS-c, but as with irisin, there is still uncertainty over exactly what it does. MOTS-c is a peptide of just 16 amino acids and is expressed by a mitochondrial gene, as shown by Pinchas Cohen and colleagues at the Leonard Davis School of Gerontology at the University of Southern California in Los Angeles, USA [4]. According to Cohen, their work is further evidence that mitochondria play a key role in signalling in addition to producing energy. “The skeletal muscle is the major target tissue of MOTS-c”, he said. “It enhances insulin sensitivity and increases glucose uptake in myocytes by activating the AMPK pathway, without increasing insulin secretion”. AMPK, or AMP-activated protein kinase, was identified in 1999 as the metabolic master switch and the central regulator of both lipid and glucose metabolism, making it an obvious target for therapeutic intervention against metabolic conditions, especially type-2 diabetes. “In that sense, we believe it is fair to call MOTS-c an exercise-mimetic”, Cohen added. “Exercise also increases muscle glucose uptake without stimulating insulin secretion. Thus, there is a possibility that MOTS-c may be involved in exercise-dependent muscle metabolism, and we are currently focusing our efforts to elucidate this matter”.

MOTS-c looks like a bigger player than irisin in modulating the link between muscle activity and metabolism. But the same caveat applies, as it is just one molecule among many others. Another key point is that the benefits of exercise are not

conferred by signalling molecules alone, but also result from larger scale physiological processes such as oxygen transport and increased heart rate. For this reason, the benefits of exercise cannot be simply bottled or encased in a pill, commented Ismail Laher, a specialist in pharmacology at the University of British Columbia Faculty of Medicine in Vancouver, Canada. “Exercise has a composite effect, which importantly makes it quite different from ‘exercise pills’ that target single molecular events in specific cell types”, he said. “So exercise reduces inflammation, altering cytokine release, reducing free radical levels and activity, while significantly improving endothelial function or the inner ‘Teflon’ lining of all blood vessels”.

Cohen said that the latter, in addition to benefitting cardiovascular function, also reduces inflammation. “The important thing to remember is that there is very credible and quite convincing evidence that most if not all cardiovascular diseases have a huge underlying component of inflammation”, he said. Inflammation is also known to play a role in some cancers and so research has been trying to identify how exercise might prevent cancer, and also whether it might benefit cancer patients alongside the traditional therapies of surgery, radiotherapy or chemotherapy.

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“There is now relatively consistent evidence that exercise improves survival after breast and colon cancer and emerging evidence that it is also beneficial for prostate cancer”, said Christine Friedenreich, Scientific Leader in Cancer Epidemiology and Prevention Research at the University of Calgary in Canada, one of the leading centres on the application of exercise in oncology. “Other cancer sites have not yet been adequately studied, but there is a strong likelihood that physical activity done either before or after diagnosis will improve survival in cancer patients”. Like Laher, Friedenreich is not keen on the idea of an exercise pill, partly because there is only

patchy knowledge about how physical activity influences multiple regulatory pathways that link to cancer.

What is known, though, is that some signalling molecules associated with metabolic syndrome can play a role in cancer development and are downregulated by exercise. This is the case with adipokines—cytokines released by adipose tissue—that are associated with the development of breast cancer in many obese post-menopausal women [5]. “Adipokines are released by fat depots, particularly related to visceral fat and are very harmful substances”, Laher explained. He added that exercise reduces the release of adipokines even in the absence of weight loss. “One does not need to have an obligatory weight loss in order to benefit from exercise—these are two independent effects”, Cohen said.

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These effects also mean that even if an “exercise pill” could not mimic all the beneficial aspects of the real thing, it might still help people who are currently unable to exercise to get to the point where they can start working out. “What we can do is find those peptides and pathways that have an influence on metabolic health”, Febbraio said. “That may lead to development of a therapeutic that will aid metabolic health in people who can’t exercise”.

Meanwhile, at the University of Sydney in Australia, Nolan Hoffman and his colleagues have been analysing multiple pathways of exercise in the search for therapeutic targets. “At this stage we have generated a blueprint of the molecular signals that occur in skeletal muscle after a single bout of high intensity exercise in healthy, untrained males”, Hoffman explained. “The next step is to narrow down which components within this complex network underlie the beneficial effects of exercise on metabolic health and find either new or existing drugs that can

target these molecules". Their work has identified more than 1,000 molecular changes in skeletal muscle alone after just one session of exercise. "The physiological effects of exercise are extremely complex and elicit a broad range of short-term and long-term changes throughout the body involving many organs such as the brain, liver, fat and blood vessels", Hoffman said. "Therefore, it is clear that we will have to target not one molecular pathway, but multiple aspects of exercise physiology to harness exercise's beneficial effects".

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Hoffman also highlighted that not all exercise is the same, but that outcomes depend on many variables: different regimens, variations in duration, type and intensity, and the physiology of the person doing the exercise. "For example, the determination of exercise intensity can involve measurements of heart rate, percentage of maximal oxygen uptake ( $VO_{2max}$ ) and maximal watts produced ( $W_{max}$ )", Hoffman said. "Additional metabolic parameters such as blood lactate and blood glucose levels are also

used to define the physiological responses to exercise". Research on exercise pathways is therefore not just aimed at developing mimetics to yield the beneficial effects, but also to optimize exercise regimens for particular conditions and patients. Drugs could then be used to augment or kick-start a tailor-made exercise regimen, for example to accelerate muscle rebuilding in patients who have been inactive for a long time.

These kinds of enhancements will create enormous potential for drug abuse and doping by athletes, which will again raise the question of how legally available drugs could be regulated for use in sport, if at all. More seriously, though, such advances could impact public health by encouraging people to overeat and stay on their couch, believing that they can alleviate a sedentary lifestyle by "popping exercise pills". After many decades of public health campaigns encouraging people to work out and stay active, exercise mimetics might set such public health efforts back.

Such concerns, however, are ultimately a distraction from the primary focus of exercise research, which is to help millions of people with severe metabolic conditions. Advances in the field will benefit many patients and sufferers and might also save a lot of money for health agencies. For example, more than 100,000 obese patients receive gut bypass surgery each year in the

USA alone. A drug that provided the same outcome—weight loss and improved metabolic health—would surely be a more palatable alternative.

## References

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