Is exercise physiology a real science?

Donal J. O'Gorman

Centre for Preventive Medicine and School of Health and Human Performance, Dublin City University, Ireland

Correspondence to:

Donal O'Gorman, Centre for Preventive Medicine and School of Health and Human Performance, Dublin City University, Glasnevin, Dublin 9, Ireland
donal.ogorman@dcu.ie

Abstract

Exercise physiology has not always been held with the same regard as other scientific disciplines. Despite the often held view that it is confined to the study of sport, exercise physiology has contributed to some of the most important scientific advances, particularly in understanding metabolic function. The physiological stress of exercise provides a unique model to understand the regulation of energy expenditure, gene expression, and glucose utilisation. In the future, it will also be required to better understand how physical inactivity contributes to the development of chronic diseases. Therefore, the contribution of exercise physiology to the advancement of scientific knowledge should not be underestimated.

Keywords: Exercise physiology, Physical activity, Metabolism, Gene expression, Mitochondrial function, Glucose transport

Introduction

The role of exercise in the realm of scientific endeavour is not always met with acceptance. In some eyes, exercise is merely the participation in sporting activities that require little in the way of experimentation, objectivity, or the creation of knowledge. For others, exercise is recognised as something we should do but a relatively insignificant contributor to our understanding of chronic diseases. However, for a small but dedicated group of physiologists, exercise is one of the most fascinating and powerful experimental models.

Physiology is an integrated science that advances our understanding of the function of the human body. It provides the basis for broad areas covered by medicine and disease prevention as well as more specific disciplines such as molecular biology, immunology, and environmental biology. Exercise physiology is a sub-discipline that focuses on the functional responses and adaptations associated with physical activity or inactivity. As physiology is often best studied under extreme conditions, exercise provides an excellent experimental model to answer important scientific questions.

One of the best and earliest examples of this approach was the research of Professor A.V. Hill for which he received the Nobel Prize in 1922. In order to better understand heat production in muscle, Professor Hill measured total work performed during exercise and the energy expended to perform the work. He was able to establish that the human body was not very efficient at converting stored energy into mechanical energy and instead produced heat which had to be dissipated from the body. This work is still relevant today and has formed the basis for much of the exercise physiology textbooks.

Glucose transport and diabetes

In more recent years, the dramatic increase in the prevalence of type 2 diabetes has focused research to better understand glucose uptake. Under normal circumstances, ingested glucose stimulates the release of insulin. When insulin binds to receptors, mainly on muscle, liver, and fat cells, a series of intracellular events occur that result in glucose transport proteins being translocated into the cell surface and facilitate glucose uptake. Individuals who increase body weight or develop type 2 diabetes become resistant to the action of insulin. As a result, a smaller number of glucose transport proteins are inserted into the cell membrane and compensatory actions, such as increased insulin production, are initiated to maintain glucose homeostasis.[1] A concerted effort to characterise the insulin signalling cascade has produced thousands

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of papers in the past two decades but the pathway is not yet fully characterised.

While insulin is the most important hormone for lowering blood glucose, it has been known for some time that exercise also lowers blood glucose levels in healthy individuals and those with abnormal glucose tolerance.[1] When the insulin signalling cascade was studied during exercise, it was found not to be activated[2] though glucose transporters were translocated.[3] Therefore, exercise facilitates glucose disposal independently of the actions of insulin, providing a scientific basis for exercise in the treatment of type 2 diabetes, but also a model to identify novel pharmacological targets. This work has found that stress responsive cascades (AMPK and p38 MAPK) and calcium signalling, resulting from the contractile process, are the main pathways that promote glucose uptake during exercise.[1] The significance of these pathways and their potential as non-insulin-mediated glucose-lowering targets continue to be explored.

Gene expression and epigenetics

The genomic era brought great promise of gene targets that would explain the basis of human health and disease. The advancement in technology that made these techniques accessible and affordable was of benefit, but also influenced the nature of research questions. A lot of emphasis was placed on determining the effect of individual genes on whole body and tissue-specific responses. As this research is not possible in humans, with the exception of rare monogenetic diseases, there was a shift towards animal and cell-based research. The impact of exercise physiology during this period was blunted but the post-genomic era has greater potential. The proportion of human diseases with genetic causes, even polygenetic, might be smaller than initially anticipated, but the interaction between environmental factors and the epigenome may play a major role.

Epigenetic modification has emerged as a key regulator of gene expression. While the DNA sequence remains unchanged, some of the individual nucleotides that make up the DNA are methylated, altering efficiency of gene transcription. The epigenetic signature is heritable and much of the focus has been on determining if traits of chronic diseases are passed from parent or grandparent to offspring in this manner. However, it has also recently emerged that DNA methylation can be modified by exercise. In healthy but inactive individuals, whole-genome methylation was decreased after an acute bout of exercise.[4] It was also reported that hypomethylation of the promoter region of key metabolic genes, and the subsequent expression of mRNA, was dependent on the intensity of the exercise. These changes were evident 3 hours after exercise but were not observed following a period of exercise training, which suggests that exercise acutely regulates the epigenetic profile and gene expression. Further research is required to determine the time course of these changes and whether exercise can modulate the heritability of epigenetic modification.

The argument for exercise-mediated regulation of gene expression is quite strong. The human genome has evolved to support physical activity, and if our ancestors could not hunt and gather effectively, they would not have survived. Consequently, the gene expression profile, in particular the metabolic gene profile, reflects the demand for energy production and the amount of physical activity.[5] One clear example of this is the number and size of mitochondria, the aerobic powerhouse of cells. Individuals who exercise on a regular basis have a greater number of mitochondria than inactive, obese or type 2 diabetic individuals. Exercise is quite a potent stimulator of metabolic gene expression and can significantly increase the expression of many mitochondrial proteins in 7–14 days, leading to mitochondrial biogenesis in just a few weeks. However, the amount of mitochondria is malleable and a sustained period of inactivity will require a smaller amount of energy production and therefore a reduction in the energy-producing machinery of mitochondria.

At another level, exercise has played an important role in elucidating the regulation of transcription factor complexes. Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) is a transcriptional co-activator that has been proposed as a coordinator of metabolic gene expression. PGC-1α expression is increased in skeletal muscle by exercise and has been implicated in many of the adaptations associated with exercise, including mitochondrial biogenesis, angiogenesis, muscle fibre composition, and glucose transport.[6] In fact, the same intracellular proteins activated by exercise to facilitate glucose transport are translocated to the nucleus and mediate PGC-1α transcription.

A consequence of this work has been the identification of an exercise-activated, PGC-1α-dependent protein, irisin that is released into circulation.[7] Irisin is a chemical messenger with endocrine action on adipose tissues, promoting

the conversion of white adipose tissue to the more bioenergetic brown adipose. Over-expressing the gene encoding irisin was shown to improve glucose homeostasis and obesity in high-fat-fed mice. Interestingly, irisin was required for many of the exercise effects on gene expression in adipose tissues. Therefore, exercise is an excellent model for understanding the regulation of gene expression and also identifying chemical messengers called myokines that are released from skeletal muscle and communicate with other tissues and regulate physiological processes in an endocrine fashion.

Physical inactivity and risk of disease

The main focus in exercise physiology has been to understand the responses and adaptations to exercise in healthy individuals and those with chronic diseases. However, a paradigm shift is occurring that will very likely change our view of activity, or more importantly inactivity. It has long been assumed that the positive benefits of regular exercise are simply lost with the cessation of training. This view is being challenged by recent findings that physical inactivity can induce separate physiological processes that actively promote, amongst others, muscle atrophy and insulin resistance.[8] Physical inactivity has been linked to more than 30 chronic diseases but mainly by association studies. The next phase of experimentation will require more direct evidence of a cause and effect relationship by mechanistic studies and randomised controlled trials.

As previously mentioned, the human genome has evolved to support physical activity and in particular our ability to hunt and gather food for survival.[5] This required a large amount of energy expenditure until recently. Advances in technology have dramatically decreased the requirement to expend energy for feeding. These changes have also impacted on occupational and recreational energy expenditure while at the same time energy intake has increased due to the consumption of energy dense, industrialised products. The net outcome is a positive energy balance and energy storage leading to an increase in fat mass, ectopic fat accumulation, and the development of risk factors associated with the metabolic syndrome, type 2 diabetes, and cardiovascular diseases. In tackling obesity-related diseases, most emphasis has been placed on dietary modification but the contribution of physical inactivity appears to have been underestimated. It is not feasible to continue recommending calorie restriction as we cannot consume enough of the vitamins and minerals required to maintain normal function. Instead, we need to increase physical activity and allow for nutrient intake that will match expenditure and contribute to health.

Physical inactivity is most often associated with metabolic diseases, but there is increasing evidence for a role in other chronic conditions. One area that is already attracting attention is the link between inactivity and the age-related decline in cognitive function. Those who are less active or have low fitness levels tend to be at greater risk of incident dementia and Alzheimer's disease. Population demographics show an increase in the number of older people.[9] Those who exhibit cognitive impairment require more support, supervision, and clinical management with serious implications for the cost of healthcare systems. It is speculated that the increased risk may be associated with a decrease in blood flow to the brain, atrophy of different parts of the brain, or a reduction in neural plasticity, but the evidence is not robust enough at this time to make conclusive statements. In the next decade, exercise/inactivity physiology has the potential to make a major impact on our understanding of chronic diseases.

Conclusion

In conclusion, the contribution of exercise physiology to scientific endeavour cannot be underestimated. The physiological stress of exercise provides a unique model to investigate normal body function and advance our understanding of the factors that contribute to the development and progression of chronic diseases. Exercise has been used to answer some of the most basic research questions relating to heat production and the role of muscle as an endocrine organ. It has also been used to help treat patients with chronic diseases and will hopefully continue to contribute to the advancement of scientific knowledge.

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Author information

Dr Donal O'Gorman is an exercise physiologist who established, and is director of, the Centre for Preventive Medicine (CPM) at Dublin City University (DCU). The CPM integrates basic, translational, and applied research to reduce the development and progression of common clinical conditions. He also leads the 3U Diabetes Research Consotium, an initiative integrating the research expertise of DCU, the Royal College of Surgeons in Ireland, and the National University of Ireland Maynooth. Dr O'Gorman's research focuses on metabolic physiology, in particular the whole body regulation of insulin sensitivity and energy expenditure as well as the cellular regulation of gene expression and mitochondrial function.