We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Exercise Mimetics: An Emerging and Controversial Topic in Sport and Exercise Physiology

Mohamed Magdy Aly Hassan ElMeligie

Abstract

Over the previous decade, there has been growing and fervent interest in scientific and commercial circles regarding the potential of bioactive compounds that mimic, or augment, the effects of exercise. These developments have given rise to the moniker ‘exercise pills’ or ‘exercise mimetics’. The emergence of such orally-delivered bioactive compounds could hold substantial therapeutic value for combating metabolic disease. Such treatments might also present therapeutic value for morbidly obese individuals or those recovering from severe injury. This topic is not without controversy, however, as the search for a ‘one size fits all’ solution is not likely to bear fruit, given the complexity of the molecular and physiological mechanisms involved. The primary goal of this chapter is to explore the challenges of designing a pill that might reliably deliver the myriad and complex adaptations afforded by exercise training, with a focus on skeletal muscle. Furthermore, it will consider the issues, rationale, and practicality of implementing such therapeutics as a credible substitute to engaging in regular exercise training.

Keywords: exercise pill, bioactive, pharmaceuticals, human adaptation, skeletal muscle, homeostasis

1. Introduction

Physical exercise is recognized as a highly effective non-pharmaceutical intervention for a range of health conditions in humans. In the first instance, systematic review evidence (comprising millions of participants) has indicated that engagement in regular physical exercise is associated with a reduced risk for all-cause mortality, and in a dose-response manner [1]. Furthermore, it also has important benefits in the prevention and treatment of a range of chronic metabolic conditions [1], such as cardiovascular disease [2], diabetes [3], and cancer [4]. The benefits of regular physical exercise are not restricted solely to metabolic diseases, however. The whole-body homeostatic perturbations brought about by exercise-induced stress also encompass the central nervous system, skeletal muscle, skin, oxygen transport processes, and hepatic function [5]. An important observation is that the relationships between physical activity and health outcomes tend to be curvilinear, in that clinically relevant health benefits can be obtained from relatively little amounts of physical activity [1].

Despite its wide-ranging, multifaceted, and complex health benefits, almost one third of the global population over 15 years of age fails to meet the minimum prescription of physical exercise to obtain worthwhile health benefits [6]. In the United States, 8.3% (95% confidence interval: 6.4–10.2) of deaths have been attributed to inadequate levels of physical activity [7], a sobering statistic when considering the modifiable nature of this risk factor [8]. Yet more worrisome is the growing trend towards increasing sedentary behaviors (i.e., sitting time, computer use) over the previous decade [9, 10]; a fact made all the more severe by the ongoing COVID-19 pandemic and its associated government-mandated lockdown measures to protect public health [11]. Despite the seemingly global trend towards increased sedentari-ness and inadequate physical activity, impracticalities exist with regards to mandating an entire community, country, and/or global population to optimize their exercise habits [12]. It must also be noted that certain populations may not be able to engage in physical exercise due to injury, disease, or age-associated frailty, and thus would benefit from alternative solutions [13].

The potent effects of regular physical exercise on numerous important domains of human health have given rise to the notion of pharmacological compounds that mimic, or enhance, these effects. Such ‘exercise mimetics’ or ‘exercise pills’ have been touted as a potential, but not entirely probable, therapeutic solution [12, 14] for an otherwise challenging and ongoing public health problem. Although exercise brings about a range of physiological benefits to human health, compliance is often low and in certain groups may not be possible [15]. In recent decades, our understanding of the molecular determinants and physiological processes involved in exercise has improved at an alarming rate. This work has led to the emergence of chemical interventions that can induce the beneficial aspects of exercise, without necessitating actual skeletal muscle activity [15]. Such pharmacologic interventions may represent a viable strategy for addressing metabolic diseases associated with physical inactivity [16] or serve as an intermediary treatment for the morbidly obese or people recovering from serious injury [17]. The mechanistic basis for this supposition, and the opportunities and difficulties associated with such a strategy are the focal considerations of this chapter.

2. The identification of cellular and molecular targets in skeletal muscle

Skeletal muscle is the most abundant tissue in the human body, accounting for around 40% of total body weight, and is the most robustly activated organ in response to physical exercise [13]. In recent years, the effects of physical exercise on several molecular pathways and cellular targets in skeletal muscle have received significant attention. This investigative work has yielded numerous potential factors with relevance for ‘exercise mimetic’ applications in human health.

2.1 The AMPK-SIRT1-PGC1 α pathway

The repeated muscular contractions brought about during physical exercise activate numerous signaling pathways in skeletal muscle, one of which is the AMPK-SIRT1-PGC1 α axis that plays a key role in skeletal muscle energy metabolism and mitochondrial biogenesis [13].

2.1.1 AMPK

AMPK, or AMP-activated protein kinase, is a master regulator of energy homeostasis and metabolism within the cell. It is a heterotrimeric protein complex

that comprises a catalytic subunit (α) and two regulatory subunits (β and γ) of which numerous isoforms exist [18]. AMPK integrates important signals from metabolic pathways and balances nutrient availability with energy demand. During exercise, muscle contractions deplete adenosine triphosphate (ATP), which reduces the ATP:AMP and ATP:ADP ratios within the cell, subsequently activating AMPK [19]. In skeletal muscle, the activation of AMPK induces a switch from anabolic cellular metabolism to a catabolic state of metabolism, blocking energy-consuming activities and promoting the synthesis of ATP from fatty acid oxidation, glycosylation, and glucose uptake [13]. These effects are mediated acutely by direct phosphorylation of metabolic targets, whereas a more chronic effect is brought about by gene transcription [13]. Inactivation of AMPK in skeletal muscle leads to the loss of oxidative fibers, suppressed fat metabolism, and impaired mitochondrial biogenesis [20].

Exercise is perhaps the most prominent physiological activator of AMPK in skeletal muscle. Acutely, exercise intensities above 60% of maximal aerobic capacity can induce AMPK activation, as can lower intensities of a prolonged duration [21]. Given its 'global' role as a regulator of cellular energy stress in response to environmental factors such as caloric restriction, physical exercise, and metabolic disease [22], AMPK has garnered substantial attention. It continues to represent a promising potential target for pharmaceutical intervention, particularly when considering its interactions with other effectors.

2.1.2 SIRT1

Sirtuin 1 (SIRT1) is a central regulator of metabolic processes in response to energy availability, and is primarily localized in the nucleus [23]. It is responsive to NAD^+ to NADH concentrations, and thus cellular energy availability, through its activation by AMPK [20], and it also senses changes in intracellular redox state [13, 23]. The activation of SIRT1 deacetylates and activates peroxisome proliferator-activated gamma coactivator 1-alpha (PGC1- α), upregulating its specific activity as a transcription factor on genes related to mitochondrial respiration and fatty acid metabolism [13, 24]. In conditions of overexpression or knock-out however, there is evidence to suggest that SIRT1 can also serve as a PGC1- α inhibitor, thus reducing mitochondrial activity [13]. In addition, during low nutrient availability, SIRT1 induces a shift in cellular metabolism towards fatty acid oxidation due to the scarcity of glucose [23]. SIRT1 helps to support cellular energy balance by inducing catabolic processes while inhibiting anabolic processes, thus maintaining energy homeostasis [23].

Physical exercise, specifically high-intensity interval training, has been shown to elevate SIRT1 activity in human skeletal muscle, and this was also associated with mitochondrial biogenesis [25]. Moreover, chronic exercise results in systemic adaptations that increase the levels of SIRT1 expression in the kidney, liver and brain in patients with neurodegenerative diseases, normalizing cellular processes and decreasing disease severity [26]. Defects in the pathways mediated in part by SIRT1 are known to lead to numerous metabolic disorders. Therefore, given the potential benefits of exercise-associated activation of SIRT1 for health and disease, the pharmacological manipulation of this target might elicit multiple benefits, and as such remains an area of focused attention.

2.1.3 PGC1- α

PGC1- α plays an integral role in cellular metabolism, serving as a co-activator of a vast range of downstream transcriptional factors and effectors involved in

fatty acid oxidation and mitochondrial biogenesis [13]. In skeletal muscle, PGC1- α is activated by endurance exercise-mediated stimulation of p38 mitogen-activated protein kinase (MAPK) [13], subsequently enhancing mitochondrial biogenesis. Importantly, both acute and chronic physical exercise robustly increase the mRNA expression of PGC1- α in rodent muscle, therefore underscoring its importance in exercise training adaptations [20]. PGC1- α mediates the remodeling of skeletal muscle towards a more metabolically oxidative and less glycolytic fiber-type composition [27]. In muscle-specific PGC1- α knock-out models, impaired endurance, abnormal fiber composition, and inconsistent mitochondrial gene regulation have been documented [13], thus reinforcing the indispensable role of PGC1- α in exercise-mediated adaptations. It has also been posited that PGC1- α is a key factor in metabolic disorders, such as diabetes, obesity, and cardiomyopathy. These notions, allied to its regulatory action in lipid metabolism, make PGC1- α a potentially attractive target for pharmacological intervention [27].

2.2 PPAR δ

Peroxisome proliferator-activated receptor delta (PPAR δ) is a nuclear hormone receptor that transcriptionally regulates over 100 genes, playing a vital role in many biological processes [13], particularly those relating to energy balance [28] and fatty acid oxidation [29]. Although expressed abundantly in a range of metabolically active tissues, in skeletal muscle PPAR δ is predominantly expressed in oxidative slow-twitch as opposed to glycolytic fast-twitch fibers. This expression is further induced by endurance-type exercise activity known to trigger an oxidative and/or slow-twitch phenotype [20]. Its role in skeletal muscle includes the regulation of slow/fast-twitch fibers, lipid metabolism, oxidative processes, mitochondrial biogenesis, weight reduction, impairment of liver gluconeogenesis, and management of inflammatory processes [13, 20]. In rodent models, muscle-specific activation of PPAR δ has demonstrated 'exercise-like' effects, such as increasing running endurance and guarding against diet-induced obesity and type II diabetes [30]. Furthermore, ablation of PPAR δ in skeletal muscle induces an age-dependent loss of oxidative muscle fibers, running endurance, and insulin sensitivity [31], thus further reinforcing the role of PPAR δ in fiber type remodeling. The weight of this evidence has led to the assumption that PPAR δ is a central transcriptional regulator of oxidative metabolism the slow-twitch phenotype [20] thus representing a major 'exercise mimetic' target of interest.

2.3 ERR α/γ

Estrogen-related receptors (ERRs) are key nuclear regulators in mitochondrial energy metabolism [29], with their transcriptional activity determined by co-factors such as PGC-1 α . ERR α is expressed in a range of tissues with high energy turnover, including skeletal muscle. ERR γ has a similar expression pattern but is selectively expressed in tissues with high rates of oxidation such as brain, heart, and muscle [29]. When PGC-1 α is induced, ERR α plays a major role in controlling the mitochondrial biogenic gene network; in its absence, the ability of PGC-1 α to enhance the expression of mitochondrial genes is drastically reduced [29].

In skeletal muscle, ERR α is expressed in oxidative and glycolytic fibers, whereas ERR γ is expressed in oxidative fibers only [29, 32]. Notably, ERR γ regulates oxidative metabolism not just in skeletal muscle, but in other tissues as well [33], and is a key determinant of the oxidative muscle fiber phenotype [15]. As such, it is highly expressed in type I skeletal muscle fibers. In rodent models, when ERR γ is transgenically expressed in type II fibers, it induces metabolic and vascular adaptations,

in the absence of exercise [32]. These adaptations include prominent vascularization, the secretion of proangiogenic factors, and an alarming increase in endurance performance of 100% [32]. Given these characteristics, ERR γ is a prominent target for exercise mimetics because of its direct regulation of genes associated with mitochondrial oxidation, however there is a paucity of research on the topic [12]. When applied ectopically in glycolytic fibers, ERR γ instigates a shift in fiber type from glycolytic to oxidative, inducing mitochondrial biogenesis and bring about increased vascularization [29].

2.4 REV-ERB α

The nuclear receptor REV-ERB α (also known as nuclear receptor subfamily 1 group D member 1 (NR1D1)), is highly conserved across species and plays important roles in circadian rhythm and metabolism [33]. In skeletal muscle, REV-ERB α are prominently involved in the regulation of mitochondrial biogenesis, mitophagy, the promotion of an oxidative fiber type, and the processes underpinning a higher endurance capacity [34]. In rodents, muscle-specific ablation of REV-ERB α was shown to blunt the AMPK-SIRT1-PGC-1 α signaling pathway, decrease mitochondrial density, reduce oxidative phosphorylation activity, and downregulate genes associated with fatty acid metabolism [34]. Conversely, overexpression of REV-ERB α in C2C12 cells activated these regulators of training adaptations, increased mitochondrial biogenesis and induced fatty acid metabolism genes [35]. REV-ERB α also appears to play a role in modulating muscle mass, with its deficiency leading to increased expression of atrophy genes, and overexpression leading to diminished atrophy genes and increased fiber size [36]. Therefore, REV-ERB α has been identified as a promising pharmacological target for exercise mimetic applications.

3. 'Exercise mimetic' pharmacologic compounds as putative therapeutics for human health

The attractive properties of physical exercise for human health have garnered fervent interest from the pharmaceutical industry in recent years, likely due to the large and untapped market of sedentary individuals that, for varying reasons, do not engage in sufficient physical exercise [37]. Chiefly, the development of novel therapeutic approaches to replicate an exercise-training phenotype [38] by activating selected molecular targets—so-called 'exercise pills' [15] or 'exercise mimetics'—remains an area of substantial investment and effort. In using natural or synthetic compounds, it is possible to induce exercise-mimicking effects even in sedentary test animals [12], by activating molecular targets and genomic regulators such as those previously described. The foremost of these therapeutic approaches will now be discussed.

3.1 AMPK activators

AICAR, or 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside, is at the forefront of several 'exercise-mimetic' compounds developed to target AMPK, a master regulator of cellular and organismal metabolism [39]. It is a well-known adenosine analog that is intracellularly converted into ZMP, which directly associates with and allosterically stimulates AMPK [12, 22] in a time- and dose-dependent manner [40]. Acutely, AICAR activates AMPK to bring about an increase in fatty acid oxidation, whereas chronic AICAR treatment promotes skeletal muscle fiber type transition from fast- to slow-twitch, and increases the expression of enzymes

associated with aerobic respiration [20]. This fiber type reorganization, in concert with mitochondrial biogenesis, has been shown to significantly increase exercise performance (by an unexpected 44%) in sedentary mice following AICAR administration alone [39]. AICAR also induces skeletal muscle glucose uptake by effecting the translocation of the GLUT4 receptor to the sarcolemma [22]. These findings highlight the potential of AICAR as a potential agent to address the insulin resistance seen in type II diabetes.

Metformin is a drug of the biguanide class known to function in an AMPK-dependent manner, and is one of the most broadly available antidiabetic agents presently available [22]. It represents a first line medication used to treat type II diabetes, and activates AMPK in the liver through inhibition of mitochondrial complex I, which concomitantly reduces cellular ATP generation [12]. The glucose-lowering action of metformin is at least partly mediated by the activation of AMPK [38]. Although the mode of activation is different, metformin activates AMPK in a similar manner to AICAR, and they both have similar roles in hepatic glucose production [13]. In diabetic patients, metformin can reduce blood pressure and also improve multiple cardiovascular risk factors in obese individuals [13]. It may also possess anti-inflammatory properties, the specifics of which are still being explored.

3.2 Resveratrol

Resveratrol, a naturally occurring plant-derived polyphenol, is recognized as an activator of SIRT1 and AMPK [13, 22], but has multiple biological targets [20]. In yeast it has been shown to promote longevity, whereas in rodents this capacity is uncertain [33]. Although abundant in the human diet, resveratrol is perhaps most notably consumed in the seeds and skin of grapes [13]. It is highly lipophilic but has scarce bioavailability; nevertheless it is capable of extracellular, intracellular, and nuclear interactions [13]. Its role on the SIRT1-AMPK axis, as well as PGC1- α [38, 41], has received interest as a potential metabolism-regulating, 'exercise mimetic' compound. However, evidence in rodents is conflicting and it has been postulated that resveratrol might actually improve performance when used in synergy with exercise, rather than as a substitute [13]. In human clinical trials, resveratrol was shown to induce the expression of SIRT1 and AMPK in skeletal muscle, albeit in obese type II diabetic males [42]. From the perspective of exercise performance, resveratrol administration suppressed exercise-dependent improvements in aerobic respiration in aged inactive males, thus blunting the beneficial effects of training [43]. Therefore, further research is needed to cogently understand the mechanisms of action and optimal dose before it can be recommended in 'exercise mimetic' applications. It should also be noted that novel, more potent synthetic activators of SIRT1, such as SRT1720, have been developed that might represent promising candidates for application in a clinical setting [33], although research on these compounds is still in its infancy.

3.3 GW501516

The compound GW501516 is a selective agonist of PPAR δ , and was initially developed for possible beneficial applications in metabolic and cardiovascular diseases [13]. However, pre-clinical work in animals highlighted its carcinogenic effects in multiple organs and the compound was subsequently abandoned [44]. Nevertheless, numerous studies from the past decade have linked this drug with potential 'exercise mimetic' effects [39]. For instance, a metabolomic study in mice showed that GW501516 treatment enhanced exhaustive running endurance

in both trained and untrained animals, by increasing the specific consumption of fatty acids and sparing blood glucose [45]. The expression of genes regulated by PPAR δ , including PGC1- α and pyruvate dehydrogenase kinase 4 (PDK4) were also significantly increased following treatment, as were other markers of fatty acid metabolism in skeletal muscle. Importantly, in untrained mice the administration of GW501516 alone was sufficient to increase running endurance, even following just 1 week of provision. Similar findings have been previously reported, albeit without any benefits to endurance capacity, demonstrating that GW501516 establishes an endurance gene signature, sharing 50% of the gene expression pattern with exercise [39]. Elsewhere, GW501516 administration improved endurance function in a mouse model of myocardial infarction when compared to placebo, and preserved oxidative capacity and fatty acid metabolism [46]. Collectively, these findings suggest that the activation of PPAR δ at least partially mimics the effects of exercise.

3.4 GSK4716

GSK4716 is a synthetic ERR γ agonist that can activate the receptor with a similar potency to that of its ligand PGC-1 α [15, 47]. It robustly activates genes involved in mitochondrial biogenesis, fatty acid oxidation, and the tricarboxylic acid cycle (TCA) when used to treat primary muscle cells [12], and promotes an endurance-trained phenotype in mice [32]. However, there is a discrepancy between acute and chronic activation of ERR γ in ligand-treated primary muscle cells and transgenic animals, respectively [33]. Although GSK4716 has been heralded as a candidate 'exercise pill' [15], the aforementioned 'exercise-mimicking' effects have not been established *in vivo* [12], and the compound is not yet approved for human use.

3.5 SR9009

The synthetic REV-ERB α agonist SR9009 was developed at the Scripps Research Institute in 2012 and has been identified as an 'exercise pill' of promise [15]. A single injection of SR9009 brought about 'exercise-like' effects in rodents, such as enhanced mitochondrial activity and the induction of genes associated with fatty acid metabolism [34]. After 12 days, energy consumption was enhanced without changing the respiratory exchange ratio, and after 30 days mouse running performance was significantly prolonged. Despite these positive findings, REV-ERB independent effects on cell proliferation, metabolism and gene expression have been found in a double-ablation model [48]. Therefore, positive outcomes with respect to the physiological and molecular effects of exercise should be interpreted with a degree of caution. More importantly, SR9009 has not been approved for human use at the time of writing, however tests have been devised against its surreptitious use [49].

4. The challenges and controversies of developing an 'exercise pill'

A pharmacological method of replicating the multifaceted and complex effects of physical exercise would no doubt be of value to populations that for whatever reason cannot engage in physical activity, such as people with disabilities, disease, frailty, or injury. For example, it might serve as an avenue towards reengaging with physical exercise after a severe injury, or a 'stepping stone' for individuals that are morbidly obese. However, there are several important considerations that need to be addressed.

4.1 Can physical exercise be realistically replaced?

There are inherent dangers in a ‘reductionist’ approach to exercise mimetics, as rodent knockout models have shown that no single ‘exercise gene’ or signaling pathway exists [37]. Even though PGC-1 α has, for example, been described as the ‘master regulator’ of endurance exercise adaptations, evidence suggests that it may not be a prerequisite for exercise training-induced mitochondrial adaptations [37]. The biological responses to acute and chronic physical exercise in humans are characterized by a high degree of physiological redundancy at the molecular, cellular, organ-system, and whole-body levels [50]. Furthermore, the exercise-induced skeletal muscle phenotype is independent of a chosen few genes, proteins, and signaling pathways [51, 52]. Therefore, irrespective of the promising research findings discussed above, it is extremely unlikely that the emergence of a single pharmaceutical compound will be able to deliver the myriad and complex physiological, metabolic, and homeostatic disruptions brought about by exercise [5]. The multiplicity of responses, at a macro, ‘system-wide’ level [37], have been described as too diverse for a single pharmaceutical approach to address, and therefore a ‘one size fits all’ panacea is unlikely to come forward. It appears then that there is no true replacement for actual exercise, at least at present, due to the distinct and multifaceted metabolic responses that take place, especially in skeletal muscle. Despite these reservations, ‘exercise mimetics’ might represent an avenue to obtain at least some of the important benefits in those unable to achieve adequate amounts of physical exercise [12]. However, it could be argued that improving adherence to existing evidence-based exercise guidelines and pharmaceutical strategies (e.g., statins for cardiovascular disease) would be a more fruitful and productive objective for the promotion of human health.

4.2 Doping implications for elite athletes

From the perspective of performance sport, ‘exercise mimetics’ raise important and challenging questions. PPAR δ agonists were added to the WADA Prohibited List that became effective in 2009, with AICAR also banned in the same year. In 2012, both GW501516 and AICAR were moved to class S4 (hormone and metabolic modulators) [53], and at the time of writing, this is still the case. Both of these compounds have received significant media attention over the last decade. For example, in 2012 members of the Spanish cycling team, including the team doctor, were arrested in connection with an international network supplying AICAR, due to its effectiveness on performance [12]. Despite this, it must be emphasized that AICAR is not approved for therapeutic use anywhere in the world, given its status as an experimental compound. In a separate instance, Russian race walker Elena Lashmanova tested positive for GW501516 in 2014 and was subsequently sanctioned. A very stable drug, GW501516 possesses a long half-life and is therefore easily detected in blood and urine samples [12], which poses major consequences for athletes seeking to obtain this compound for performance enhancement. By way of comparison, resveratrol is a natural, albeit weak, compound that has been shown to improve endurance performance in animals, yet it is not a prohibited substance. This is likely due to its low bioavailability and lack of consistently beneficial effects in humans [12]. Therefore, due care and attention must be observed when selecting compounds in pursuit of performance enhancement to ensure compliance with the WADA Prohibited List and mitigate the risk of compromising one’s career.

4.3 Side effects of human metabolic modulators

The constant activation of metabolic pathways by pharmaceutical means, so-called 'metabolic overdrive', could have undesirable health effects [37, 54]. For example, the chronic activation of AMPK (i.e., via AICAR) and concomitant inhibition of the mechanistic target of rapamycin (mTOR; a central regulator of protein synthesis and anabolism) could bring about a state of chronic catabolism, or breakdown [37]. This problem would be exacerbated if multiple exercise mimetics or pills, targeting diverse pathways, were consumed. More specifically, and with relevance to the exercise mimetics discussed above, GW501516 demonstrated serious toxicity and multi-organ carcinogenicity in rodent studies, whereas human clinical trials reported no adverse effects, likely due to the short duration and low dose administered [53]. Even the naturally occurring compound resveratrol has been associated with side effects in humans, albeit to a lesser extent than the synthetic compounds previously discussed. In *in vitro* studies, the concentration-dependent cytotoxicity of resveratrol has been demonstrated, with high doses associated with deleterious effects [55]. Although safe and well-tolerated at doses of up to 5 g per day in humans, diarrhea has been documented as a frequent side effect at doses of 2000 mg [56], and there may be implications of high dose resveratrol supplementation for people with underlying health conditions [55].

5. Non-pharmacological 'exercise mimetic' alternatives

There do exist non-pharmacological alternatives to 'exercise pills' that can potentially be applied to mimic the characteristics of exercise training. For example, neuromuscular electrical stimulation (NMES) has been used to induce involuntary muscle contractions and support the maintenance of muscle mass in injured athletes [57]. This can potentially serve as a surrogate for physical activity, as it has been shown to stimulate muscle protein synthesis rates in older men, and can ameliorate the muscle atrophy associated with limb immobilization to a certain extent [57]. In contrast to the pharmacological methods described above, NMES can maintain muscle mass without safety concerns or appreciable side effects [58], thus representing a potential strategy for mimicking, at least in part, the metabolic effects of physical exercise. These findings may have the most utility in clinical populations observing periods of bed rest or immobilization, by reintroducing a degree of muscle contraction. This activity can enhance muscle protein synthesis in the fasted and fed states, which might support muscle health during short-term periods of disuse in a clinical setting [59].

Acute passive heating has demonstrated some exercise mimetic properties in humans, namely type II diabetics, when implemented in proximity to an oral glucose tolerance test (OGTT) [60]. One-hour of passive heating in water at 40°C either 30 min before or 30 min after commencing an OGTT increased extracellular heat shock protein 70 in the blood and increased heart rate and total energy expenditure (via increased fat oxidation) [60]. However, passive heating did not affect blood glucose concentrations or insulin sensitivity compared with a control group. In skeletal muscle, there is preliminary evidence that chronic passive heating can promote hypertrophy in animal and human models, alongside augmented voluntary and involuntary strength [61]. With further study, passive heating might be a worthwhile non-pharmacologic and exercise mimetic strategy for people that are unable to complete sufficient exercise.

6. Conclusions

Exercise mimetics remains an area of considerable effort and inquiry but is not without its challenges and controversies. Although early clinical research has identified numerous promising molecular targets for pharmaceutical intervention, there is a lack of human clinical data to support their implementation. This, allied to the multifaceted nature of the human physiological response to exercise, and the redundancy inherent in such a response, suggests that a 'one size fits all' approach will be unlikely to manifest. As such, efforts should be focused on increasing adherence to existing evidence-based exercise guidelines and pharmaceutical interventions for the promotion of human health. Notwithstanding, it is possible that multiple pharmaceutical approaches could emerge in the future that target specific molecular pathways for cumulative benefit. These strategies may offer substantial value for populations unable, or unwilling, to engage in actual physical exercise. Nonetheless, the implications of exercise pills for doping in elite sport, and the potential side effects associated with the administration of these compounds for human health, are areas of cautious consideration for the next decade and beyond.

Acknowledgements

The authorship criteria are listed in our Authorship Policy: <https://www.intechopen.com/page/authorship-policy>.

Conflict of interest

The author declares no conflict of interest.

Author details

Mohamed Magdy Aly Hassan ElMeligie
Faculty of Physical Therapy, Department of Basic Sciences, October 6 University,
6th of October City, Egypt

*Address all correspondence to: mohamed.magdy.pt@o6u.edu.eg

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Warburton DER, Bredin SSD. Health benefits of physical activity: A systematic review of current systematic reviews. *Current Opinion in Cardiology*. 2017;**32**:541-556
- [2] Tian D, Meng J. Exercise for prevention and relief of cardiovascular disease: Prognoses, mechanisms, and approaches. *Oxidative Medicine and Cellular Longevity*. 2019;**2019**:3756750. DOI: 10.1155/2019/3756750
- [3] Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*. 2016;**39**:2065-2079
- [4] Fong DYT, Ho JWC, Hui BPH, et al. Physical activity for cancer survivors: Meta-analysis of randomised controlled trials. *BMJ*. 2012;**344**:17
- [5] Hawley JA, Hargreaves M, Joyner MJ, et al. Integrative biology of exercise. *Cell*. 2014;**159**:738-749
- [6] Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: Surveillance progress, pitfalls, and prospects. *Lancet*. 2012;**380**:247-257
- [7] Carlson SA, Adams EK, Yang Z, et al. Percentage of deaths associated with inadequate physical activity in the United States. *Preventing Chronic Disease*. 2018;**15**:E38
- [8] Thornton JS, Frémont P, Khan K, et al. Physical activity prescription: A critical opportunity to address a modifiable risk factor for the prevention and management of chronic disease: A position statement by the Canadian Academy of Sport and Exercise Medicine. *British Journal of Sports Medicine*. 2016;**50**:1109-1114
- [9] Yang L, Cao C, Kantor ED, et al. Trends in sedentary behavior among the US population, 2001-2016. *JAMA*. 2019;**321**:1587-1597
- [10] Guthold R, Stevens GA, Riley LM, et al. Worldwide trends in insufficient physical activity from 2001 to 2016: A pooled analysis of 358 population-based surveys with 1.9 million participants. *The Lancet Global Health*. 2018;**6**:e1077-e1086
- [11] Stockwell S, Trott M, Tully M, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: A systematic review. *BMJ Open Sport & Exercise Medicine*. 2021;**7**:e000960
- [12] Fan W, Evans RM. Exercise mimetics: Impact on health and performance. *Cell Metabolism*. 2017;**25**:242-247
- [13] Guerrieri D, Moon HY, van Praag H. Exercise in a pill: The latest on exercise-mimetics. *Brain Plasticity*. 2017;**2**:153
- [14] Gubert C, Hannan AJ. Exercise mimetics: Harnessing the therapeutic effects of physical activity. *Nature Reviews. Drug Discovery*. 2021;**2021**:1-18
- [15] Li S, Laher I. Exercise pills: At the starting line. *Trends in Pharmacological Sciences*. 2015;**36**:906-917
- [16] Warden SJ, Fuchs RK. Are “exercise pills” the answer to the growing problem of physical inactivity? *British Journal of Sports Medicine*. 2008;**42**:862-863
- [17] Hunter P. 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. *EMBO Reports*. 2016;**17**:136

- [18] Kjøbsted R, Hingst JR, Fentz J, et al. AMPK in skeletal muscle function and metabolism. *The FASEB Journal*. 2018;**32**:1741
- [19] Gowans GJ, Hawley SA, Ross FA, et al. AMP is a true physiological regulator of AMP-activated protein kinase by both allosteric activation and enhancing net phosphorylation. *Cell Metabolism*. 2013;**18**:556-566
- [20] Matsakas A, Narkar VA. Endurance exercise mimetics in skeletal muscle. *Current Sports Medicine Reports*. 2010;**9**:227-232
- [21] Richter EA, Ruderman NB. AMPK and the biochemistry of exercise: Implications for human health and disease. *The Biochemical Journal*. 2009;**418**:261
- [22] Wall CE, Yu RT, Atkins AR, et al. Nuclear receptors and AMPK: Can exercise mimetics cure diabetes? *Journal of Molecular Endocrinology*. 2016;**57**:R49-R58
- [23] Nogueiras R, Habegger KM, Chaudhary N, et al. Sirtuin 1 and sirtuin 3: Physiological modulators of metabolism. *Physiological Reviews*. 2012;**92**:1479-1514
- [24] Pardo PS, Boriek AM. The physiological roles of Sirt1 in skeletal muscle. *Aging (Albany NY)*. 2011;**3**:430
- [25] Gurd BJ, Perry CGR, Heigenhauser GJF, et al. High-intensity interval training increases SIRT1 activity in human skeletal muscle. *Applied Physiology, Nutrition, and Metabolism*. 2010;**35**:350-357
- [26] Radak Z, Suzuki K, Posa A, et al. The systemic role of SIRT1 in exercise mediated adaptation. *Redox Biology*. 2020;**35**:101467
- [27] Liang H, Ward WF. PGC-1 α : A key regulator of energy metabolism. *American Journal of Physiology. Advances in Physiology Education*. 2006;**30**:145-151
- [28] Liu Y, Colby JK, Zuo X, et al. The role of PPAR- δ in metabolism, inflammation, and cancer: Many characters of a critical transcription factor. *International Journal of Molecular Sciences*. 2018;**19**:3339. DOI: 10.3390/IJMS19113339
- [29] Fan W, Evans R. PPARs and ERRs: Molecular mediators of mitochondrial metabolism. *Current Opinion in Cell Biology*. 2015;**33**:49-54
- [30] Luquet S, Lopez-Soriano J, Holst D, et al. Peroxisome proliferator-activated receptor δ controls muscle development and oxydative capability. *The FASEB Journal*. 2003;**17**:2299-2301
- [31] Schuler M, Ali F, Chambon C, et al. PGC1 α expression is controlled in skeletal muscles by PPAR β , whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metabolism*. 2006;**4**:407-414
- [32] Narkar VA, Fan W, Downes M, et al. Exercise and PGC-1 α -independent synchronization of type i muscle metabolism and vasculature by ERR γ . *Cell Metabolism*. 2011;**13**:283-293
- [33] Handschin C. Caloric restriction and exercise “mimetics”: Ready for prime time? *Pharmacological Research*. 2016;**103**:158
- [34] Woldt E, Sebti Y, Solt LA, et al. Rev-erb- α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. *Nature Medicine*. 2013;**19**:1039-1046
- [35] Fan W, Atkins AR, Yu RT, et al. Road to exercise mimetics: Targeting nuclear receptors in skeletal muscle. *Journal of Molecular Endocrinology*. 2013;**51**:T87-T100

- [36] Mayeuf-Louchart A, Thorel Q, Delhay S, et al. Rev-erb- α regulates atrophy-related genes to control skeletal muscle mass. *Scientific Reports*. 2017;**7**:1-11
- [37] Hawley JA, Joyner MJ, Green DJ. Mimicking exercise: What matters most and where to next? *The Journal of Physiology*. 2021;**599**:791-802
- [38] Carey AL, Kingwell BA. Novel pharmacological approaches to combat obesity and insulin resistance: Targeting skeletal muscle with 'exercise mimetics'. *Diabetologia*. 2009;**52**:2015-2026
- [39] Narkar VA, Downes M, Yu RT, et al. AMPK and PPAR δ agonists are exercise mimetics. *Cell*. 2008;**134**:405-415
- [40] Sullivan JE, Brocklehurst KJ, Marley AE, et al. Inhibition of lipolysis and lipogenesis in isolated rat adipocytes with AICAR, a cell-permeable activator of AMP-activated protein kinase. *FEBS Letters*. 1994;**353**:33-36
- [41] Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell*. 2006;**127**:1109-1122
- [42] Goh KP, Lee HY, Lau DP, et al. Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure. *International Journal of Sport Nutrition and Exercise Metabolism*. 2014;**24**:2-13
- [43] Gliemann L, Schmidt JF, Olesen J, et al. Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men. *The Journal of Physiology*. 2013;**591**:5047-5059
- [44] Sahebkar A, Chew GT, Watts GF. New peroxisome proliferator-activated receptor agonists: Potential treatments for atherogenic dyslipidemia and non-alcoholic fatty liver disease. *Expert Opinion on Pharmacotherapy*. 2014;**15**:493-503
- [45] Chen W, Gao R, Xie X, et al. A metabolomic study of the PPAR δ agonist GW501516 for enhancing running endurance in Kunming mice. *Scientific Reports*. 2015;**5**:1-13
- [46] Zizola C, Kennel PJ, Akashi H, et al. Activation of PPAR δ signaling improves skeletal muscle oxidative metabolism and endurance function in an animal model of ischemic left ventricular dysfunction. *American Journal of Physiology. Heart and Circulatory Physiology*. 2015;**308**:H1078
- [47] Wang L, Zuercher WJ, Consler TG, et al. X-ray crystal structures of the estrogen-related receptor- γ ligand binding domain in three functional states reveal the molecular basis of small molecule regulation. *The Journal of Biological Chemistry*. 2006;**281**:37773-37781
- [48] Dierickx P, Emmett MJ, Jiang C, et al. SR9009 has REV-ERB-independent effects on cell proliferation and metabolism. *Proceedings of the National Academy of Sciences*. 2019;**116**:12147-12152
- [49] Geldof L, Deventer K, Roels K, et al. In vitro metabolic studies of REV-ERB agonists SR9009 and SR9011. *International Journal of Molecular Sciences*. 2016;**17**:1676
- [50] Joyner MJ, Dempsey JA. Physiological redundancy and the integrative responses to exercise. *Cold Spring Harbor Perspectives in Medicine*. 2018;**8**:a029660. DOI: 10.1101/CSHPERSPECT.A029660
- [51] Qi Z, Zhai X, Ding S. How to explain exercise-induced phenotype from molecular data: Rethink and reconstruction based on AMPK and

mTOR signaling. Springerplus. 2013;**2**:1-10

[52] Kupr B, Schnyder S, Handschin C. Role of nuclear receptors in exercise-induced muscle adaptations. Cold Spring Harbor Perspectives in Medicine. 2017;**7**:029835. DOI: 10.1101/CSHPERSPECT.A029835

[53] Pokrywka A, Cholbinsk P, Kaliszewsk P, et al. Metabolic modulators of PPAR-delta. Journal of Physiology and Pharmacology. 2014;**65**:469-476

[54] Weihrauch M, Handschin C. Pharmacological targeting of exercise adaptations in skeletal muscle: Benefits and pitfalls. Biochemical Pharmacology. 2018;**147**:211-220

[55] Shaito A, Posadino AM, Younes N, et al. Potential adverse effects of resveratrol: A literature review. International Journal of Molecular Sciences. 2020;**21**:2084. DOI: 10.3390/ijms21062084

[56] Salehi B, Mishra AP, Nigam M, et al. Resveratrol: A double-edged sword in health benefits. Biomedicine. 2018;**6**:91. DOI: 10.3390/BIOMEDICINES6030091

[57] Wall BT, Morton JP, van Loon LJC. Strategies to maintain skeletal muscle mass in the injured athlete: Nutritional considerations and exercise mimetics. European Journal of Sport Science. 2015;**15**:53-62

[58] Dirks ML, Wall BT, Snijders T, et al. Neuromuscular electrical stimulation prevents muscle disuse atrophy during leg immobilization in humans. Acta Physiologica. 2014;**210**:628-641

[59] Dirks ML, Wall BT, Van Loon LJC. Interventional strategies to combat muscle disuse atrophy in humans: Focus on neuromuscular electrical stimulation and dietary protein. Journal of Applied Physiology. 2018;**125**:850-861

[60] James T, Corbett J, Cummings M, et al. Timing of acute passive heating on glucose tolerance and blood pressure in people with type 2 diabetes: A randomized, balanced crossover, control trial. Journal of Applied Physiology. 2021;**130**:1093-1105

[61] Rodrigues P, Trajano GS, Wharton L, et al. Effects of passive heating intervention on muscle hypertrophy and neuromuscular function: A preliminary systematic review with meta-analysis. Journal of Thermal Biology. 2020;**93**:102684