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REVIEW

EXERCISE MIMETICS: FACT OR FANTASY?

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Abstract

The abundant health benefits of physical exercise are not being translated into practice. In an effort to short circuit the need for physical activity to promote health, exercise-mimetic agents are being developed; they mimic the action of peptide molecules released from exercised muscles. The intention is to mimic biochemical responses even without performing exercise. Technologies have advanced to identify various exercise-induced proteins, called myokines, and to develop ligands which bind to the myokine receptors. A number of such chemicals exist that mimic the effects of activating Peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1α (PGC-1 α), Peroxisome proliferator-activated receptor β/δ (PPAR β/δ) and AMP-activated protein kinase (AMPK). Most such agents were tested in animal models with varying degrees of success and mostly undesirable adverse effects. The increasing complexity of exercise response is being recognized, making the development and use of single 'exercise-mimetics' ineffective, except for some narrow indications. In addition, some of the performance enhancing exercise-mimetics are being misused by endurance athletes, with the chemicals being banned as doping agents. In a fascinating interaction between physiology and pharmacology, agents that can mimic the beneficial effects of physical exercise are an enticing possibility over the distant horizon.

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Introduction

While evidence is building up for the benefits of exercise, the prevalence of sedentary living is rising. Were it not for the evolutionarily wired survival instincts for physical activity, lack of exercise could not have had such ill-effects. The ability to be physically active was essential for viability during periods of fasting and feasting (1). Being physically inactive has been listed as being the fourth leading cause of death (2). Epidemiological, clinical, experimental and biochemical evidence exists for the unequivocal benefits of physical exercise. The evidence ranges from building mass, preserving musculoskeletal integrity, promoting cardiometabolic function, preserving cognition that prevent a number of modern-day illnesses: cardiovascular disease, diabetes, obesity, cognitive impairment, sarcopenia, cancer and osteoporosis (1). Yet, evidence from different parts of the globe separated by two decades shows that sedentary habits, even those who could benefit most from physical exercise, are the rule rather than the exception (3,4).

Considering the health benefits of physical exercise and the inability to translate principles into practice, inter-

est turned to identifying bioactive substances that could mimic or potentiate the beneficial effects of exercise; these were termed 'exercise pills' or 'exercise mimetics' (2).

What is meant by physical activity?

Physical activity is defined as 'bodily movement produced by skeletal muscles that requires energy expenditure' (1). Exercise training, which is covered by the term 'physical activity' can be grouped under two main categories, viz aerobic exercise and resistance or strength training (5). The two forms of exercise lead to different biochemical and biomarker responses.

Physical inactivity leads to disease by a cascade of effects: loss of muscle mass, chronic systemic inflammation leading to insulin resistance, atherosclerosis, tumorigenesis, poor formation of bone and their attendant complications (6). Contrariwise physical activity reverses all the above effects. When evolutionary programming to minimize expenditure of energy is coupled with sedentary lifestyle and availability of energy-rich food, it becomes difficult to break the chain; other means are therefore necessary (5). The currently available approaches to management of obesity comprise a range from pharmacological agents to reduce weight, use of antidiabetic medicines that result in weight loss, bariatric surgery and lifestyle modifications. None of these is either universally accessible or is cost-effective across the population (5).

Basis for novel approaches to mimic exercise

Recognizing the unbridged gap between the health-benefits of physical activity and difficulty of inducing people to exercise, efforts were made to design chemical agents that either simulate or improve the effects of exercise, without really exercising (2). These exercise 'pills' caught the fancy of both sedentary individuals and the pharmaceutical industry, which recognized the potential windfall from such agents.

At the outset one must recognize the term 'exercise mimetic' is an approximation for the many effects of exercise which influence many cells and tissues via complex responses (2). The currently proposed exercise mimetics influence only a few of the many metabolic networks that are activated by physical exercise. They fall short of the other adaptations induced by exercise besides activation of skeletal muscle pathways influencing the 'oxidative/endurance phenotype' (2).

Together with adipose tissue, skeletal muscle has been recognized as a secretory organ. Humoral secretions from skeletal muscles are released in response to exercise to meet the demand for increased glucose during muscle contraction (6). These myokines, which have effects as autocrine, paracrine and endocrine factors may counteract the effects of adipokines produced by adipose tissue. Ultimately myokines may be the mediators for the protective effects of physical exercise (6).

To indicate the broad scope of biochemical response to the effect of exercise, myokines were considered to be part of 'exercise factors', viz, secretions produced by skeletal muscle following exercise. This implies that myokines, which are proteins along with metabolites are included as exercise factors. A working definition of myokine is a protein secreted by skeletal myocytes that has a signaling role in an autocrine, paracrine and endocrine transmission (7; more about myokines, see Chaldakov *et al* in this volume of *Adipobiology*). It implies that myokines are produced by tissues other than the skeletal muscle. Such distinction is necessary because biochemical responses to acute and prolonged exercise may activate different exercise factors.

Potential regulators of exercise-induced skeletal muscle adaptation

Among the growing list of regulators modulating adaptation of skeletal muscle to exercise, the following have been well studied.

Peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1α (PGC-1 α)

PGC-1 α is expressed in many tissues that are mitochondria-rich and therefore have high oxidative capacity. It has a key role in the metabolism of glucose and fatty acids and is a potent regulator of cell energy metabolism (8). Both human and rodent studies showed that it is inducible in skeletal muscle by both acute and endurance exercise training. Essentially, PGC-1 α interacts with and activates many transcription factors, proving to be a potential drug target for exercise mimetics (9).

Peroxisome proliferator-activated receptor β/δ (PPAR β/δ)

PPARβ/δ is highly expressed in skeletal muscle where, upon binding to ligands such as fatty acids, it dimerizes with retinoid X receptors and ultimately stimulates expression of target genes. They have dual roles by both activating and inhibiting molecules involving in metabolic processes leading to obesity, diabetes and atherosclerosis (10). Based on its presence in the skeletal muscle and the availability of a ligand-binding domain, it is a potential drug target as an exercise mimetic.

AMP-activated protein kinase (AMPK)

AMPK, involved in the initiation of mitochondrial biogenesis is an upstream regulator of skeletal muscle PGC-1 α (11) which has a role in sensing cellular energy levels (9). Studies in animal models showed that it can improve endurance capacity, while

enhancing protein degradation. The role in humans is yet to be established.

Mammalian target of rapamycin (mTOR)

mTOR is a serine/threonine protein kinase that has an important role in many cellular processes. Specifically, it plays a major role in hypertrophy of skeletal muscle, acting through mitochondrial regulation (9). Current pharmacological agents acting on the mTOR pathway are used for their immunosuppressive properties, with their role in influencing skeletal muscle metabolism still remaining unclear (12).

Other factors secreted in response to muscle fiber contraction

A number of other potential myokines have been recognized including but not limited to, interleukins, decorin, follistatin-like 1, fibroblast growth factor-21, chemokine CXC motif ligand-1 and meteroin (2).

Myokines and resistance training

Resistance training results in hypertrophy of skeletal muscle; cytokines released in response to resistance training have beneficial effects on cardiovascular, metabolic, mental and immunological processes (13). Regular repetitive training leads to adaptations through mechanical tension, muscle damage and metabolic stress (14). Interleukin 6 is well known to mediate the anti-inflammatory effect of exercise (15).

Interaction of myokines with adipose tissue

While the role of adipose tissue as an endocrine organ has been established, the role of muscle derived hormonal effects are being explored. There is increasing evidence for an interaction between secretory products of skeletal muscle and adipose tissue. Myokines regulate lipid metabolism related to exercise (15). The interaction between exercise induced interleukin-6 (IL-6) and fat metabolism is the most well studied. Il-6 increases lipolysis and fat oxidation through activation of AMPK. It is involved in mediating the link between exercise and the deposition of abdominal fat. Exercise induced IL-6 is necessary for reducing visceral adipose tissue (16).

In addition, browning of white adipose tissue could be affected by myokines. Exercise releases irisin, which stimulates uncoupling protein 1 (UCP1) leading to browning of white adipose tissue (15). However, it is not clear if irisin levels increase following exercise. The amino acid sequence of irisin is nearly identical among mammalian species, implying it participates in conserved functions. It closely interacts with myostatin, a myokine released from skeletal muscles (17). In turn irisin acts *via* PGC-1 α in browning of white fat (18). The levels of irisin increase, particularly after a bout of acute exercise (19). Yet other myokines and circulating factors involved in browning of white adipose tissue include meteorin-like (Metrnl), interleukin-6, β-aminoisobutyric acid, haptokines such as FGF-21 and follistatin (15). These were mostly studied in rodent models. A recent addition to the list is indirubin, which induces UCP1 expression in brown adipose tissue acting *via* PKA and p38MAPK pathways (20).

Skeletal muscle contains not only muscle fibres, but connective cells, immune cells and adipocytes (21). Interleukin-33 (IL-33) controls the immune cell activity and immune homeostasis in white adipose tissue (22). Similarly, interleukon-13 (IL-13) has been shown to drive metabolic conditioning of muscle following endurance exercise in rodents (23). The action is mediated by signal transduction and activation of transcription 3 (STAT3) (24).

Calorie restriction

Time restriction feeding and calorie restriction have been increasingly recommended in prevention and treatment of obesity. Exercise-mimetic agents could play a role in bringing about the effects of calorie restriction (25). Targets include nutrient sensors and anabolic signaling pathways such as SIRT1, AMPK and mTOR signaling.

Myokines and cognition

Physical activity prevents cognitive decline. Muscle secretory products, which mediate the effects are a potential source for developing exercise mimetic agents (15). Exercise induces changes in the brain function which include increased neurogenesis in adult brain, enhanced synaptic plasticity, improved cognition and antidepressant effects (26). A number of mediators interacting with the brain function were identified, originally as correlates, although some of them are showing to play a causative role. These include brain derived neurotropic factor, other neuropeptides, noncoding RNAs, exosomes, other orphan neuclear receptors, along with myokines (26).

Methodological aspects of studying exercise chemicals

The number of biomarkers following exercise is increasing by the use of new analytical methods. Translation into druggable targets is lagging. As an example, to identify the human muscle acute exercise signaling repertoire from the human muscle, substrate prediction of AMPK was done. Targeted validation of exercise-regulated AMPK substrates was performed in human muscle cells. To explore the exercise signaling network, a global

analysis of protein phosphorylation was assessed in human skeletal muscle biopsies from untrained healthy males before and after a single high-intensity exercise bout. This revealed 1,004 unique exercise-regulated phosphatases on 562 proteins (27). Analysis of just one metabolic pathway reveal the unexplored complexity of acute exercise signaling and provide insights into the role of AMPK in mitochondrial biochemistry. Similarly methodological advances can be expected to reveal changes in metabolome and lipidome to provide a molecular snapshot of changes in metabolic alterations, which are both rapid and complex (28).

Current status of exercise-mimetics

Understanding the molecular changes in exercise-induced muscle allowed the design of drugs that can simulate the effects of exercise even in sedentary animals (29). They mimic the effects of exercise by activating key regulators.

PPARγ coactivator 1α PGC-1 α

Sustained elevation of PGC-1 α results in benefits that resemble adaptation to endurance exercise (30). Tissue specific modulatory agents would be useful to normalize PGC-1 α levels leading to increased skeletal muscle PGC-1 α action, while inhibiting hepatic and pancreatic PGC-1 α (9). Proof of concept agents have been identified that reduce the activity of PGC-1 α in the liver, viz, SR-18292. It reduces blood glucose, strongly improves insulin sensitivity, and thereby glucose homeostasis (31). However, it must be possible to regulate PGC-1 α in time and space to avoid potential adverse effects (32).

PPAR β/δ

In view of its role in the pathogenesis of a variety of common metabolic disorders, ligands were developed that target its binding domain. GW501516, or Cardarine is an agonist that has promising skeletal muscle effects. However, its use has been overshadowed by athletes misusing it as a performance-enhancing agent (33). In addition, due to its carcinogenic effects clinical trials of the compound were terminated (34). Despite its ability to induce fatty acid oxidation and energy expenditure, it is on the banned list of the World Anti-Doping Agency. Due to its stability and long half life, it can be easily identified in blood and urine samples (29). It is however possible for the development of other safe ligands.

AMP-activated protein kinase

AMPK activators are some of the most effective exercise mimetics (29). Unfortunately, GW501516 too has been in the news for the wrong reasons, as a performance enhancing drug. It induces fatty acid oxidation and expenditure of energy (35). Animal studies showed the potential beneficial effects of AMPK activators in the treatment of metabolic disorders (36). R419, a mitochondrial complex-1 inhibitor acutely activates AMPK. Administration to rats improved skeletal muscle insulin sensitivity independent of its action through skeletal muscle AMPK, along with improvement of mitochondrial function (37). Specific AMPK agonists such as MK-8722 a small molecule ligand leads to biochemical responses similar to a bout of exercise in many tissues (38), suggesting a potential exercise mimetic. More recently, O304, an activator of AMPK was shown to improve metabolic function and exercise capacity in aged mice (39).

SIRT1 activators and other agents

Resveratrol, found in the skin of red grapes, and its derivative pinostilbene showed exercise-mimetic effects in skeletal muscle (40). Resveratrol improved aerobic capacity in mice via induction of genes for oxidative phosphorylation and mitochondrial biogenesis, acting through PGC-1 α activation. Though a weak exercise-mimetic, it still protects against diet-induced obesity (41). Other NAD^+ boosting chemicals such as a natural NAD^+ precursor nicotinamide riboside were shown to protect against diet-related metabolic abnormalities (42).

Newer ligands of REV-ERB α a nuclear receptor such as SR9009 and SR9011 were identified (29); their role in the regulation of circadian energy metabolism were studied: They inhibit clock transcription and when suppressed, enhance the transcription of clock gene. Another target for exercise-mimetics in ERRγ, which regulates mitochondrial oxidative genes. GSK4716, a synthetic agonist of ERRγ led to upregulation of genes of mitochondrial biogenesis, fatty acid oxidation and TCA cycle (43); the *in vivo* effects are not known.

Is exercise all about myokines?

In our quest toward reductionism, we tend to overlook the broad picture. There is no single exercise gene or for that matter, a single exercise pathway. Exercise, as in all complex integrative systems is characterized by redundancy resulting in a variety of downstream targets that have complex temporal and spatial interactions (2). This in turn brings out the risk of interfering with one component of the complex; it may lead to undesirable outcomes. Therefore, not just an exercise-mimetic, but a cocktail of exercise-mimetics could be required, adding to the complexity. What and at what doses, at what time and for how long are they required? Finally, one must answer a fundamental question: which if any of the multiple benefits of exercise do exercise-mi-

metics seek to benefit? The cardiovascular system, atherosclerosis, cognition, life-span? (see 44).

In addition, exercise induces the production and secretion of a number of factors other than myokines, such as α-Ketoglutaric acid, β-Aminoisobutyric acid, Kyneurenic acid, β-Hydroxybutyrate, Lactate and 12,13-Dihydroxy-9Z-octadecenoic which have effects on the skeletal muscle, hepatic tissue and brown adipose tissue (45).

Scope and limitations of exercise-mimetic compounds

It is evident that a single 'exercise pill' cannot mimic all the beneficial effects of exercise; a number of systems are involved, not just mitochondrial number or oxidative capacity of muscle. Protective effects of exercise are not accounted for by correction of known risk factors. Other pathways include improved endothelial function, remodeling of large blood vessels, collateral vessel formation and beneficial psychological effects among others (2). Exercise entails human movement, which cannot be mimicked by chemical agents. Besides, and most importantly, most of the exercise mimetics were carried out in animal studies; many trials were stopped because of adverse effects. At best exercise-mimetics can be adjuvants in special situations (46). More practical efforts would be in devising methods to motivate people to be physically active. Understanding the cellular and molecular mechanisms of exercise needs further studies (26). In addition, search should extend to an omics approach to map exercise biological networks and identify potential drug targets (47). While major gaps in understanding the beneficial physiological effects are ongoing (1), one must be conscious about not searching for drugs from an economic view for lifestyle associated diseases only from an economic viewpoint (25).

Conflict of interest

The authors declare no conflict of interest.

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