

PHARMACOLOGICAL EXERCISE MIMETICS IN THERAPY: DELUSION OR FUTURE?

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The increase in the prevalence of a large number of metabolic disorders is attributed to the sedentary lifestyle associated with increased energy intake of food. Scientists warn that our genes are not selected for a sedentary existence and that the complex homeostatic system is being seriously undermined. Regular physical activity induces a number of physiological adaptations both within skeletal muscle and the whole organism, which have positive effects in the prevention and treatment of many metabolic disorders. Recognizing the impact of these beneficial effects of physical activity on health outcomes, and taking into account the trend of inactivity population, researchers have focused on the active substances that mimic or potentiate the effects of exercise without the actual energy consumption, and big pharmaceutical companies see a potentially huge market and profit in this. This paper discusses the real possibility and potential of pharmacological mimetic of exercise in the treatment of metabolic diseases. *Acta Medica Medianae 2013;52(4):58-62.*

Key words: skeletal muscle, exercise mimetics, nuclear receptors, metabolic disorders

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Introduction

It is generally accepted that the increase in the prevalence of a large number of metabolic disorders, including obesity, type 2 diabetes and cardiovascular disease, is the result of sedentary lifestyle associated with increased energy intake of food. Evidence of epidemiological, experimental and clinical studies have shown a positive correlation between physically inactive lifestyle and chronic diseases (1,2). Regular physical activity does not only regulates body weight, expenditure of energy, metabolic homeostasis, but also increases the oxidative capacity of skeletal muscle as it leads to alterations in intracellular proteins and lipids involved in cellular signaling, improves insulin sensitivity and cardiovascular function. In this way, it represents the effective prevention of metabolic disorders (3). Recognizing the beneficial effects of the impact of physical activity on health, and taking

into account the trend of inactivity population, some pharmaceutical companies have conducted research in order to find the active substances that mimic or potentiate the effects of exercise, the so-called "exercise pills". The very concept of the pill is based on the beneficial effects of physical exercise with no real energy consumption and the big pharmaceutical companies see a potentially huge market and profit in this. Describing the recent advances in the understanding of the molecular pathways that trigger transcriptional remodeling of skeletal muscle, we estimate whether "exercise mimetics" have any potential to affect metabolic diseases.

Adaptations of skeletal muscles

Skeletal muscles play an important role in energy metabolism and insulin resistance present in conditions such as obesity and diabetes. The ability of adult muscle fibers to change in response to external stimuli is referred to as muscle plasticity and it reflects changes in contractile activity and substrate availability (4). The skeletal muscles are heterogeneous and plastic tissues composed of oxidative slow-twitch (type I), oxidative-glycolytic fast-twitch (type IIa), oxidative fast-twitch (type IIx) and glycolytic fast-twitch (IIb) myofibers that vary in metabolic and contractile properties (5). Slow-twitch fibers contain high levels of fat-oxidizing enzymes, mitochondria and slow contractile proteins. Type II myofibers predominantly and

anaerobically metabolize glucose based on a limited mitochondrial content and express the fast contractile proteins. Endurance exercise triggers trans-differentiation of skeletal muscles towards oxidative slow-twitch phenotype by increasing slow-twitch contractile machinery, mitochondrial biogenesis and fatty acid oxidation, all of which lead to the increase in aerobic capacity (6,7). These adaptations are usually associated with increased expression of genes involved in the slow-twitch contractile apparatus, mitochondrial respiration and fatty acid oxidation (8-10). Such remodeling does not only improves exercise performance itself, but also retards obesity and type 2 diabetes that are commonly associated with loss of aerobic muscles. However, exercise as a therapy for obesity, cardiovascular disorders and metabolic disorders is often impractical because of physical limitations, but alternative approaches in the form of drugs that mimic endurance exercise have the promising therapeutic implications in these diseases.

What does evolution say?

The escalation of obesity and chronic diseases is explained by the disruption of evolutionarily programmed minimum energy expenditure by life circumstances in the developed world. How does evolution explain that?

Nature of selection of our present genome determines the physical activity as a key factor for physiological gene expression. Evolutionary survival of *Homo sapiens* was dependent on food procurement, and it required a physical activity. Given that the food supply was irregular, there were cycles of feast and famine, also referred to as periods of physical activity and rest. Survival during periods of famine was possible owing to the inclusion of certain genes in the regulation of efficient intake and utilization of fuel stores. Neel marked these genes as "thrifty" and efficient, giving them a selective advantage of human genome (11). During the period of famine, people with this genotype had the advantage based on the stored energy to maintain homeostasis, as these genes regulate the two major sources of fuel storage in humans: glycogen and triglycerides. However, in the last hundred years, there has been a change in the human environment associated with physical activity and food availability (12). Modern society is remarkably sedentary and as a consequence those alleles that were responsible for the function, selective advantage and survival in the Late-Paleolithic era are now faced with a sedentary lifestyle, fat-rich and fiber-poor diets, positive caloric intake, increased longevity, which all result in a selective disadvantage with the appearance of health disorders (13). Scientists warn that genes of our ancestors were not selected for sedentary existence and that it disturbs the complex homeostatic system. The constant availability of food with a lack of

physical activity leads to a discordance in gene-environmental interactions, lack of expression of genes programmed genome results in pathology and is manifested as the modern chronic diseases (14). The clinical consequences of impaired cycle is reflected in the case of type 2 diabetes, where its prevalence in hunter-gatherer, agricultural, and pastoral communities is only 1.1%, compared with a much higher prevalence rate in industrialized nations (15). Therefore, evolutionists believe that physical activity is the core catalyst of the physiological regulation of "thrifty" genes in order to maintain the cycle of muscle glycogen, triglycerides and their regulatory proteins that prevent the organism to cross biological threshold beyond which chronic health conditions develop (16).

Potential target candidate

Exercise activates a large number of transcription regulators, transporters and enzymes that are responsible for adaptive responses in skeletal muscle. Those factors that are activated by exercise, such as AMPK (5AMP'activated protein kinase), heat shock proteins, PGC-1 α (coactivator 1 α), calcium-associated signaling, MAPK (p38-mitogen-activated protein kinase) are logical targets for pharmacological modulation to mimic the biochemical responses to exercise. The second category are those that increase exercise capacity when overexpressed in muscle, or are activated pharmacologically and experimentally, but are not necessarily modulated by exercise training. These include PEPCK (phosphoenolpyruvatecarboxykinase), silent information regulator of transcription (SIRT)1, PPAR δ (peroxisome proliferator-activated receptor δ). From the pharmacological perspective, they are also the target candidates or mimetics of certain aspects of the response to exercise.

PPAR δ is a member of the nuclear receptor family of transcriptional regulator and is considered as a key regulator that mimics exercise in the context of metabolic effects, fiber type remodeling and running endurance. Within the skeletal muscles, predominantly is expressed in the oxidative slow-twitch fibers, and its expression is induced further by endurance-type exercise that normally triggers adaptive increase in oxidative or slow-twitch phenotype (17,18). More evidence of the physiological regulatory effects of PPAR δ on metabolism, energy homeostasis and endurance is obtained from the study of genetic engineering in mice. Thus, Wang et al. found that overexpression of this receptor induces mitochondrial biogenesis and higher proportion of oxidative type I muscle fibers, and is involved in the regulation of fatty acid metabolism of skeletal muscle and adipose tissue (19). Most importantly, these authors have shown that the muscle PPAR δ activation is sufficient to induce effects similar to exercise, increased endurance and protection from obesity and type 2 diabetes. Demonstration

of pharmacological activation of the nuclear receptor resulted in a rapid enhancement of oxidative capability of the tissue by increasing both oxidative fiber number and capillary density possibly via calcineurin pathway and thus demonstrated its key role in muscle morphology of oxidative phenotype (20).

AMPK is a master regulator of cellular metabolism, participates in glucose homeostasis, appetite and exercise physiology (21,22). It is often referred to as "metabolic master switch" that mediates cellular adaptation to nutritional and external variations that deplete intracellular levels of ATP, such as heat shock, hypoxia, starvation or prolonged exercise. The result of AMPK activation is the inhibition of the energy consuming biosynthetic pathways (such as fatty acid synthesis in the liver and adipocytes, cholesterol synthesis in the liver, protein synthesis in the liver and muscle, and insulin secretion from β cells) and the activation of ATP-producing catabolic pathways (such as fatty acids uptake and oxidation in the tissues, glycolysis in heart and mitochondrial biogenesis in muscle (23). AMPK may also modulate the transcription of specific genes involved in energy metabolism, thus confirming a long-term metabolic control. This protein kinase is heterotrimeric complex composed of a catalytic α subunit and regulatory β and γ subunits, and subunits exist in different isoforms. All of AMPK subunit isoforms are expressed in skeletal muscle and are activated by acute or chronic exercise depending on the intensity of exercise (24).

Although diet and exercise are the first choice in the treatment and prevention of obesity and type 2 diabetes, there are patients groups for whom this therapy is not appropriate for some medical reasons, social factors or poor motivation. In these cases, drugs acting on the signaling pathways that induce the favorable changes, particularly insulin sensitivity and glucose transport in skeletal muscle, are attractive candidates for therapy and prevention. Such properties have AICAR (5-aminoimidazole-4-carboxamide-1- β -d-ribofuranoside), thiazolidinediones and metformin (25). In the insulin-resistant states, insulin stimulation of glucose transport in muscle and inhibition of gluconeogenesis in the liver is impaired, but hepatic lipogenesis which insulin normally stimulates is increased. These AMPK activators regulate precisely this situation in cases of obesity and type 2 diabetes. Animal studies with pharmacological activation of AMPK by the synthetic compound AICAR showed enhanced running endurance of untrained animals, increased regulation of genes related to oxidative metabolism, increased fat oxidation and angiogenesis (26). Moreover, chronic treatment with AICAR stimulates fiber type transition in the direction of fast to slow and increases the expression of several metabolic enzymes linked to aerobic respiration

(27). Similar results were obtained in the pharmacological activation of AMPK with metformin.

SIRT1 belongs to a class of deacetylases and its role consists of deacetylation of transcription factors, coregulators and enzymes. It is present in various biological processes such as differentiation, metabolism and inflammation, and a disturbed function is implicated in obesity, cancer and aging (28). It is thought that SIRT1 regulates a variety of metabolic processes such as glucose homeostasis, insulin secretion, mitochondrial biogenesis and lipid metabolism. Acute exercise increases the expression of SIRT1 in skeletal muscle, but the effect of chronic exercise is not fully explored. In animal models both low and high intensity endurance training increases its expression in skeletal muscle (29). Synthetic SIRT1 activators in experimental studies are a group of promising candidates in clinical applications, but there are activators of the group of natural compounds, such as resveratrol. Resveratrol (RSV) is a natural polyphenol compound found in the skin of grapes and is known for its phytoestrogen and antioxidant properties. In animal models of obesity, it proved to be a calorie restriction mimetic. Lagouge et al. confirmed that RSV strongly induced mitochondrial activity through the activation of PGC-1 α , leading to an increase in oxidative muscle fibers and increased resistance to muscle fatigue (30). Although direct activation of SIRT1 is not excluded, recent data suggest that RSV achieves its effects through the activation of AMPK (31,32). Resveratrol supplementation reduces energy consumption, improves metabolic profile, regulates homeostasis of glucose, lowers blood pressure and improves endothelial and cardiovascular function (33). Further studies will better define the long-term metabolic effects of resveratrol supplementation in humans in order to determine its true potential in the treatment of obesity and metabolic aberrations.

Similar effects of AMPK activation and other nuclear receptors are shown by caffeine, green tea extracts whose catechins activates AMPK in a similar way as AICAR and resveratrol, myokines etc. (34,35).

Conclusion

Exercise induces a variety of physiological adaptations not only in skeletal muscle, but also at the level of the whole organism. A number of biochemical pathways transmitting signals activate in different tissues, so that is why beneficial effects of exercise are being deployed by different organ systems. All these pharmacological receptor activators have shown in animal models of promising results that are rational basis for further research and clinical application. This application would be particularly useful in the treatment of obesity and type 2 diabetes in patients who are unable to exercise because of certain musculoskeletal or cardiovascular conditions. So, when lifestyle modification and oral antidiabetic agents which are typically used to

manage the disease fail to achieve or sustain adequate glycemic control, pharmacological, but also nutritional (polyphenols) activators may be useful in the treatment of these metabolic disorders. But, the activation of specific target has a limited field of action which, however, cannot achieve the full potential of the overall adaptive response exercise. In addition, mimicking activation of exercise signaling pathways can lead to chronic catabolic state. For example, activation of AMPK can inhibit protein synthesis and stimu-

lates autophagy, or skeletal muscle overproduction of PGC1 α can result in muscle atrophy, and because of that potential therapeutic applications are limited to transient, short-term, optimally balanced activation (36,37). Until the appropriate pharmacological exercise mimetic does not become well-tailored and clinically applicable with minimal side effects, physical activity will, if possible, remain an important preventive and therapeutic way to treat metabolic diseases.

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FARMAKOLOŠKI MIMETICI VEŽBANJA U TERAPIJI: ZABLUDA ILI BUDUĆNOST?

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Porast prevalencije velikog broja metaboličkih poremećaja pripisuje se sedentarnom načinu života udruženim sa povećanim energetske unosom hrane. Naučnici upozoravaju da naši geni nisu selektovani za sedentarnu egzistenciju i da se ozbiljno narušava kompleksni homeostatski sistem. Redovna fizička aktivnost indukuje veliki broj fizioloških adaptacija, kako unutar skeletnih mišića tako i na nivou celog organizma, koje imaju pozitivan ishod u prevenciji i tretmanu mnogih metaboličkih poremećaja. Prepoznajući ove korisne efekte uticaja fizičke aktivnosti na zdravlje, a imajući u vidu trend neaktivnosti populacije, naučnici su se fokusirali na aktivne supstance koje imitiraju ili potenciraju efekte vežbanja bez stvarnog utroška energije, u čemu velike farmaceutske kompanije vide potencijalno tržište i profit. Rad razmatra realnu mogućnost i potencijal farmakoloških mimetika vežbanja u tretmanu metaboličkih bolesti. *Acta Medica Medianae* 2013; 52(4):58-62.

Ključne reči: *skeletni mišići, mimetici vežbanja, nuklearni receptori, metabolički poremećaji*