CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Exercise Pill — Too Good to Be True?

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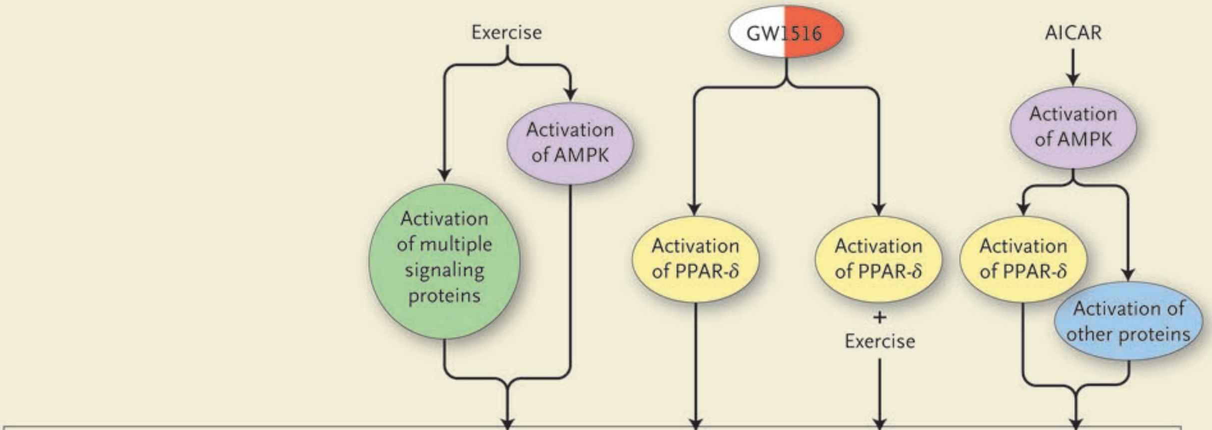
Regular physical exercise has undisputed health benefits in the prevention — and in some cases, the treatment — of many diseases. The problem is that for the great majority of Americans, probably as much as 70% of the population, there is an inability or unwillingness to meet the minimum physical activity guidelines established by the American College of Sports Medicine. The idea of taking a pill to gain the benefits of exercise is extremely attractive for the millions of "couch potatoes." A recent study by Narkar et al.[1] suggests that a couple of molecules could mimic some effects of exercise training.

Skeletal muscle is an extraordinary tissue that is critical not only in locomotion but also in controlling an organism's metabolic homeostasis. Skeletal muscles are composed of different types of elongated, multinucleated cells called myofibers. Type I myofibers have a slow-twitch speed of contraction, are exceedingly oxidative, and have a reddish appearance. Type II myofibers have a faster-twitch speed of contraction, can have both oxidative and glycolytic metabolic properties, and are fairly white in appearance.

Skeletal muscle is highly adaptable, or plastic, in that exercise training effects a change in metabolic and contractile properties of the myofibers. For aerobic exercise training, such as running and swimming, myofibers take on a slow-twitch phenotype, with an increase in the levels of oxidative enzymes, glycogen, and glucose transporter 4 (GLUT4), the protein that transports glucose into the muscle. These changes are accompanied by an increase in insulin sensitivity of the muscle and an overall improvement in glucose homeostasis in the body. When a rodent or human becomes inactive, a number of myofibers may convert to the fast-twitch phenotype, making them less able to perform sustained aerobic work and contributing to an insulin-resistant state.

Studies have suggested a role for both the peroxisome-proliferator–activated receptor δ (PPAR-δ) and AMP-activated protein kinase in regulating the metabolic and contractile characteristics of myofibers. The PPAR proteins are nuclear receptors that function as transcription factors and regulate the expression of multiple genes. AMP-activated protein kinase has been described as a master metabolic regulator. It too controls gene expression and can do so through direct phosphorylation of some nuclear proteins.[2] Narkar et al. hypothesized that PPAR-δ and AMP-activated protein kinase may interact to control the metabolic phenotype of myofibers. Indeed, their findings suggest that AMP-activated protein kinase is part of a transcriptional complex with PPAR-δ, and they speculate that AMP-activated protein kinase directly or indirectly potentiates the receptor's activity.

The authors discovered that administering the PPAR-δ agonist GW1516 to sedentary mice for 4 weeks led to significant increases in the expression of oxidative genes in muscles but did not increase conversion to the slow-twitch type I fibers or the length of time or distance run by mice in a test of endurance (Fig. 1).[1] However, when GW1516 was given to mice that concurrently underwent exercise training on a treadmill for 4 weeks, there was significant conversion to type I fibers and an increase in endurance by about 70% over that seen in exercise-trained control mice. When the authors treated sedentary mice with an activator of AMP-activated protein kinase called AICAR (5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside), they observed an improvement in exercise performance by 44% over that in controls — mimicking the effects of training. These latter findings are consistent with those in previous studies showing that as little as 5 days of AICAR treatment is accompanied by an increase in levels of glycogen, GLUT4, and mitochondrial enzymes in skeletal muscles of the rat,[3] and increasing the activity of AMP-activated protein kinase in mouse skeletal muscle by



Enhanced exercise performance	+	−	+	+
Adaptations to muscle				
More oxidative phenotype	+	+	+	+
Fiber-type conversion	+	−	+	+
Increased insulin sensitivity	+	?	?	+
Multiorgan health benefits	+	?	?	?

Figure 1. Exercise and Elicitation of Endurance.

A recent study by Narkar et al.[1] suggests that two agents, GW1516 and AICAR (5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside), agonists of peroxisome-proliferator–activated receptor δ (PPAR-δ) and AMP-activated protein kinase (AMPK), respectively, can mimic some of the beneficial effects of exercise in skeletal muscle. The authors show that the signaling of AMPK and that of PPAR-δ interact, resulting in many adaptations in skeletal muscle. Previous studies have shown that aerobic exercise activates AMPK and a host of other signaling pathways in skeletal muscle, leading to a more oxidative and insulin-sensitive phenotype, and exercise also has numerous beneficial effects on organs throughout the body. Data are from the study by Narkar et al. and several previous studies.

means of genetic manipulation results in robust increases in performance of endurance exercise and in mitochondrial enzymes.[4] Other studies have shown that AICAR can increase glucose uptake into muscle, lower blood glucose levels, and even decrease adiposity.[5]

Should we therefore turn to AICAR to improve muscle function? Will AICAR become the latest choice for doping athletes? Can we cure obesity and type 2 diabetes with the use of AICAR or other agonists of AMP-activated protein kinase? Not quite. There are many factors to consider. For one, AMP-activated protein kinase is a complex protein, a heterotrimer composed of an α catalytic subunit and β and γ regulatory subunits. Each subunit has multiple isoforms, and there are 12 complexes of AMP-activated protein kinase that vary in tissue distribution and sensitivity to activating agents.

AICAR is an adenosine-regulating agent that increases the bioavailability of adenosine. As such, it has been studied extensively in patients with myocardial ischemia and during cardiac bypass surgery, showing improvement in cardiovascular outcomes. However, AICAR has a short half-life after intravenous administration and poor bioavailability after oral ingestion and is accompanied by an increase in blood levels of lactic acid and uric acid, making it a poor candidate for long-term use.[5] The search continues for new compounds that activate AMP-activated protein kinase, but seekers beware: there are naturally occurring mutations in the gene encoding the $\gamma 2$ subunit of AMP-activated protein kinase (expressed in the heart) that result in activation of the kinase and are associated with ventricular preexcitation and hypertrophic cardiomyopathy. Moreover, AMP-activated protein kinase has also been implicated in the regulation of apoptosis; its activation could have unwanted effects on cell proliferation. In the hypothalamus, activated AMP-activated protein kinase can increase the consumption of food, which would be undesirable in persons with obesity and type 2 diabetes.

It is precisely these complexities that have challenged the estimated two dozen or so pharmaceutical companies that have been working on developing activators of AMP-activated protein kinase for the past decade. Recent findings that such activators can have isoform-specific effects provide hope that a specific activator of AMP-activated protein kinase may be developed in the future.

There is general consensus among scientists who study skeletal muscle that agents, like AICAR, that activate AMP-activated protein kinase may eventually be useful in the treatment of obesity and diabetes. This could be especially important for patients who are unable to exercise because of severe musculoskeletal or cardiovascular conditions. However, agonists of AMP-activated protein kinase might be beneficial in mimicking only some of the effects of aerobic exercise in muscle, since contracting skeletal muscles elicit a host of metabolic and mechanical signals that contribute to adaptations to the muscle (Fig. 1). We now know that regular exercise has profound beneficial effects on almost all organs in the body. It is unlikely that a single "exercise pill" will ever supply most of the benefits of regular exercise. Don't get too comfortable on that couch just yet.

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