Exercise Effects on Muscle Insulin Signaling and Action

Exercise and insulin signaling: a historical perspective

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Tomás, Eva, Antonio Zorzano, Neil B. Ruderman. Exercise and insulin signaling: a historical perspective. J Appl Physiol 93: 765–772, 2002; 10.1152/japplphysiol.00267.2002.—Over the past 30 years, a considerable body of evidence has revealed that a prior bout of exercise can increase the ability of insulin to stimulate glucose transport and glycogen synthesis in skeletal muscle. Apart from its clinical implications, this work has led to a considerable effort to determine at a molecular level how exercise causes this effect and, in particular, whether it does so by enhancing specific events in the insulin-signaling cascade. The objective of this review is to discuss from a historical perspective how our current thinking in this area has evolved and the people responsible for it. Areas to be discussed include the effect or lack of effect of prior exercise on the insulin-signaling pathway, effects of exercise on the regulation by insulin of the GLUT-4 glucose transporter in muscle, and the emerging role of AMP-activated protein kinase as a mediator of exercise-induced signaling events. In addition, we will discuss briefly some of the avenues that research in this area is likely to follow.

diabetes; glucose transport; 5-aminoimidazole-4-carboxamide ribofuranoside; AMP-activated protein kinase; skeletal muscle

CHAUVEAU AND KAUFMAN (9) in 1887 reported that when a horse chews on hay the concentration of glucose in the blood draining its masseter muscle substantially decreases. This remarkable observation was the first demonstration that glucose uptake by muscle is enhanced during exercise. In 1924, Sir Henry Dale in England (6) and Carl and Gerti Cori in the United States (11) demonstrated with their colleagues that insulin also increases glucose uptake by muscle. This review will focus on the interaction between insulin and exercise in regulating glucose uptake and in particular will focus on the question of whether a prior bout of exercise enhances the ability of insulin to stimulate glucose utilization by an effect on insulin signaling. For additional discussions of aspects of this subject and of the signaling changes induced in muscle by exercise per se, the reader is referred to a recent paper by Richter et al. (46) and to an earlier review in this series by Goodyear and Sakamoto (19).

ORIGIN OF THE NOTION THAT A PRIOR BOUT OF EXERCISE ACUTELY ENHANCES INSULIN ACTION ON MUSCLE

The first clue that exercise might enhance the ability of insulin to stimulate muscle glucose utilization was probably provided by Per Bjorntorp and his co-workers in Gothenberg, Sweden in the early 1970s. In 1972 (3), they reported that glucose tolerance was better and plasma insulin levels lower in middle-aged Swedish men who regularly participated in competitive sports than in age- and weight-matched control men. The same investigators also reported that 6 wk of physical training lowered plasma insulin levels (although it did not affect glucose tolerance) in a group of hyperinsulinemic, obese women (2, 4). Collectively, these results led to the suggestion that regular exercise can increase
whole body and presumably muscle insulin sensitivity, a notion subsequently confirmed in rats by Carl Mondon, Constantine Dolkas, and Gerald Reaven at Stanford (37).

Bjorntorp’s studies did not address the question of whether the increase in insulin sensitivity associated with physical activity is an acute or a chronic effect of exercise. The fact that adipose tissue mass, fat cell size, and plasma lipids (cholesterol and triglycerides) were lower in the athletes whom they studied than in the control men suggested the latter (3). On the other hand, their observation that acute decreases in plasma insulin could persist for several days after each individual exercise bout suggested the former (4). This question aside, Bjorntorp’s research encouraged several groups to examine the effect of several months of regular exercise on glucose tolerance in patients with Type 2 diabetes, a disorder associated with insulin resistance. In the first of these studies, reported in 1979, Bengt Saltin and co-workers in Sweden (49) and Neil Ruderman and his colleagues at the Joslin Research Laboratory in Boston (48) found modest improvements in glucose tolerance in patients with chemical diabetes (impaired glucose tolerance) and diet-controlled Type 2 diabetes, respectively. On the other hand, the relative transience of the improvement (it had disappeared by 8 days after the last exercise bout) found by the Ruderman group led them to question whether it was the result of a long-term effect of training, such as improved fitness. This and their subsequent finding that hemoglobin A1C levels can be markedly diminished by regular exercise in similar patients with Type 2 diabetes (51) led them to assess the effect of a single bout of exercise on insulin action in skeletal muscle.

In studies that they carried out at Boston University, Erik Richter and co-workers (47) used the isolated perfused rat hindquarter preparation to demonstrate that the ability of a physiological concentration of insulin (75 μU/ml) to stimulate glucose uptake and glycogen synthesis in muscle is enhanced for several hours after a 45-min treadmill run (Table 1). They showed that this effect is restricted to muscles that had performed work, as judged by glycogen depletion (47), and that it was reproduced when hindquarter muscle was made to contract by electrical stimulation of the sciatic nerve. Antonio Zorzano et al. (62), working in the same laboratory, later showed that prior exercise enhances the ability of insulin to stimulate α-aminoisobutyrate uptake by muscle, indicating that it also acts on the Na⁺-dependent A system for amino acid transport. In 1990, Greg Cartee et al. (15), in the laboratory of John Holloszy at Washington University in St. Louis, reported that the period of increased insulin sensitivity postexercise could be greatly prolonged if the rats were fasted or fed a low-carbohydrate diet, a finding that they attributed to these nutritional manipulations slowing the repletion of muscle glycogen stores. That prior exercise enhances insulin-stimulated glucose utilization in human muscle was first reported in 1987 by John Devlin and Edward Horton at the University of Vermont (13).

### Table 1. Glucose utilization by the isolated perfused rat hindquarter after treadmill running: effect of insulin

<table>
<thead>
<tr>
<th>Glucose Uptake, μmol·g⁻¹·h⁻¹</th>
<th>Control</th>
<th>Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, μU/ml</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>0</td>
<td>1.8 ± 0.2</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>2.2 ± 0.3</td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>1.9 ± 0.2</td>
<td>4</td>
</tr>
<tr>
<td>75</td>
<td>3.2 ± 0.2</td>
<td>12</td>
</tr>
<tr>
<td>500</td>
<td>6.3 ± 0.1</td>
<td>3</td>
</tr>
<tr>
<td>20,000</td>
<td>10.2 ± 0.9</td>
<td>8</td>
</tr>
<tr>
<td>40,000</td>
<td>10.6 ± 0.2</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of observations. Hindquarters were placed in the perfusion system —20 min after the cessation of a 30-min treadmill run or an equivalent period of rest. After 12 min of equilibration, glucose utilization was measured over the next 45 min. Control rats were not exercised. Insulin at the indicated concentration was added to the initial cell-free perfusate. Between 10 and 20% of the insulin was degraded during the perfusion. *P < 0.05, compared with control values. [Adapted from Ref. 47.]

Armed, in part, with the initial data from Richter’s rodent studies, Stephen Schneider and co-workers at the New Jersey College of Medicine and Boston University School of Medicine (50) carried out studies suggesting that the decrease in hemoglobin A1C in patients with Type 2 diabetes caused by physical training is due to the cumulative effect of the individual exercise bouts rather than improved fitness. More specifically, in patients who experienced decreases of hemoglobin A1C in excess of 1% after several months of physical training, Schneider et al. showed that glucose tolerance was substantially better at 12 and 17 h than at 72 h after the last bout of exercise. Concurrent studies in nondiabetic athletes by Heath et al. in Holloszy’s laboratory (23) and by Burstein and Posner and colleagues at McGill (7), demonstrating that the high insulin sensitivity of trained individuals diminishes rapidly (days) when these individuals cease exercising, strongly supported this conclusion.

In summary, these early reports established beyond question that a single bout of exercise enhances the sensitivity and responsiveness of skeletal muscle to insulin in both humans and experimental animals. They suggested that both glucose and amino acid transport are affected and that the effect of exercise is mediated in great measure by local rather than systemic factors. They also suggested that much of the apparent benefit of physical training on glycemic control and insulin sensitivity in patients with Type 2 diabetes is attributable to a residual effect of the last bout of exercise. As will be discussed later, however, cumulative effects of regular exercise in these patients almost certainly also play a major role.

**EFFORTS TO EXPLAIN AT A MOLECULAR LEVEL HOW PRIOR EXERCISE ENHANCES INSULIN-STIMULATED GLUCOSE TRANSPORT IN MUSCLE**

**Insulin signaling.** The demonstration that prior exercise enhances certain actions of insulin in skeletal muscle (47) took place at the same time that the early
steps in the insulin-signaling cascade were being elucidated (32). For this reason, repeated efforts were made over the next 15 years to determine whether prior exercise alters the ability of insulin to stimulate one or more signaling events (see Fig. 1). Initial studies by Arend Bonen and co-workers in Canada (5) and by Zorzano et al. (62) established that prior exercise does not increase insulin binding to its receptor in rat skeletal muscle. Subsequently, Judith Treadway and David James, also in the Ruderman group (53), showed that the enhanced biological effects of insulin after exercise (treadmill run for 45 min) are not paralleled by increases in either basal or insulin-stimulated tyrosine kinase activity or autophosphorylation of the insulin receptor. Laurie Goodyear at the Joslin Research Laboratory and colleagues (17) and Jorgen Wojtaszewski and colleagues (57), working jointly with Goodyear and Erik Richter, now at the Krogh Institute in Copenhagen, extended these findings in rat and human skeletal muscle, respectively. Paradoxically, they found that contraction caused a decrease in insulin-stimulated tyrosine phosphorylation (by 20–25%) and insulin response sequence (IRS)-1 immunoprecipitated phosphatidylinositol 3-kinase (PI3-kinase) activity. In addition, they found that prior exercise did not enhance the ability of insulin to induce changes in Akt or glycogen synthase kinase (GSK)-3 in human muscle (57). In contrast, Zhou and Dohm (59a) found that prior exercise increases the ability of insulin to stimulate phosphotyrosine immunoprecipitable PI3-kinase activity, and, more recently, Howlett et al. (27a), working in the Goodyear laboratory, observed an increase in IRS-2-associated PI3-kinase activity under these conditions. Likewise, an increase in insulin-stimulated Akt activity postexercise has been reported in mice by the latter group (58a).

Collectively, on the basis of these findings, it is unclear whether the increased insulin action in skeletal muscle after exercise is explained by enhanced activation of early or intermediate events in the wing of the insulin-signaling cascade that goes through PI3-kinase. Whether exercise affects the ability of insulin to alter an event distal to PI3-kinase or a PI3-kinase-independent signaling mechanism remains to be determined. With respect to these possibilities, Goodyear and co-workers (19) showed that exercise, by itself, mimics some of the signaling changes caused by insulin in rat skeletal muscle, including activation of mitogen-activated protein kinases, Akt and p70S6K, and inhibition of glycogen synthase kinase. In addition, Pessin and Saltiel (43), on the basis of studies in adipose tissue, proposed the existence of a PI3-kinase-independent mechanism by which insulin can stimulate glucose transport. However, the relevance of these observations to the enhanced insulin-stimulated glucose and amino acid transport after exercise in muscle remains to be determined.

**Recruitment of GLUT-4 glucose transporters to the plasma membrane.** Although exercise does not activate the same early events in the insulin-signaling cascade in skeletal muscle as insulin, it also stimulates glucose uptake by enhancing the translocation of GLUT-4 glucose transporters from an intracellular location to the cell surface. The first evidence for this was obtained from measurements of the subcellular distribution of GLUT-4 glucose transporters after acute exercise in

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**Fig. 1.** Potential mechanisms by which prior exercise via AMP-activated protein kinase (AMPK) could enhance the ability of insulin to stimulate glucose transport in skeletal muscle. The possibility that AMPK leads to an increase in phosphatidylinositol 3-kinase (PI3K) activity by affecting the tyrosine phosphorylation of insulin response sequence-2 is not shown. See text for details.
rat skeletal muscle by Edward Horton's group at the University of Vermont and Harriet Wallberg-Henricks
son at the Karolinska Institute of Sweden (24) and by Holloszy's laboratory working in conjunction with
Amira Klip at the University of Toronto (14). The laboratories of Holloszy (34), Morris Birnbaum at the
University of Pennsylvania (59), and Steen Lund and Oluf Pedersen (35) at Aarhus University Hospital in
Denmark later showed that such glucose transporter recruitment could occur even when activation of P3-
kinease, which is required for the stimulation of glucose transport by insulin, is inhibited by wortmannin.
These important findings proved conclusively that exercise and insulin trigger GLUT-4 translocation in
muscle by effects on different signaling mechanisms. However, they did not rule out the possibility that
insulin and exercise stimulate some common downstream signaling event.

Historically, one hypothesis put forth to explain the postexercise increase in insulin-stimulated glucose
transport relates to the possibility that insulin and exercise stimulate the translocation of GLUT-4 from
different pools. If this occurred, insulin could act on a larger number of transporters after exercise or it could
act on transporters with different properties. The notion of distinct intracellular insulin- and exercise-
recruitable GLUT-4 pools in skeletal muscle was first proposed by Amira Klip and co-workers (15) at the
University of Toronto, based on analyses of isolated intracellular membranes and plasma membranes from
control, exercised, and acutely insulin-treated rats. Subsequent to this, Lise Coderre (10) in Paul Pilch's
laboratory at Boston University was the first to isolate and characterize biochemically intracellular insulin
and exercise-recruitable GLUT-4 populations from rat skeletal muscle by using fractions separated by discon-
tinuous sucrose density-gradient centrifugation. She found that the two transporter populations had the
same protein composition but that they differed in their densities and sedimentation coefficients. The
most definitive evidence for distinct insulin and exercise-recruitable GLUT-4 pools, however, was reported
in 1998 by Torkil Ploug at the Muscle Research Center of the University of Copenhagen, working in collabora-
tion with Samuel Cushman and Evelyn Ralston at the National Institutes of Health (44). In an elegant set of
experiments, they first demonstrated by immunofluo-
rescence microscopy and immunogold electron micro-
scopy that intracellular GLUT-4 vesicles are either pos-
tive or negative for the transferrin receptor. They then
proceeded to show that only the transferrin receptor-
positive vesicles were recruited by contractions. Later
studies by Eva Tomás in Zorzano's laboratory at the
University of Barcelona suggested that both of these
pools (insulin and exercise) are derived from an endo-
somal compartment (52). Thus the evidence for distinct
exercise and insulin recruitable pools is reasonably
strong. Whether their presence will help explain the
postexercise increase in insulin-stimulated glucose
transport remains to be determined. To answer this
question will almost certainly require fundamental in-
toformation about the distal signals by which insulin and
exercise trigger GLUT-4 vesicle recruitment from in-
tracellular populations, the docking of these vesicles,
and their fusion with cell surface membranes.

Finally it has also been suggested that exercise could
increase glucose uptake by enhancing the synthesis of
GLUT-4 at the level of transcription. Thus studies from
Dohm's laboratory (39) have shown that a single bout of
exercise can moderately increase GLUT-4 mRNA in
previously untrained (1.4-fold) and trained rats for 3 h
(1.8-fold) after a single bout of exercise. Likewise, Ren
et al. working in Holloszy's laboratory (45) found a 50% increase in GLUT-4 protein and a twofold increase in
GLUT-4 mRNA 16 h after a single bout of swimming exercise. Thus exercise clearly also acutely induces
signals that lead to an increased expression of GLUT-4
mRNA and protein. As with its effect on GLUT-4 trans-
location, the precise identity of these signals is not
known. For additional information on this and other
material covered in this section, the reader is referred to
a number of excellent recent reviews (18, 26, 30, 46, 56).

AMP-ACTIVATED PROTEIN KINASE

A major advance in understanding at a molecular level
how contraction affects glucose transport in the
muscle cell was the discovery of AMP-activated protein
kinase (AMPK). This heterotrimeric enzyme, which
contains distinct α-, β-, and γ-subunits, is regulated by
changes in a cell's energy state and possibly other
factors. As first characterized in liver by David Carling
and D. Graham Hardie (21) at the University of
Dundee in Scotland, increases in the AMP-to-ATP or
creatinine-to-creatinine phosphate ratios of a cell, such as
those that occur in response to ischemia and other
stresses, can activate AMPK by several mechanisms.
The activation of AMPK, in turn, sets in motion a
number of events that both increase ATP generation
(e.g., increased fatty acid oxidation) and decrease ATP
utilization for processes not required for a cells imme-
diate viability (e.g., inhibition of cholesterol and fatty
acid synthesis).

The first indication that AMPK could be involved in
the regulation of muscle metabolism was reported by
William Winder at Brigham Young University in Utah
in a joint effort with Hardie (55). They demonstrated
that treadmill running increased AMPK activity in red
quadriiceps muscle of a rat by two- to threefold within 5
min. They also showed that this increase in activity
persisted for as long as the rat continued to run and
that it was associated with decreases in the activity of
acetyl-CoA carboxylase and the concentration of malo-
nyl-CoA, an allosteric inhibitor of carnitine palmitoyl
transferase, the enzyme that controls the transfer of
long-chain fatty acyl CoA into mitochondria where they
are oxidized. Subsequently, Demetrios Vavvas and co-
workers in the Ruderman laboratory (54) and Winder
et al. (55) reported similar changes in response to
muscle contraction induced by sciatic nerve stimula-
tion. Vavvas et al. also showed that activation of
AMPK in this setting involved the α2-isoform that it
was evident within seconds and that after 5 min of intense contraction it could persist for >1 h.

A specific role for AMPK in the regulation of glucose uptake was demonstrated in 1997 by Winder and coworkers (36). Using an isolated rat hindquarter preparation, they showed that perfusion with the AMPK activator 5-aminooimidazole-4-carboxamide ribofuranoside (AICAR) increased glucose uptake by approximately twofold. Subsequent studies carried out jointly by the Goodyear and Winder laboratories established that this effect of AICAR was due to increased glucose transport, that it involved GLUT-4 translocation (33), and that, like the increase in glucose transport induced by muscle contraction, it was not blocked when PI3-kinase is inhibited by wortmannin (22). Likewise, chronic AICAR therapy has been shown by Winder's laboratory to increase GLUT-4 protein in muscle (as does exercise) in vivo (25). A similar effect, as well as an increase in GLUT-4 mRNA has been demonstrated by Holloszy et al. (41) in epitrochlearis muscle incubated for 24 h with AICAR. Despite its array effects on GLUT-4, the precise mechanism by which AMPK activated for 24 h with AICAR. Despite its array effects on GLUT-4, the precise mechanism by which AMPK activates glucose transport is still unknown. On the other hand, the molecular events activated in a cell by AICAR in vitro should be easier to characterize than those induced by muscle contraction in vivo. For this reason, AICAR or other pharmacological AMPK activators may prove to be useful tools in determining how prior exercise enhances insulin action in muscle. In this context, Fisher and Nolte (16), working in the Goodyear and Winder laboratories established this effect of AICAR was due to increased glucose transport, that it involved GLUT-4 translocation (33), and that, like the increase in glucose transport induced by muscle contraction, it was not blocked when PI3-kinase is inhibited by wortmannin (22). Likewise, chronic AICAR therapy has been shown by Winder's laboratory to increase GLUT-4 protein in muscle (as does exercise) in vivo (25). A similar effect, as well as an increase in GLUT-4 mRNA has been demonstrated by Holloszy et al. (41) in epitrochlearis muscle incubated for 24 h with AICAR. Despite its array effects on GLUT-4, the precise mechanism by which AMPK activated for 24 h with AICAR. Despite its array effects on GLUT-4, the precise mechanism by which AMPK activates glucose transport is still unknown. On the other hand, the molecular events activated in a cell by AICAR in vitro should be easier to characterize than those induced by muscle contraction in vivo. For this reason, AICAR or other pharmacological AMPK activators may prove to be useful tools in determining how prior exercise enhances insulin action in muscle. In this context, Fisher and Nolte (16), working in the Goodyear and Winder laboratories, have recently shown that both prior exposure to AICAR and prior tetanic contraction enhance the ability of insulin to stimulate glucose transport in an incubated epitrochlearis muscle. They also found that early and intermediate events in the insulin-signaling pathway (e.g., PI3-kinase activation) were not involved. Thus AMPK, like exercise, appears to work downstream or independently of PI3-kinase to improve insulin sensitivity.

Finally, recent studies by Birnbaum's laboratory (38) have shown that expression of a dominant inhibitory mutant of AMPK completely blocks the ability of hypoxia or AICAR to activate glucose uptake, although only partially reducing contraction-stimulated glucose uptake in skeletal muscle. These authors suggested that “AMPK transmits a portion of the signal by which muscle contraction increases glucose uptake, but other AMPK-independent pathways also contribute to the response.”

SUBJECTS FOR FURTHER STUDY

The effects of prior exercise on insulin-resistant muscle. This review has focused on the effects of an acute bout of exercise on insulin action and signaling in normal skeletal muscle. However, from a clinical perspective, the effects of prior exercise are most likely to be relevant in muscle that is insulin resistant. Insulin resistance has been defined as an impaired ability of a given amount of insulin to exert its usual biological effect and could be related to a decrease in insulin sensitivity or responsiveness. It has long been appreciated that muscle of patients with Type 2 diabetes, or at risk for developing it, are insulin resistant (12). It was for this reason that regular physical activity was first considered for the therapy and prevention of Type 2 diabetes (37, 49). Despite this, investigations of the effect of a prior bout of exercise on insulin action in insulin-resistant muscle have been few. A potentially important study was carried out by Nicholas Oakes et al. (40), working in E. W. Kraegen's laboratory at the Garvan Institute in Sydney, Australia. In rats made insulin resistant by ingestion of a eucaloric, high-fat diet for 3 wk, they found that a single bout of exercise (24 h earlier) substantially reversed the impaired ability of insulin to stimulate glucose uptake into muscle during a euglycemic hyperinsulinemic clamp. They also found that the improvement in insulin sensitivity after exercise was associated with decreased in the concentrations of long-chain fatty acyl CoA and malonyl CoA. In a subsequent study, Kim Bell et al. (1) in the same laboratory found that prior exercise also reversed an increase in membrane-associated protein kinase C-0 in muscle of fat-fed rats. Although insulin signaling is altered in muscle of these rats (60), the effect of exercise on these signaling abnormalities has not been studied.

Effects of a single bout of exercise vs. those of physical training. As already noted, the increased insulin sensitivity of muscle in physically trained humans disappears rapidly (48–72 h) once they stop exercising, suggesting it is in large part related to the last bout of physical activity. On the other hand, physical training diminishes adiposity, fat cell size, and plasma insulin levels (3) and increases the expression of GLUT-4 in muscle (61), all of which could hypothetically enhance the ability of a given amount of insulin to stimulate glucose transport. Thus the relative importance of individual exercise bouts vs. chronic effects of physical training in enhancing insulin action remains unsettled.

As already noted, improvements in glucose tolerance were observed over 20 years ago in response to physical training in patients with Type 2 diabetes. Several years later, complete normalization of glucose tolerance and high plasma insulin levels were observed after 1 yr of intense training by Holloszy and coworkers (27), and more recently increased physical activity has been shown to diminish progression from impaired glucose tolerance to Type 2 diabetes by Pan et al. (42). Despite these impressive clinical findings, investigations of the effects of physical training on insulin signaling in muscle of trained humans and experimental animals have yielded inconsistent results. For further discussion of the effects of physical training on insulin action in humans and experimental animals, and in particular subjects with Type 2 diabetes and/or insulin resistance, the reader is referred to a number of recent reviews (18, 26, 46, 56) and several chapters in the recently published Handbook of Exercise in Diabetes (47a).
Effect of exercise on cells other than those in skeletal muscle. Another question for future study is whether exercise enhances insulin signaling in cells other than the skeletal muscle myocyte. Such cells could be present in the arterial wall. Thus insulin resistance, as manifested by impaired activation of PI3-kinase and Akt by insulin, has been found in the aorta of a hyperinsulinemic obese fa/fa (Zucker) rat by George King and co-workers at the Joslin Research Laboratory (31). In addition, Yasuo Ido, David Carling, and Neil Ruderman at Boston University and Hammersmith Hospital in England (29) have shown that the ability of insulin to activate Akt in cultured human umbilical vein endothelial cells is depressed after 24 h of incubation in a hyperglycemic (30 mM glucose) medium. Relevant to this review, they found that this impairment in insulin signaling caused by hyperglycemia was prevented when the human umbilical vein endothelial cells were concurrently incubated with AICAR, an activator of AMPK. Whether exercise causes a similar increase in AMPK in the endothelial cell, in vivo, and if so whether this contributes to its ability to diminish cardiovascular disease in humans (47a) is clearly a subject for further study.

CONCLUDING REMARKS

The subject of exercise and insulin signaling is somewhat unusual for a historical review, since the first key observations are barely 20 years old and papers published in the past year are also discussed. Despite this, it is increasingly clear that lifestyle changes that include physical activity will very likely play an increasing role in the prevention and treatment of Type 2 diabetes and other diseases associated with insulin resistance. In addition, it is equally clear that an understanding at a molecular level (e.g., insulin signaling) of how exercise diminishes insulin resistance and prevents cellular damage and/or dysfunction will be critical to the success of this effort.

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