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Exercise-induced increase in muscle insulin sensitivity

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Holloszy, John O. Exercise-induced increase in muscle insulin sensitivity. J Appl Physiol 99: 338–343, 2005; doi:10.1152/japplphysiol.00123.2005.—Exercise/muscle contraction activates glucose transport. The increase in muscle glucose transport induced by exercise is independent of insulin. As the acute effect of exercise on glucose transport wears off, it is replaced by an increase in insulin sensitivity. An increase in insulin sensitivity results in a shift in the insulin dose-response curve to the left, with a decrease in the concentration of insulin needed to induce 50% of the maximal response. This phenomenon, which plays a major role in rapid muscle glycogen accumulation after exercise, is not mediated by amplification of the insulin signal. Development of the increase in insulin sensitivity after contractions does not require protein synthesis or activation of p38 MAPK. It does require the presence of a serum protein during the period of contractile activity. The effect of exercise on muscle insulin sensitivity is mimicked by hypoxia and by treatment of muscles with 5-aminoimidazole-4-carboxamide-1-β-β-ribofuranoside to activate AMP-activated protein kinase. The postexercise increase in sensitivity of muscle glucose transport to activation is not specific for insulin but also involves an increased susceptibility to activation by a submaximal contraction/hypoxia stimulus. The increase in insulin sensitivity is mediated by translocation of more GLUT4 glucose transporters to the cell surface in response to a submaximal insulin stimulus. Although the postexercise increase in muscle insulin sensitivity has been characterized in considerable detail, the basic mechanisms underlying this phenomenon remain a mystery.

AMP-activated protein kinase; GLUT4; hypoxia; muscle contractions

INSULIN ACTION ON GLUCOSE transport is characterized in terms of insulin sensitivity and insulin responsiveness (32). Insulin sensitivity is defined in terms of the concentration of insulin required to cause 50% of its maximal effect on glucose transport. An increase in insulin sensitivity results in a shift in the insulin dose-response curve to the left with a decrease in the insulin concentration required to cause 50% of the maximal response. Insulin responsiveness is defined in terms of the increase in glucose transport induced by a maximally effective insulin concentration. Thus an increase in insulin responsiveness results in a larger increase in glucose transport in response to a maximally effective insulin stimulus, with a proportional upward shift of the dose response curve.

That exercise increases the sensitivity of the glucose transport process to insulin in skeletal muscle was first discovered by Richter et al. (45) in Neil Ruderman’s laboratory. At the time of this discovery, these investigators thought that the increase in muscle glucose uptake induced by exercise requires the presence of insulin. However, in an earlier study, it was found that muscle contractions increase glucose transport in the absence of insulin in frog sartorius muscle (26). This effect of contractions in frog muscle appeared to be mediated by a different mechanism than that caused by insulin.

At about the same time that Richter et al. (45) found that exercise increases insulin sensitivity, it was shown that a bout of swimming results in an increase in muscle glucose uptake in the absence of added insulin that can be measured in perfused rat muscles after cessation of exercise (31). This finding was confirmed by Ruderman’s group in a study in which they showed that enhanced glucose uptake after exercise occurs in two phases in perfused rat hindlimb muscles (14). The first phase is independent of added insulin, and, as this increase in glucose transport reverses, it is replaced by an increase in insulin sensitivity (14). Similar results were obtained in a later study in which rat epitrochlearis muscles were studied in vitro at various time points after exercise (55).

Subsequent studies have established that contractions stimulate glucose transport in the complete absence of insulin (38, 40, 56, 57), that the maximal effects of contractions and insulin are additive (6, 24, 38, 55, 69), and that contractions and...
AMP-activated protein kinase (AMPK), which is activated by fast-twitch muscle (at least in the rat) (63). The steps downstream, whereas the AMPK-mediated mechanism functions only in because it functions in both fast-twitch and slow-twitch muscles. Subsequent studies on muscles incubated in vitro showed that the increase in muscle glucose transport induced by Ca\textsuperscript{2+} was markedly increased 60 min after exercise. Eighteen hours 18 h after exercise in the absence of insulin. Glucose uptake by perfused muscles was measured 60 min and performed (68). Rats were exercised to deplete glycogen, and incubation of muscles with 33% rat D-ribofuranoside (AICAR), which is converted to the AMP analog 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), which is converted to the AMP analog 5'-monophosphate (22, 23, 49, 59, 60). Of these two pathways, the Ca\textsuperscript{2+}-activated one appears to be the more important, because it functions in both fast-twitch and slow-twitch muscle, whereas the AMPK-mediated mechanism functions only in fast-twitch muscle (at least in the rat) (63). The steps downstream of CaMKII and AMPK remain to be elucidated.

PERSISTENT EFFECT OF EXERCISE ON MUSCLE GLUCOSE TRANSPORT

Depletion of muscle glycogen by exercise is followed by an enhanced ability to synthesize glycogen (1, 47). In a study of this phenomenon, it was found that the rates of insulin stimulated glucose uptake and glycogen synthesis were higher in perfused muscles of rats 18 h after exercise when glycogen levels were kept low than when glycogen levels were raised by carbohydrate feeding (9). It was not clear whether this persistent effect of exercise was due to a persistent increase in insulin action or to a persistence of the exercise-induced, insulin independent increase in glucose transport that was additive to the effect of insulin. A follow-up experiment was, therefore, performed (68). Rats were exercised to deplete glycogen, and glucose uptake by perfused muscles was measured 60 min and 18 h after exercise in the absence of insulin. Glucose uptake was markedly increased 60 min after exercise. Eighteen hours later, only ~50% of the increase in glucose uptake had worn off in rats fed a carbohydrate-free diet, whereas the increase in uptake had completely reversed in rats fed carbohydrate to raise muscle glycogen (68). Because there was no insulin in the perfusion medium, we erroneously attributed the persistent increase in glucose uptake 18 h after exercise to a slowing of reversal of the exercise-induced, insulin-independent increase in glucose uptake as a result of prevention of glycogen repletion.

Subsequent studies on muscles incubated in vitro showed that the increase in muscle glucose transport induced by exercise reverses within 2–3 h even in the absence of glycogen repletion (19, 41, 67). Incubation of muscles with 33% rat serum or a very low concentration of insulin, 7.5 μU/ml, appeared to markedly slow reversal of the increase in glucose transport (67). However, what appeared to be a slowing of reversal actually turned out to be due to a large increase in insulin sensitivity (19). Thus the increase in glucose transport observed by Young et al. (68) 18 h after exercise in muscles perfused with insulin-free medium was likely due to the markedly enhanced action of endogenous insulin still bound to the muscle insulin receptors and to an increase in GLUT4 glucose transporters induced by the exercise (see below).

In light of evidence that glycogen depletion enhances, and glycogen supercompensation reduces insulin action (9, 30, 70), Cartee et al. (4) compared the effects of a high-carbohydrate diet and a carbohydrate-free diet on persistence of the increase in muscle insulin sensitivity after exercise. Three hours after exercise, insulin sensitivity of glucose transport was increased in epitrochlearis muscles in both carbohydrate fed and fasted rats. However, 18 h after exercise, the increase in insulin action had completely reversed, whereas it persisted for at least 48 h in rats fed a carbohydrate-free diet. We interpreted these findings to indicate that carbohydrate restriction results in a marked prolongation of the increase in insulin sensitivity. In retrospect, I think this interpretation was incorrect. The following year it was discovered that endurance exercise induces an adaptive increase in the GLUT4 isoform of the glucose transporter in skeletal muscle (11, 42, 48).

In these and a number of subsequent studies of this phenomenon, prolonged training programs were used, because it was thought that the adaptation of muscle to exercise is a slow process. However, it turned out that the GLUT4 protein has a very short half-life and that the increase in GLUT4 protein occurs very rapidly in response to a single bout of exercise (18, 44). In a study by Ren et al. (44), it was found that GLUT4 protein expression was increased by ~50% in epitrochlearis muscles 16 h after a bout of swimming. This study and others showed that maximal insulin- or contraction-stimulated glucose transport is increased in proportion to the increase in GLUT4 protein (28, 29, 34, 35, 44). This increase in glucose transport is mediated by translocation of more GLUT4 to the cell surface (34, 35, 44). Feeding a high-carbohydrate diet, with development of glycogen supercompensation, prevents the increase in insulin responsiveness (28, 34, 35). On the other hand, the increase in GLUT4 and insulin responsiveness persists for days if glycogen supercompensation is prevented by feeding a carbohydrate-free diet (13). In light of this information, I now think that the increase in insulin action that we observed 18 and 48 h after exercise was due to an increase in GLUT4 rather than a persistent increase in insulin sensitivity.

This raises the question: Why did we not detect an increase in insulin responsiveness? We calculated insulin responsiveness as the increase in glucose transport above basal in response to a maximal insulin stimulus. However, “basal” transport was significantly increased 18 h after exercise in the muscles from rats not fed carbohydrate. The absolute rate of glucose transport, which reflects the total number of GLUT4 molecules at the cell surface, was actually significantly higher in the glycogen-depleted muscles exposed to a maximal insulin stimulus 18 h after exercise. However, maximally insulin-stimulated glucose transport was only ~22% higher in the glycogen-depleted muscles 18 h after exercise than in the muscles from nonexercised controls. This effect is much smaller than the 60% increase in insulin responsiveness that we have subsequently observed 16 h after one exercise bout (44).

It is not possible at this point to explain this discrepancy; however, a difference in study design that could have influenced the results is the duration of the swimming, 2 h in the study by Cartee et al. (4) and 6 h in the study of GLUT4.
the presence of serum.

Lithium-induced increase in insulin sensitivity does not require it may not be is that, in contrast to in vitro contractions, the exercise-induced increase in insulin sensitivity of muscle glucose transport to submaximal insulin, found in muscle after exercise. In a study that evaluated this possibility that lithium might mimic the effects of exercise stimulates glycogen synthesis (5, 21, 27). These findings suggested the increase in sensitivity to occur (12). The mechanism responsible for the increase in insulin sensitivity is actually not specific for insulin. The available evidence argues against it. It has been shown, using the same protocol, that unlike the increase in insulin sensitivity, the increase in glucose transport to maximal insulin stimulus is not augmented 3 h after exercise (19). If GLUT4 intrinsic activity were increased 3 h after exercise, the effect of a maximal insulin stimulus on glucose transport, i.e., responsiveness, would also be increased.

There has been much interest in the possibility that the increase in insulin sensitivity after exercise is mediated by an amplification of the insulin signal. However, it seems well documented now that a submaximal insulin stimulus does not result in greater activation of any of the known steps of the insulin-signaling pathway in muscle after exercise (10, 16, 20, 54, 61, 62). This finding is in keeping with the evidence that the increase in insulin sensitivity is not specific for insulin but that it also involves increased sensitivity to agents that activate glucose transport via the contraction/hypoxia-stimulated pathway (3, 10). Apparently, the increase in “insulin” sensitivity is mediated by a mechanism that lies downstream of the insulin-signaling and contraction/hypoxia-signaling pathways.

It has been suggested that the activation of p38 MAPK plays a role in mediating the increases in glucose transport induced by insulin and muscle contractions (50, 51). Thong et al. (53) found that the increase in p38 phosphorylation induced by exercise in skeletal muscle lasts for at least 3 h. This finding led Thong et al. to hypothesize that p38 activation may be involved in mediating the exercise-induced increase in muscle insulin sensitivity. To evaluate this possibility, Geiger et al. (15) tested the hypothesis that activation of p38 results in an increase in muscle insulin sensitivity. To activate p38, soleus and epitrochlearis muscles were exposed to anisomycin for 30 min. The treatment with anisomycin resulted in an increase in p38 phosphorylation and also stimulated glucose transport approximately threefold. Three hours later, when the acute effect of

EXERCISE INCREASES THE SUSCEPTIBILITY OF MUSCLE GLUCOSE TRANSPORT TO VARIOUS STIMULI

The phenomenon that has been referred to as an increase in insulin sensitivity is actually not specific for insulin. The sensitivity of muscle glucose transport to stimulation by various other agents is also markedly increased (3). For example, the activation of muscle glucose transport by 20 min of hypoxia, a submaximal stimulus, is greatly amplified in epitrochlearis muscles 3 h after exercise (3). The sensitivity of glucose transport to stimulation by vanadate or hydrogen peroxide is also increased (3). That sensitivity of glucose transport to hypoxia, as well as to insulin, is increased after exercise provides evidence that a late step that is common to the insulin and contraction/hypoxia-stimulated pathways is involved in mediating the increase in sensitivity.

REQUIREMENT FOR A SERUM FACTOR

Like exercise, stimulation of muscles to contract in situ results in an increase in insulin sensitivity (3, 46). In contrast, stimulation of muscles immersed in Krebs-Henseleit-bicarbonate buffer to contract in vitro does not result in enhanced insulin sensitivity (3, 12). The explanation for this finding is that an as-yet-unidentified serum protein must be present during the contractile activity in order for the increase in insulin sensitivity to occur (12). The mechanism responsible for the permissive effect of serum has not yet been elucidated.

EXERCISE MIMETICS

Activation of AMPK is one of the mechanisms by which exercise stimulates glucose transport (49, 60). Hypoxia appears to stimulate glucose transport in muscle by the same mechanisms as exercise (2, 63). Like contractile activity, hypoxia and activation of AMPK using AICAR both induce increases in the insulin sensitivity of muscle glucose transport (10). Also like contractile activity, the effects of exercise and AICAR on insulin sensitivity require the presence of serum during the treatment period (10). Treatment of insulin-sensitive tissues with lithium increases glycogen synthase activity and potently stimulates glycogen synthesis (5, 21, 27). These findings suggested the possibility that lithium might mimic the effects found in muscle after exercise. In a study that evaluated this possibility, lithium was shown to markedly increase the sensitivity of muscle glucose transport to submaximal insulin, hypoxia, contractions, a phorbol ester, and phospholipase C (52). It is not known whether this effect of lithium is mediated by the same mechanism that is responsible for the exercise-induced increase in insulin sensitivity. A finding that suggests it may not be is that, in contrast to in vitro contractions, the lithium-induced increase in insulin sensitivity does not require the presence of serum.

STUDIES OF THE MECHANISMS BY WHICH THE INCREASE IN MUSCLE INSULIN SENSITIVITY IS MEDIATED

Insulin, contractions, and hypoxia all induce increases in muscle glucose transport by stimulating movement of GLUT4 from intracellular storage sites to the cell surface (25). It has been suggested that, in addition to GLUT4 translocation, insulin increases the intrinsic activity of the GLUT4 at the surface of muscle cells (50, 51). To try to differentiate between these possibilities, Hansen et al. (20) used the 2-N-4-((1-azido-2,2,2-trifluoroethyl)-[2-3H]benzoyl)-1,3-bis-(o-mannos-4-olxy)-2-propylamine exofacial photolabeling technique to determine whether a greater increase in cell-surface GLUT4 occurs in response to a submaximal insulin stimulus 3 h after exercise. The increase in photolabeling of GLUT4 was more than twofold greater in the exercised than in control muscles, and it was very similar in magnitude to the increase in insulin sensitivity of glucose transport. We interpreted this finding to indicate that the increase in insulin sensitivity of glucose transport after exercise is completely accounted for by translocation of more GLUT4 to the cell surface.

It has been argued that this conclusion is incorrect and that the increase in GLUT4 photolabeling may be explained by an increase in GLUT4 intrinsic activity that results in both an increase in glucose transport and an increase in binding of the photolabel to GLUT4. Direct testing of this alternative hypothesis will require development of new technology. However, available evidence argues against it. It has been shown, using the same protocol, that unlike the increase in insulin sensitivity, the response of glucose transport to a maximal insulin stimulus is not augmented 3 h after exercise (19). If GLUT4 intrinsic activity were increased 3 h after exercise, the effect of a maximal insulin stimulus on glucose transport, i.e., responsiveness, would also be increased.
Anisomycin on glucose transport had largely worn off, insulin sensitivity of muscle glucose transport was markedly increased. Pretreatment of muscles with the inhibitor of p38 SB-202190 completely prevented both the activation of p38 and the increase in insulin sensitivity. At this point of the study, it seemed likely that activation of p38 might be the mechanism by which exercise induces an increase in insulin sensitivity. So these findings generated considerable excitement until it was discovered that blocking activation of p38 with SB-202190 does not prevent the increase in muscle insulin sensitivity induced by contractions. Thus it appears that activation of p38 results in increased muscle insulin sensitivity, contractions activate p38, yet activation of p38 is not necessary for the contraction-induced increase in insulin sensitivity.

A HYPOTHESIS REGARDING THE MECHANISM UNDERLYING INCREASED MUSCLE “INSULIN SENSITIVITY”

In unstimulated muscle, most of the GLUT4 are located in intracellular storage sites. The stimulation of muscle glucose transport by insulin and by contractions/hypoxia is mediated by the movement of GLUT4 from some of these storage sites to the cell surface (2, 7, 8, 33, 37, 43, 58). A phenomenon that has been given little attention in the development of models of GLUT4 trafficking and the regulation of glucose transport is the graded response to insulin and to contractions. For example, in our epitrochlearis muscle preparation, the magnitude of the increase in glucose transport can vary over a fivefold range when insulin concentration is raised from 20 μU/ml to 1 mU/ml (55). An observation by Govers et al. (17) that seems relevant to this graded effect is that insulin appears to release GLUT4 from intracellular compartments into a cell surface-recycling pathway in a graded, insulin concentration-dependent manner. The size of this cell surface-recycling pool of GLUT4 progressively increased as insulin concentration was raised.

Our current working hypothesis is that the graded response is explained by generation of a weaker insulin, or contraction, signal in some regions of the muscle cell than in others. The GLUT4 that are translocated in response to a weak signal are in regions where the strongest signal is generated. Increasing the strength of the signal results in progressive recruitment of GLUT4 from regions in which the signal is more attenuated. In keeping with this hypothesis, the peroxovanadium compound bisperoxo(1,10-phenanthroline)oxovanadate anion, which generates a much more powerful insulin signal than does a maximally effective insulin concentration, results in increases in GLUT4 translocation and glucose transport that are twice as great as those induced by a maximal insulin stimulus (39).

In the context of this hypothesis, an increase in insulin sensitivity could be mediated by movement of a larger proportion of the GLUT4 that are available for translocation into regions in which the insulin signal is strongest. A finding that does not fit with this scenario is that sensitivity of glucose transport to activation by the exercise/hypoxia pathway is also increased after exercise. To accommodate this finding, it was necessary to modify and extend the hypothesis as follows: when the stimulus that caused GLUT4 translocation is removed, and its effect reverses, the GLUT4 leaves the cell surface and move into an intracellular compartment in which they are highly susceptible to recruitment by either a weak insulin signal or weak contraction/hypoxia signal. The increase in sensitivity of glucose transport to activation persists for as long as the GLUT4 remains in this “high-susceptibility compartment.”

CONCLUDING REMARKS

Considerable information regarding the postexercise increase in insulin sensitivity phenomenon has accumulated since it was first reported by Ruderman’s group in 1982. This information includes these findings: 1) the increase in sensitivity is not just to insulin but also to stimulation of glucose transport by the contraction/hypoxia pathway; 2) the increase in sensitivity is mediated by translocation of more GLUT4 to the cell surface in response to a submaximal stimulus; 3) it requires the presence of serum during the period of stimulation by contractions, hypoxia, or AICAR; and 4) the increase in sensitivity does not require protein synthesis. However, this new information is all descriptive, and essentially no progress has been made in elucidating the mechanism(s) responsible for mediating this phenomenon. This lack of progress is not too surprising when viewed in light of the very slow progress that has been made in explaining how insulin stimulates glucose transport despite enormous expenditure of effort and resources by hundreds of talented investigators over the past 60 yr. Similarly, there has been little progress in determining how exercise/hypoxia stimulates muscle glucose transport despite considerable research activity. Clearly, these are extremely complex processes. That, and their importance, is what makes trying to understand how they work so challenging and exciting. I think that the additional research needed to explain how glucose transport and insulin sensitivity are regulated will keep all of us who are working in this area, including those just beginning their careers, intellectually stimulated and motivated for the rest of our research careers.

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