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highlighted topics

Exercise Effects of Muscle Insulin Signaling and Action
Invited Review: Effects of acute exercise and exercise training on insulin resistance

ERIK J. HENRIKSEN
Muscle Metabolism Laboratory, Department of Physiology, University of Arizona College of Medicine, Tucson, Arizona 85721-0093

Henriksen, Erik J. Invited Review: Effects of acute exercise and exercise training on insulin resistance. *J Appl Physiol* 93: 788–796, 2002; 10.1152/japplphysiol.01219.2001.—Insulin resistance of skeletal muscle glucose transport is a key defect in the development of impaired glucose tolerance and Type 2 diabetes. It is well established that both an acute bout of exercise and chronic endurance exercise training can have beneficial effects on insulin action in insulin-resistant states. This review summarizes the present state of knowledge regarding these effects in the obese Zucker rat, a widely used rodent model of obesity-associated insulin resistance, and in insulin-resistant humans with impaired glucose tolerance or Type 2 diabetes. A single bout of prolonged aerobic exercise (30–60 min at ~60–70% of maximal oxygen consumption) can significantly lower plasma glucose levels, owing to normal contraction-induced stimulation of GLUT-4 glucose transporter translocation and glucose transport activity in insulin-resistant skeletal muscle. However, little is currently known about the effects of acute exercise on muscle insulin signaling in the postexercise state in insulin-resistant individuals. A well-established adaptive response to exercise training in conditions of insulin resistance is improved glucose tolerance and enhanced skeletal muscle insulin sensitivity of glucose transport. This training-induced enhancement of insulin action is associated with upregulation of specific components of the glucose transport system in insulin-resistant muscle and includes increased protein expression of GLUT-4 and insulin receptor substrate-1. It is clear that further investigations are needed to further elucidate the specific molecular mechanisms underlying the beneficial effects of acute exercise and exercise training on the glucose transport system in insulin-resistant mammalian skeletal muscle.

skeletal muscle glucose transport; obese Zucker rat; impaired glucose tolerance; Type 2 diabetes

NUMEROUS METABOLIC AND HEMODYNAMIC factors can contribute to the improvements in glucose homeostasis that are seen after acute exercise and exercise training in individuals with insulin resistance. These adaptive responses include enhanced insulin action on the skeletal muscle glucose transport system, reduced hormonal stimulation of hepatic glucose production, improved blood flow to skeletal muscle, and normalization of an abnormal blood lipid profile. This mini-review will focus only on the adaptive responses to exercise of the glucose transport system in skeletal muscle. In this context, one purpose of this article is to examine the present body of knowledge regarding the influence of a single bout of prolonged aerobic [30–60 min at ~60–70% of maximal oxygen consumption ($\dot{V}O_{2\,max}$)] exercise on whole-body glucose tolerance and on insulin-stimulated skeletal muscle glucose transport activity in conditions of insulin resistance. Moreover, this document will briefly review the effects of endurance exercise training on the skeletal muscle

Address for reprint requests and other correspondence: E. J. Henriksen, Dept. of Physiology, Ina E. Gittings Bldg. 93, Univ. of Arizona, Tucson, AZ 85721-0093 (E-mail: ejhenrik@u.arizona.edu).

glucose transport system in insulin-resistant states, with a particular emphasis on the beneficial adaptive responses of the protein expression and functionality of insulin signaling factors and of GLUT-4 protein to this intervention. Because of space limitations, coverage will be restricted to the obese Zucker (*fa/fa*) rat, a widely used rodent model of obesity-associated insulin resistance, and to insulin-resistant humans with impaired glucose tolerance (IGT) or Type 2 diabetes.

REGULATION OF SKELETAL MUSCLE GLUCOSE TRANSPORT

Skeletal muscle, which makes up ~40% of the body mass of humans and other mammalian species, is the primary tissue responsible for the peripheral disposal of glucose in response to a glucose or insulin challenge or during an exercise bout (6, 24). Glucose transport into the myocyte is acutely regulated by insulin and insulin-like factors through the activation of a series of intracellular proteins (for a review of insulin signaling and glucose transport activation, see Refs. 103 and 117). Insulin binding to the α-subunit of the insulin receptor causes an enhancement of the tyrosine kinase activity of the intracellular β-subunits, leading to autophosphorylation of the insulin receptor and to tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1). The tyrosine-phosphorylated IRS-1 molecule can then dock with the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3-kinase), which in turn activates the p110 catalytic subunit of this enzyme. PI3-kinase catalyzes the production of phosphoinositide moieties, which can subsequently activate 3-phosphoinositide-dependent kinases (PDK), including PDK1. A downstream target of PDK1 is Akt/protein kinase B (Akt/PKB), a serine/threonine kinase. Several lines of investigation support a role of Akt/PKB in the regulation of glucose transport (44, 77, 112), although other studies indicate that Akt/PKB is not involved in this process (76). Clearly, the exact role of Akt/PKB in the glucose transport process in skeletal muscle remains to be defined. The activation of these steps ultimately results in the translocation of a regulatable glucose transporter protein isoform (GLUT-4) to the sarcolemmal membrane and the t tubules, where glucose transport takes place via a facilitative diffusion process. GLUT-4 is only one of several isoforms in a family of facilitative glucose transporter proteins, and available evidence supports the idea that it is the magnitude of GLUT-4 translocation that dictates the capacity of a skeletal muscle to enhance glucose transport activity (53).

Glucose transport into skeletal muscle is also stimulated by an insulin-independent mechanism that is activated by contractions (54, 87), hypoxia (3, 15, 16), nitric oxide (5, 94), and bradykinin (83, 107). The translocation mechanism for increasing plasma membrane GLUT-4 also functions in response to contractions (37, 41), hypoxia (15), nitric oxide (33), and bradykinin (2, 107). It is likely that there is an important role of Ca^{2+} in the activation of glucose transport by these insulin-independent mechanisms (see Refs. 43, 53, and 98 for reviews). Whereas relatively little is currently known about the specific intracellular factors that allow muscle contractions to stimulate GLUT-4 translocation and glucose transport in skeletal muscle, recent evidence supports a role of the activation of 5′-adenosine monophosphate-activated protein kinase (AMP kinase), an enzyme activated by a decrease in cellular energy charge (80).

DEVELOPMENTAL ASPECTS OF INSULIN RESISTANCE

Insulin resistance of skeletal muscle glucose transport represents a major defect in the normal maintenance of euglycemia (117). This insulin resistance is frequently accompanied by a variety of metabolic and cardiovascular abnormalities, including hypertension, glucose intolerance, Type 2 diabetes, dyslipidemia, atherosclerosis, and central obesity, a condition referred to as "syndrome X" (92, 93) or the "insulin resistance syndrome" (23). The link among these disorders has been attributed to hyperinsulinemia, a consequence of the insulin resistance (23).

The obese Zucker (*fa/fa*) rat is an animal model of severe skeletal muscle insulin resistance that is also characterized by marked hyperinsulinemia, glucose intolerance, dyslipidemia, and central adiposity (84) and therefore is a suitable animal model of the insulin resistance syndrome. GLUT-4 protein expression in skeletal muscle of the obese Zucker rat is generally not defective (Refs. 35, 36, 63; but also see Ref. 52). However, insulin-stimulated GLUT-4 protein translocation (35, 74) and glucose transport activity (21, 35, 49) are substantially impaired in isolated skeletal muscle from these obese animals. Anai et al. (1) demonstrated that in skeletal muscle from the obese Zucker rat there are significant defects in crucial aspects of the insulin signaling cascade. In hindlimb muscle from insulin-resistant obese Zucker rats, IRS-1 protein expression is 60% less and insulin-stimulated IRS-1 tyrosine phosphorylation is 38% less, despite elevated basal levels, than in muscle from age-matched, insulin-sensitive lean Zucker rats. The amount of the p85 regulatory subunit of PI3-kinase associated with the tyrosine-phosphorylated IRS-1 in the insulin-stimulated state is 29% of lean control levels. Finally, IRS-1-associated PI3-kinase activity in muscle immunoprecipitates from these obese animals is only 54% of the level observed in lean animals (1).

Similar findings have been made in skeletal muscle from insulin-resistant humans. Insulin resistance in Type 2 diabetes, except for that observed in morbidly obese humans (29), is not generally associated with a decreased skeletal muscle level of GLUT-4 protein (117). However, insulin stimulation fails to induce normal GLUT-4 protein translocation to the sarcolemma in skeletal muscle from subjects with Type 2 diabetes (99, 116). Moreover, Goodyear et al. (40) and Björnholm et al. (10) demonstrated that significantly less insulin stimulation of insulin receptor and IRS-1 tyrosine phosphorylation and of IRS-1-immunoprecipi-

table PI3-kinase activity is detected in muscle from insulin-resistant subjects compared with insulin-sensitive controls. In addition, insulin-stimulated Akt/PKB kinase activity is significantly reduced in skeletal muscle from insulin-resistant Type 2 diabetic subjects (79), although this is not a consistent finding (72). Insulin-stimulated glycogen synthase activity is generally reduced (Refs. 7, 19, 109; but also see Ref. 78), and the reduction in nonoxidative glucose disposal in these individuals is thought to be secondary to defects in glucose transport (19). No reduction in insulin-stimulated mitogen-activated protein kinase (MAP kinase) phosphorylation is detected in incubated muscle preparations from Type 2 diabetic subjects (78). Therefore, there are marked defects in specific signaling proteins and in GLUT-4 protein translocation that define the insulin-resistant state.

PREMISE FOR EXERCISE AS AN INTERVENTION IN INSULIN RESISTANCE

It is well established that acute physical activity and endurance exercise training lead to enhancements of insulin-mediated glucose metabolism in healthy individuals and in normal rodent models (see reviews in Refs. 43, 45, 5, and 62). In normal rodent models, moderate- or high-intensity exercise training can improve glucose tolerance (9, 64), whole body insulin sensitivity (65, 66), and insulin action on skeletal muscle glucose transport (48, 96, 97, 105). The protein expression of GLUT-4 appears to play an important role in the capacity of a skeletal muscle for insulin stimulation of glucose transport (47, 69). The increased insulin action on skeletal muscle glucose transport after exercise training is associated with increased GLUT-4 protein expression (42, 48, 88, 96, 97, 101, 105), as well as adaptive responses of enzymes involved in glucose phosphorylation and oxidation (summarized in Refs. 53 and 62). On the bases of these observations, exercise represents an important potential intervention for improving the metabolic status of insulin-resistant individuals.

An improvement in insulin action on skeletal muscle glucose metabolism in insulin-resistant individuals could decrease conversion rates to overt diabetes, as well as reduce cardiovascular mortality. Indeed, the results of the recently concluded Diabetes Prevention Program in the United States convincingly demonstrated that the introduction of a lifestyle modification program, including at least a 7% reduction in body weight and a minimum of 150 min of physical activity per week, could, over a 3-yr period, reduce the incidence of Type 2 diabetes by 58% in individuals at significant risk for the development of the disease (28). These results are essentially identical to those from a recent Finnish study in which a weight-loss and exercise intervention reduced the incidence of Type 2 diabetes in overweight men with IGT (111) and are consistent with earlier epidemiological studies indicating that increased physical activity can prevent the development of Type 2 diabetes in men (46).

ACUTE EXERCISE AND INSULIN RESISTANCE

Glucose tolerance and glucose disposal. The various metabolic responses to a single bout of exercise performed by insulin-resistant rodents (primarily the obese Zucker rat) and humans are summarized in Tables 1 and 2, respectively. An acute bout of exercise (30 min at ~70% of $\dot{V}O_{2\,max}$) by untrained rats does not improve intravenous glucose tolerance (64). Likewise, a single bout of prolonged aerobic exercise (30–60 min at ~60–70% of $\dot{V}O_{2\,max}$) will normally not improve the diminished glucose tolerance of insulin-resistant Type 2 diabetic subjects, as evaluated with a standard oral glucose tolerance test (95). In contrast, a prior bout of prolonged moderate-intensity exercise (45 min of cycle ergometry at 45% of $\dot{V}O_{2\,max}$) performed by Type 2 diabetic subjects can reduce the glycemic excursions and elevated plasma insulin levels during the 4-h period after a breakfast meal containing 56% carbohydrate, 30% fat, and 14% protein (81). Interestingly, this exercise effect was not observed when a lunch meal was subsequently consumed 4 h after the breakfast meal (81), indicating the transient nature of this acute exercise effect.

It is, however, well established that, during a single bout of physical activity, a significant glucose-lowering effect in obese rodents (38) and in Type 2 diabetic individuals can be elicited (58, 81, 86, 114). Plasma insulin is also reduced in these individuals during the exercise bout (86). Whole body glucose disposal during a euglycemic, hyperinsulinemic clamp can also be enhanced in obese rats after a single bout of exercise (14, 38, 89) and is associated with an increase in insulin-stimulated glucose transport in skeletal muscle (89). The effect of acute exercise on glycemia is likely due to the ability of contractile activity to activate skeletal muscle glucose transport, as this pathway appears to be normal in animal models of insulin resistance (11, 12, 30, 49, 73) or in Type 2 diabetic subjects (3, 68). In addition, the enhanced glucose transport activity resulting from the exercise bout by Type 2 diabetic humans persists into the immediate postexercise period (27, 58, 85) and is associated with enhanced insulin sensitivity immediately after (85) and 20 h after (27) exercise. At 24 h after exercise, the enhanced insulin sensitivity was not observed (22). The mechanisms for these responses of Type 2 diabetic subjects to acute exercise are currently unknown.

Skeletal muscle glucose transport and insulin signaling. One underlying cellular mechanism for this glucose-lowering effect of acute exercise in insulin resistance has been addressed in a study of exercise-induced GLUT-4 translocation in a cohort of Type 2 diabetic individuals (68). Immediately after a single bout of exercise (45–60 min of cycling at 60–70% of $\dot{V}O_{2\,max}$), there was a 74 ± 20% increase in plasma membrane GLUT-4 protein in vastus lateralis muscle, which was nearly identical to the postexercise increase (71 ± 18%) seen in nondiabetic subjects. Protein expression of GLUT-4 was not enhanced by this single bout of exercise (68). Consistent with this finding are

the results of King et al. (73), which demonstrated that the exercise-induced translocation of glucose transporter protein in skeletal muscle of the obese Zucker rat was not different from that in lean animals. Therefore, a single bout of moderate-intensity exercise can increase muscle glucose transport via a normal induction of GLUT-4 translocation into the plasma membrane (68, 73).

The longer term effect of a single bout of exercise on insulin signaling in insulin-resistant skeletal muscle is less definitive. Twenty-four hours after a single exercise session (1 h of cycle ergometer exercise at 65% of $\dot{V}O_{2\,max}$) performed by Type 2 diabetic subjects, the response to insulin of skeletal muscle tyrosine phosphorylation of the insulin receptor and of IRS-1 was significantly enhanced (22). However, insulin stimulation of IRS-1-associated PI3-kinase activity was not enhanced by the prior exercise, and at this time point whole body insulin-stimulated glucose disposal (assessed with a euglycemic, hyperinsulinemic clamp) was not increased relative to the sedentary state (22). It is clear that further investigations, incorporating shorter postexercise time points, are needed to elucidate the mechanisms whereby acute exercise can augment skeletal muscle glucose uptake by insulin-resistant skeletal muscle.

CHRONIC EXERCISE AND INSULIN RESISTANCE

Glucose tolerance and glucose disposal. The adaptive responses of whole body and skeletal muscle glucose metabolism to an increase in physical activity by insulin-resistant rodents are shown in Table 1, and those observed in insulin-resistant humans are displayed in Table 2. As mentioned previously, one characteristic feature of the abnormal metabolic state of obese Zucker rats is glucose intolerance. In one of the first investigations of the potential beneficial effects of exercise training that used this animal model of obesity-associated insulin resistance, Becker-Zimmermann et al. (8) demonstrated that mild exercise training (treadmill running) by older (25-wk-old) obese Zucker rats could significantly improve glucose disposal during an oral glucose tolerance test and reduce the exaggerated insulin response to a glucose challenge. Moreover, these investigators showed that exercise training by younger (7-wk-old) obese Zucker rats could prevent the deterioration of glucose tolerance experienced by these animals as they develop into adulthood (8). This exercise training-induced improvement in the whole body insulin sensitivity of obese Zucker rats was soon confirmed with swim training (113). Several subsequent investigations also demonstrated that the impaired whole body glucose tolerance (20, 100, 106) and the reduced insulin sensitivity at the whole body (20, 52, 100, 106) and hindlimb (primarily skeletal muscle) levels (60, 61, 115) of the obese Zucker rat can be substantially improved by aerobic exercise training.

The impaired whole body glucose metabolism in humans with IGT or Type 2 diabetes can likewise be beneficially modified by exercise training (67). Endurance exercise training leads to improvements in glucose tolerance (59, 95) and whole body insulin-mediated glucose disposal (25) in insulin-resistant subjects with IGT or Type 2 diabetes. Interestingly, Eriksson et al. (32) reported that a chronic circuit training regimen, in which resistance-type exercises are performed,

Table 1. *Summary of effects of acute exercise or exercise training on whole body glucose disposal and skeletal muscle insulin action in insulin-resistant rodent models*

	Response to Acute Exercise	Reference	Response to Exercise Training	Reference
Whole body glucose tolerance postexercise, ivGTT or OGTT	↔	64	↑	8, 20, 100, 106
Whole body glucose disposal	↑	14, 38, 89	↑	52
Insulin-stimulated skeletal muscle glucose transport	↑	89	↑	4, 13, 20, 34, 60, 61, 100, 106, 115
GLUT-4 translocation	↑	73	↑	13, 34
GLUT-4 expression	ND		↑	4, 13, 34, 36, 52, 100, 104, 106
Insulin-stimulated insulin receptor				
Protein expression	ND		↔	52, 102
Tyrosine phosphorylation	ND		↑	52
			↔	18
Insulin-stimulated IRS-1				
Protein expression	ND		↑	102
Tyrosine phosphorylation	ND		↑	52
			↔	18
Insulin-stimulated PI3-kinase				
Protein expression	ND		↔	52, 102
Activity	ND		↔	18
Insulin-stimulated Akt/PKB				
Protein expression	ND		↔	52
Serine phosphorylation	ND		↔	18, 52

Changes due to the exercise intervention are relative to the sedentary, insulin-resistant control groups and are either no change (↔), an increase (↑), or a decrease (↓). ND, not determined; ivGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; IRS-1, insulin receptor substrate-1; PI3-kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B.

Table 2. *Summary of effects of acute exercise or exercise training on whole-body glucose disposal and skeletal muscle insulin action in insulin-resistant humans*

	Response to Acute Exercise	Reference	Response to Exercise Training	Reference
Whole body glucose tolerance				
Postexercise, OGTT	↔	95	↑	59, 95
Postexercise, breakfast meal	↑	81	ND	
Whole body glucose disposal	↔	27, 58, 85	↑	25, 32, 59
Insulin-stimulated skeletal muscle glucose transport	↑	27, 58, 85	↑	91
GLUT-4 translocation	↑	68	↑	ND
GLUT-4 expression	↔	68	↑	26, 55, 57, 59
Insulin-stimulated insulin receptor				
Protein expression	ND		ND	
Tyrosine phosphorylation	↑	22	ND	
Insulin-stimulated IRS-1				
Protein expression	ND		ND	
Tyrosine phosphorylation	↑	22	ND	
Insulin-stimulated PI3-kinase				
Protein expression	ND		ND	
Activity	↔	22	↔	108
Insulin-stimulated Akt/PKB				
Protein expression	ND		ND	
Serine phosphorylation	ND		↔	108

Changes due to the exercise intervention are relative to the sedentary, insulin-resistant control groups and are either no change (↔), an increase (↑), or a decrease (↓).

also enhances insulin-mediated whole-body glucose disposal in insulin-resistant subjects with IGT.

Skeletal muscle glucose transport and insulin signaling. Several investigations have convincingly shown that skeletal muscle is the primary cellular locus for the beneficial adaptive responses of whole body insulin sensitivity to exercise training by the obese Zucker rat. Moderate- and high-intensity aerobic training results in an increased maximal aerobic capacity (20, 100, 106, 110) and in greater locomotor skeletal muscle levels of enzymes involved in glucose catabolism (e.g., hexokinase and citrate synthase) (4, 13, 20, 100, 106, 110). The enhanced exercise training-induced glucose tolerance and glucose disposal in the obese Zucker rat are primarily due to adaptations in the insulin-dependent glucose transport system in skeletal muscle. Exercise training leads to enhanced insulin action on glucose transport in locomotor muscles of the perfused hindquarter (4, 13, 20, 60, 61, 115) and in isolated, incubated locomotor skeletal muscles (34, 100, 106). Two critical adaptive responses that underlie the enhanced insulin-stimulated glucose transport activity after exercise training in these animals are an upregulation of GLUT-4 protein expression (4, 13, 34, 36, 52, 100, 104, 106) and increased GLUT-4 translocation (13) and cell surface GLUT-4 (34) after insulin stimulation.

Exercise training of animals with normal insulin signaling leads to an enhancement of specific steps in the insulin signaling cascade, including increased mRNA and protein expression and functionality of the insulin receptor, IRS-1, PI3-kinase, and MAP kinase [extracellular-regulated kinase 1 (ERK1)] (17, 70, 71). However, much less is known regarding the adaptive responses to exercise training of the insulin signaling pathway in muscle of the obese Zucker rat. Exercise training of these insulin-resistant animals leads to upregulation of insulin receptor tyrosine phosphorylation (52) and enhanced IRS-1 protein expression (102) with no alteration in protein expression of insulin receptor β-subunit (52, 102), the p85 subunit of PI3-kinase (52, 102), or Akt/PKB (52). However, in a recent study by Christ et al. (18), 7 wk of exercise training by obese Zucker rats did not cause any increases in insulin action on insulin receptor or IRS-1 tyrosine phosphorylation, PI3-kinase activity, or Akt/PKB serine phosphorylation.

Muscle contractions lead to activation of ERK1/2, isoforms of MAP kinase (39), and there is speculation that increases in MAP kinase signaling may be associated with several exercise-associated adaptive responses in skeletal muscle (82, 98). Interestingly, exercise training by obese Zucker rats leads to upregulation of ERK2 protein expression (90). This finding raises the intriguing possibility that enhanced signal transduction through the MAP kinase signaling cascade may play an important role in the increased expression of glucose catabolic enzymes, GLUT-4, and insulin signaling proteins after exercise training by the obese Zucker rat.

Our knowledge of the underlying mechanisms for the beneficial effects of exercise training on insulin-resistant human skeletal muscle is much less extensive. Endurance exercise training also leads to improvements in insulin action on skeletal muscle glucose metabolism in insulin-resistant human subjects with IGT (95) or Type 2 diabetes (59, 95). Six weeks of exercise training by insulin-resistant offspring of human Type 2 diabetic subjects was associated with an enhancement of insulin-stimulated glucose transport and phosphorylation in skeletal muscle (91). As in rodent models of insulin resistance, an important molecular mechanism for the adaptive response to training by middle-aged men (55, 57) and by human Type 2

diabetic subjects (26, 59) is the upregulation of GLUT-4 protein expression in skeletal muscle. Whether exercise training can enhance insulin-stimulated GLUT-4 translocation in insulin-resistant human muscle is not presently known.

Exercise training by insulin-sensitive humans results in upregulation of insulin-stimulated PI3-kinase activity, both in longitudinal (56) and in cross-sectional (75) studies. These studies support a role of altered protein expression and functionality of insulin signaling factors in the enhanced insulin sensitivity of human skeletal muscle after exercise training. However, it has recently been shown that 1 wk of exercise training (60 min/day at 70% of peak oxygen consumption) did not enhance insulin stimulation of PI3-kinase activity or Akt/PKB activity in vastus lateralis muscle of middle-aged men (~58 yr old and presumably insulin resistant) (108). Other potential adaptive responses of the insulin signaling cascade in insulin-resistant skeletal muscle to regular exercise are currently unknown.

EXERCISE AND INSULIN RESISTANCE: FUTURE DIRECTIONS

The beneficial effects of an acute bout of exercise and of chronic exercise training on insulin action in insulin-resistant states are well established. However, there is a relative paucity of information on the specific molecular mechanisms in the skeletal muscle glucose transport system to explain these exercise effects. How contractile activity by skeletal muscle causes an enhancement of insulin sensitivity is not clear. Particularly intriguing is the very recent finding that components of the kallikrein-kininogen system may play a role in the development of enhanced insulin sensitivity after contractions by muscles from insulin-sensitive rats (31). This information is especially relevant in light of findings that treatment of insulin-resistant obese Zucker rats with bradykinin, a product of the kallikrein-kininogen system, can enhance whole body glucose tolerance (50) and insulin action on skeletal muscle glucose transport (50, 51). An important area of future investigation would be the potential interactions between products of the kallikrein-kininogen system, including bradykinin, and insulin signaling factors in insulin-resistant skeletal muscle.

A critical aspect that must be addressed in future investigations is a better understanding of the underlying mechanisms for upregulation of GLUT-4 protein and of specific insulin signaling factors after exercise training by insulin-resistant rodent models, such as the obese Zucker rat, and by humans with IGT and Type 2 diabetes. Specifically, the potential roles of increased intracellular Ca^{2+} and Ca^{2+}-activated pathways, such as the MAP kinase pathway, and of a chronically altered energy charge, such as the activation of AMP kinase, in these exercise training-induced responses in insulin-resistant skeletal muscle require further investigation. The elucidation of these mechanisms will assist clinicians and exercise physiologists in the design of the most effective exercise regimens for the improvement of insulin action in insulin-resistant human subjects with IGT and Type 2 diabetes.

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