Interaction of Exercise and Insulin in Type II Diabetes Mellitus

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In skeletal muscle, at the level of glucose transport, insulin resistance appears to be a major alteration responsible for decreased glucose disposal rates in non-insulin-dependent (type II) diabetes mellitus. This study focuses on in vitro studies of the glucose transport process in human and rat skeletal muscle. Muscle strips from a group of lean type II diabetic patients demonstrated a 50% decrease in insulin responsiveness for glucose transport when compared with nondiabetic subjects. These findings indicate the presence of postreceptor defects in type II diabetic muscles. Furthermore, in an isolated muscle preparation, it could be demonstrated that epitrochlearis muscles from streptozocin-induced diabetic rats were not only resistant to insulin, but also to exercise-induced increase in glucose transport. However, both regular physical exercise and insulin therapy normalized the decreased capacity for glucose transport in the diabetic rat muscles. Therefore, it appears that regular physical exercise and, in some cases insulin therapy, would be advisable for type II diabetic patients with marked muscular insulin resistance to improve peripheral glucose disposal rates.

Pathogenesis of non-insulin-dependent (type II) diabetes mellitus involves several organ systems, including abnormalities of insulin secretion (1,2), peripheral tissue insulin resistance (3–5), and hepatic insulin resistance (6). Generally, obese patients with type II diabetes mellitus are characterized by high insulin levels and hyperglycemia (7), which indicate marked peripheral insulin resistance. Because skeletal muscle constitutes the body's largest insulin-sensitive tissue, insulin resistance in muscle (3) has a significant impact on overall glucose homeostasis in type II diabetic patients.

The goal in the treatment of type II diabetes mellitus includes therapeutic programs aimed at preventing and/or treating perturbations of glucose homeostasis. In order to achieve this, it is necessary to understand the mechanisms behind alterations in different organ systems. The aim of this study is to discuss the cellular alterations underlying insulin resistance in type II diabetic muscle. In addition, consideration is given to whether exercise and/or insulin therapy can abolish the insulin resistance in diabetic muscles.

INSULIN RESISTANCE IN TYPE II DIABETIC MUSCLE

In vivo studies

Defects at the level of the β-cell, liver, and/or muscle can result in the development of insulin resistance in type II diabetes mellitus. Neither suppression of hepatic glucose production nor splanchnic glucose uptake has been reported to be impaired in type II diabetic subjects during insulin clamp studies (8,9). Consequently, peripheral tissues seem to be the primary site of insulin resistance. However, in mild type II diabetic patients, an increase in glucose cycling in the postabsorptive state and during glucose infusion, regardless of obesity, has been reported (10), indicating hepatic insulin resistance. Subnormal total glucose disposal rates (11,12) have been demonstrated in patients with type II diabetes mellitus. Because <1% of an infused or ingested glucose load is taken up by adipose tissue (13,14), it appears that the major portion of the impairment in insulin-stimulated glucose uptake can be accounted for by a defect (or defects) in skeletal muscle glucose metabolism.

In vitro studies

Previously, in vitro studies of human skeletal muscle have not been possible to perform. However, Dohm et al. (15) presented a human skeletal muscle in vitro technique that allows detailed metabolic studies of human muscle. By using this technique, we studied skeletal muscle from healthy controls and from type II diabetic subjects treated with oral hypoglycemic agents (16). Muscle specimens were obtained from the rectus abdominis muscle during abdominal surgery and clamped at both ends with a specially constructed clamp. Six to 12 smaller muscle strips were dissected free from the larger muscle specimen and clamped with plexiglass clamps at resting length. Muscle strips were incubated in vitro in the presence of increasing insulin concentrations, whereupon 3-*O*-methylglucose uptake was analyzed according to Wallberg-Henriksson et al. (17).

During incubation in increasing concentrations of insulin, the muscle strips from the type II diabetic subjects demonstrated a marked decrease in the response to maximal insulin concentrations when compared with muscles from

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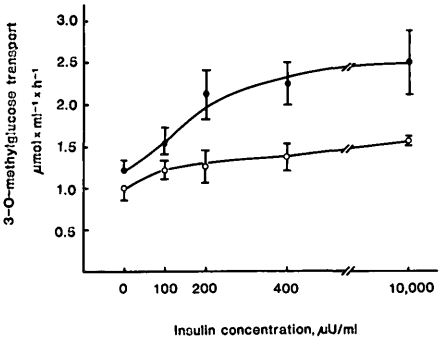

Figure 1—*Response of 3-O-methylglucose transport in muscle strips from healthy controls (●) and non-insulin-dependent (type II) diabetic patients (○) after exposure to increasing concentrations of insulin. Values are means ± SE for 5–8 (control) and 3–5 (type II diabetic) muscle strips. Insulin responsiveness was decreased by 49% in the type II diabetic subjects (P < 0.01). From Andréasson et al. (16). © by Acta Physiologica Scandinavica.*

healthy individuals (Fig. 1). This result indicates the presence of one or several postreceptor defects in type II diabetic skeletal muscle (16).

Insulin action

Insulin and contractile activity constitute the two most potent stimulators of glucose transport in skeletal muscle (3). The mechanism by which these two stimuli increase the rate of glucose entry into the cell is not completely understood. However, during the past decade, the action of insulin on glucose transport has attracted much attention and, as a result, this process is somewhat better understood (Fig. 2) compared with that of exercise. Insulin binds to a specific receptor, a glycoprotein located on the cell membrane, which consists of two α-subunits and two β-subunits linked by disulfide bonds. α-Subunits are located extracellularly and contain the insulin binding site. The β-subunit is an insulin-sensitive protein kinase, which has the ability to phosphorylate itself and other substrates on tyrosine residues (18). Exactly how the β-subunit transmits the insulin signal is not clear. The prevailing model involves a phosphorylation cascade (i.e., insulin gives rise to a receptor autophosphorylation that activates the receptor kinase, which then phosphorylates some cellular substrates; e.g., serine kinases [Fig. 2]).

However, not all of the action of insulin can be attributed to changes in phosphorylation. Some monoclonal antibodies to the insulin receptor have been demonstrated to stimulate glucose transport without activating the receptor kinase (19). Thus, a second potential mechanism for insulin action involves conformation changes in the β-subunit, which would result in an interaction with some other effector system (Fig. 2). These effector systems may be linked by a guanylnucleotide binding protein (G-protein) (20,21).

Recent studies have produced evidence that facilitated glucose transport in mammalian tissues is effectuated by a family of structurally related proteins, termed glucose transporter molecules, which demonstrate tissue specificity (22–24). Insulin stimulation in skeletal muscle gives rise to an increased number of glucose transporters at the plasma membrane and a decreased number of transporters in an intracellular pool (25–27). Similarly, muscle contraction gives rise to an increased number of glucose transporters at the plasma membrane (26,28–31); however, this increase can only account for part of the exercise-induced increase in glucose transport. Thus, in addition to an increased number of transport molecules at the plasma membrane, muscle contraction seems to induce an increase in the activity of the transporters at the plasma membrane (31).

Cellular alterations

Regarding glucose transport, insulin resistance can occur at several different levels in the chain of events taking place in the cell after insulin stimulation (Fig. 2). Decreased insulin sensitivity is generally believed to be caused by defects at the receptor level and changed insulin responsiveness by defects at a postreceptor level. Thus, changes in insulin sensitivity are generally caused by altered insulin binding. Furthermore, at the receptor level, at a postbinding step, alterations can be caused by decreased tyrosine kinase activity. At the postreceptor level, defects might be due to a decreased number of glucose transporters or a defect in the translocation mechanism of the transporters.

In skeletal muscles from a group of morbidly obese type II diabetic patients, Caro et al. (7) demonstrated decreased insulin binding and decreased

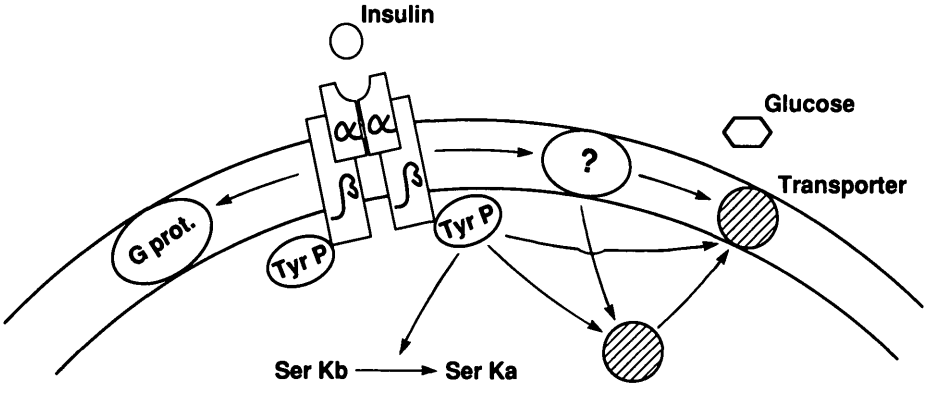

Figure 2—*Model of insulin action on glucose transport in insulin-sensitive cells. G prot, G-protein; Tyr P, tyrosine kinase phosphorylation; Ser, serine.*

insulin receptor tyrosine kinase activity. Decreased binding and tyrosine kinase activity of solubilized muscle insulin receptors also have been demonstrated in type II diabetic patients, who are not morbidly obese (32–34). However, morbidly obese type II diabetic patients appear to have a decreased number of glucose transporters in their muscles (7,35), whereas an unaltered number of glucose transporters in muscles from both lean and obese diabetic subjects have been demonstrated (36). Thus, in skeletal muscle from type II diabetic patients, defects exists at multiple sites. Probably depending on the severity of the metabolic disturbances and whether obesity is present, the frequency and degree of these alterations differ in different groups of patients.

INTERACTION OF EXERCISE AND INSULIN

Exercise-induced increase in glucose transport

Thus far, studies of the direct effect of exercise on human type II diabetic skeletal muscle have not been performed. Therefore, animal models are the source of information on exercise-induced increases in glucose transport in diabetic skeletal muscle. We have been using the rat epitrochlearis muscle preparation in several studies on the regulation of glucose transport in diabetic skeletal muscle. The epitrochlearis muscle is a very small, thin muscle located on the forelimb on the rat and has been shown to be one of the most suitable in vitro muscle preparations (3).

To answer the question of whether diabetic muscle is resistant to an exercise-induced increase in glucose transport comparable with that observed in insulin-stimulated states, rats were made diabetic by an intraperitoneal injection of streptozocin (37). The epitrochlearis muscles were isolated and studied either in the resting state or during electrical stimulation. The diabetic muscles were found to increase the rate of glucose transport in response to muscle contraction. However, compared with healthy control muscles, the increase was considerably lower (Fig. 3), indicating a decreased capacity of the exercise-dependent glucose transport system, similar to what has been demonstrated for the insulin-stimulated glucose transport (37).

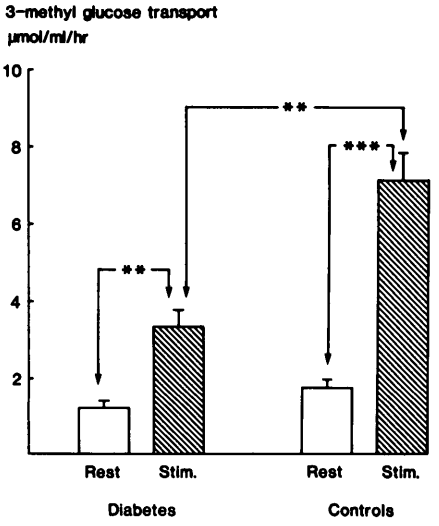

Figure 3—*Effect of contractile activity on 3-O-methylglucose transport in epitrochlearis muscles of diabetic rats. Rate of 3-O-methylglucose transport was determined in the absence of insulin immediately after the muscles had been stimulated (stim.) for 10 min (50 Hz for 5 sec at a rate of 1 contraction/min). Results are expressed per ml of intracellular water. Values are means ± SE for 7–8 muscles. **P < 0.01, ***P < 0.001. From Wallberg-Henriksson and Holloszy (37). © by the American Journal of Physiology.*

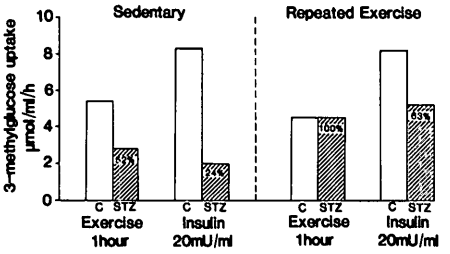

Figure 4—*Effect of insulin, 1 exercise session, and 3 days of training on 3-O-methylglucose transport rates above basal values in epitrochlearis muscles of diabetic and control rats. Sedentary exercise group was subjected to 1 h of swimming immediately before investigation. Repeated exercise groups performed 6 consecutive swimming sessions (1 h/session) over a 72-h period, and were studied immediately after the final exercise session. Insulin-stimulated 3-O-methylglucose transport was measured after preincubation for 30 min in a supramaximal dose of insulin (20 mU/ml). Percentage of control values are indicated in the bars for the diabetic groups. C, control muscles; STZ, muscles from streptozocin-induced diabetic rats. From Wallberg-Henriksson (38). © by Acta Physiologica Scandinavica.*

Effect of physical training

The hypothesis that a muscle's habitual level of contractile activity may act as a long-term regulator of glucose transport was investigated using isolated rat epitrochlearis muscle preparation (38). Glucose transport was measured in muscles from rats with streptozocin-induced diabetes. Plasma glucose before the experiment was 33 in the diabetic and 8.3 in control rats. The diabetic rats were totally insulin-deficient. Insulin-stimulated glucose transport was found to be reduced to 24%, and contraction-induced glucose transport was diminished to 52% of the control capacity (Fig. 4). When repeated 1-h swimming sessions (twice a day) were performed during a 3-day period of insulin deficiency, the contraction-induced glucose transport capacity of the diabetic muscles was no longer significantly different from that of the controls. In diabetic muscles, repeated exercise sessions also improved the insulin-stimulated glucose transport capacity (Fig. 4). Thus, it is evident that repeated exercise can affect insulin resistance and the decreased capacity for exercise-induced glucose transport. In obese Zucker rats, the decreased basal and insulin-stimulated glucose transports were reversed by exercise training, except in soleus and white gastrocnemius muscles (39).

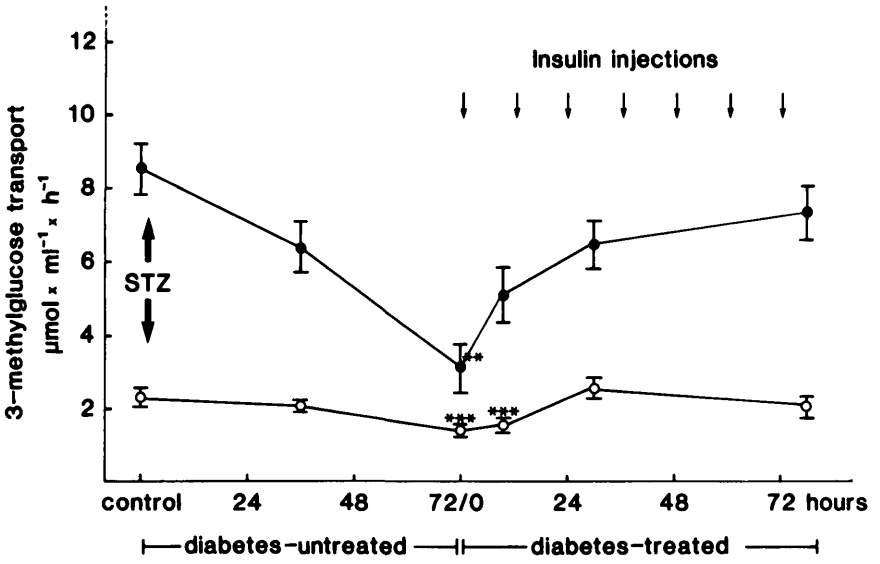

Figure 5—*Basal (○) and insulin-stimulated (●) 3-O-methylglucose transport in incubated epitrochlearis muscles from streptozocin (STZ)-induced diabetic rats. Insulin injections (4 IU/100 g body wt) were given every 12 h as indicated. Results are expressed per ml of intracellular water. Values are means ± SE for 5–6 muscles. **P < 0.01, ***P < 0.001 vs. control value (ANOVA followed by the Newman-Keul test). From Wallberg-Henriksson (40). © by Acta Physiologica Scandinavica.*

Effect of insulin treatment

The aim of another set of experiments was to find out if the decreased muscle glucose transport capacity, induced by sustained insulin deficiency, could be normalized by insulin treatment (40).

For this purpose, rats were made insulin-deficient by a single injection of streptozocin. Thereafter, the rats were given no insulin treatment for 72 h and were then treated with insulin (4 IU/100 g of body wt) every 12 h for another 72-h period. At the end of the period of untreated diabetes, both basal and insulin-stimulated 3-*O*-methylglucose transport rates were significantly reduced (Fig. 5). The marked decrease in responsiveness to insulin (28% of the control value) was gradually reversed by insulin treatment: 57% of the control value after one insulin injection, 63% after three injections, and 85% of the control value after seven injections (Fig. 5). Decreased basal glucose transport value remained unaffected after the first insulin injection, but 30 h after the start of the insulin treatment (three insulin injections), the basal glucose transport was completely normal. These results are consistent with a report on adipocytes (41), in which streptozocin-induced diabetes was associated with a 67% loss of the maximally insulin-stimulated glucose transport rate. Insulin therapy normalized insulin responsiveness in these adipocytes in 4 days. The molecular basis for the reversal in adipocytes has been suggested to be attributed to changes in both the number of glucose transporters translocated to the plasma membrane from an intracellular pool and to alterations in the intrinsic activity of the glucose transporters (41).

Interaction of exercise and insulin

As discussed previously, 3 days of untreated diabetes (Fig. 4) resulted not only in a marked decrease in the responsiveness to insulin, but also in a significant lowering of the contraction-induced glucose transport. Insulin-induced transport amounted to 30–40% of the control value, whereas contraction-induced transport reached 40–50% of the control value (17,37,38,40). This suggests that diabetes affects both the insulin- and exercise-induced glucose transport, but that the insulin-stimulated transport is affected to a greater extent. The fact that both insulin- and contraction-dependent glucose transport are affected is somewhat surprising because there is a considerable amount of evidence suggesting that insulin and contractile activity stimulate muscle glucose transport by two independent mechanisms (42,43). On this basis, it would be reasonable to expect that insulin deficiency only affects the insulin-dependent glucose transport system. However, there seems to be a "cross-regulation" (i.e., the insulin-deficient state affects both the insulin- and contraction-dependent glucose transport systems).

CONCLUSIONS — In type II diabetes mellitus, the diabetic state (i.e., hyperglycemia concomitant with either insulin deficiency or hyperinsulinemia) gives rise to metabolic alterations that affect the muscular glucose transport system. The metabolic alterations responsible for changes at the cellular level are not fully understood. It seems reasonable, however, to believe that there is a multifactorial influence of hormonal and metabolic alterations on the peripheral tissues, resulting in insulin resistance (Fig. 1). It has been demonstrated in animal models that the activity level of the muscle can affect the glucose transport system on a long-term basis. Thus, frequent physical exercise was shown to prevent the impairment of contraction-induced glucose transport and improve the insulin responsiveness in insulin-deficient diabetic rat muscle. Furthermore, the decreased insulin-stimulated glucose transport capacity in insulin-deficient muscles was shown to be reversible in vivo by treating previously untreated rats with insulin.

It might be hypothesized that insulin therapy and frequent exercise cor-

rect or normalize the metabolic alterations that give rise to the cellular changes responsible for muscle insulin resistance. Thus, provided no contraindications are present, it appears that regular physical exercise and, in some cases, insulin therapy, would be advisable for type II diabetic patients with marked muscular insulin resistance in order to improve peripheral glucose disposal rates and thereby possibly prevent severe hyperglycemia.

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