Delayed Transcapillary Transport of Insulin to Muscle Interstitial Fluid in Obese Subjects

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Insulin-resistant subjects have a slow onset of insulin action, and the underlying mechanism has not been determined. To evaluate whether a delayed transcapillary transport is part of the peripheral insulin resistance, we followed the kinetics of infused insulin and inulin in plasma and muscle interstitial fluid in obese insulin-resistant patients and control subjects. A total of 10 lean and 10 obese men (BMI 24 ± 0.8 vs. 32 ± 0.8 kg/m², P < 0.001) was evaluated during a hyperinsulinemic-euglycemic clamp (insulin infusion rate 120 mU · m⁻² · min⁻¹) combined with an inulin infusion. Measurements of insulin and inulin in plasma were taken by means of arterial-venous catheterization of the forearm and microdialysis in brachioradialis muscle combined with forearm blood flow measurements with vein occlusion plethysmography. The obese subjects had a significantly lower steady-state glucose infusion rate and, thus, demonstrated a delayed appearance of insulin (time to achieve half-maximal concentration [$T_{1/2}$] 72 ± 6 vs. 46 ± 6 min in control subjects, P < 0.05) as well as inulin ([$T_{1/2}$] 83 ± 3 vs. 53 ± 7 min, P < 0.01) in the interstitial fluid. Also, the obese subjects had a delayed onset of insulin action ($T_{1/2}$ 70 ± 9 vs. 45 ± 5 min in control subjects, P < 0.05), and their forearm blood flow rate was significantly lower. These results demonstrate a delayed transcapillary transport of insulin and inulin from plasma to the muscle interstitial fluid and a delayed onset of insulin action in insulin-resistant obese subjects. Diabetes 51:2742–2748, 2002

At steady state, insulin concentrations in the interstitial fluid and in the lymph are markedly lower than in plasma, suggesting an endothelial barrier for the transcapillary transport of insulin (1–3). Additionally, a bulk of data suggests that the equilibration of insulin over the endothelium is a time-consuming process and that, as a result, the time kinetics of insulin are slower in the interstitial fluid than in plasma (2,4,5). In a study of perfused rat hearts (6), the endothelial wall seemed to delay the transcapillary transport of insulin. Also, when insulin is infused, levels of interstitial insulin in lymph (1) and in adipose tissue (2), as well as in skeletal muscle (7), lag behind plasma insulin.

Furthermore, dynamics of glucose uptake correlate closely with the changes in interstitial insulin rather than with plasma insulin, suggesting that interstitial insulin levels determine the uptake rate of glucose (4,8). In subjects with obesity and type 2 diabetes, insulin-mediated glucose disposal and leg glucose uptake are delayed (9), suggesting that a delayed transcapillary transport of insulin could contribute to the insulin resistance in these subjects. Moreover, it has recently been demonstrated that insulin transport was markedly delayed in obese insulin-resistant animals (10,11).

In vitro studies in cultured cells have demonstrated that transendothelial insulin transport is saturable (12), which is compatible with a receptor-mediated transport process. Also, insulin receptors have been identified on endothelial cells (13). On the other hand, in vivo investigation in dogs demonstrated a reduced plasma/lymph gradient of insulin during an insulin infusion, indicating that diffusion, rather than a receptor-mediated saturable mechanism, regulates the transcapillary delivery of insulin (14). A nonsaturable transfer of insulin through the endothelium was indicated in another study in which the transport of insulin from the vascular to the interstitial fluid was shown to be concentration dependent (6). Further support for a nonsaturable process, such as diffusion as a mode of insulin transport over the capillary wall, has been demonstrated in a study in dogs in which the transport of an insulin analog with a low receptor affinity was not affected by the presence of insulin levels sufficiently high to saturate endothelial insulin receptors (15). The dynamics of infused insulin and inulin in human muscle interstitial fluid has, to our knowledge, not been explored. The aim of this study was 1) to investigate whether a delay in transcapillary insulin transport could contribute to the insulin resistance in obese subjects and 2) to compare the transcapillary transport of inulin and insulin. The study was therefore designed to measure the time of distribution of insulin and inulin from plasma to the interstitial fluid in human skeletal muscle in obese subjects and age-matched lean control subjects.

The time course of changes in plasma and muscle interstitial insulin and inulin was assessed by means of microdialysis during a constant infusion of insulin and inulin. Measurements of blood flow and arterial-venous (A-V) concentration gradients were conducted in parallel to evaluate capillary permeability.
Subjects. Ten obese and ten lean control subjects, none of whom were taking any regular medication, were investigated. The clinical characteristics of the participants are listed in Table 1. Two lean control subjects were smokers, and two lean and four obese subjects used tobacco snuff. All subjects gave informed consent, and the study was approved by the ethical committee of the University of Göteborg.

Study protocol. The investigations started at 8:00 A.M. after an overnight fast. The subjects were studied in the supine position in a room kept at 25°C. In the left arm, blood sampling cannulas were inserted into an antecubital vein draining deep forearm tissues (16) and into the radial artery for A-V measurements. A vein in the contralateral arm was cannulated and used for infusion of insulin, glucose, and potassium chloride. The study protocol is shown in Fig. 1.

Fasting plasma glucose and insulin were measured. A euglycemic-hyperinsulinemic clamp was started as previously described (17). The clamp protocol was modified to not include any prime infusion of insulin. The insulin infusion rate was 120 mU·m⁻²·min⁻¹ for 240 min and was paralleled with glucose infusion to maintain euglycemia. Potassium chloride (0.1 mmol/l) was infused at a rate of 10 mmol/h during the clamp to prevent hypokalemia. Paralleled to the insulin infusion, inulin was infused at a constant rate (24 ml/h) for 300 min. Arterial and venous blood samples were taken every 15 min for insulin and insulin and every 30 min for glucose. Each sample was stored at −18°C before analysis.

Three microdialysis catheters (CMA Microdialysis AB; CMA, Stockholm) were inserted at a 45° angle (through the steel mandarin of a 20-gauge cannula) into the right brachioradialis muscle. Control experiments in our laboratory, including computed tomography (CT) examinations or electromyogram, have shown that catheter position is satisfactorily ascertained by this procedure. For insulin and insulin measurements, two catheters with a dialysis membrane of 12 × 0.5 mm 100-kDa molecular cutoff were used, and for glucose, another catheter with 16 × 0.5 mm 20-kDa molecular cutoff was applied. The principle of muscle microdialysis has been described in previous detail (3,18,19). The inlets of the catheters were connected to a microdialysis pump (CMA 100). The perfusion fluid consisted of isotonic saline with addition of 1.5 mmol/l glucose and 1% albumin. The perfusion rate was 2.5 µl/min (glucose measurements) and 1.5 µl/min (in catheter measuring insulin and inulin). After 45 min equilibration, the dialysates for insulin, inulin, and glucose measurements were collected at 15-min intervals.

Calibration of the catheters for glucose measurements was performed using urea as an internal reference (20). In this study, the mean in vivo recovery obtained was 18 ± 1% for glucose. Measurements of interstitial insulin were taken according to the external reference calibration technique (3) at steady state. The relation between recovery of insulin and insulin in vitro was 1.7. The mean relative recovery of insulin (dialysate insulin/plasma insulin) in experiments performed in vivo was 6.7 ± 0.4%. The in vivo recovery of insulin was then calculated for each subject. The mean calculated in vivo recovery of insulin was 3.4 ± 0.2%. The in vivo recovery factor was used for recalculating steady-state dialysate insulin contents to interstitial insulin concentrations. Forearm blood flow was measured by venous occlusion plethysmography using a Whitney strain gauge (21).

CT was conducted to determine body composition. Examinations were made with a General Electric HiSpeed Advantage CT system (HSA, release RP2; GE Medical Systems, Milwaukee, WI) with the following settings: 120 kV, 5-mm slice thickness, and fixed filtration. One scan was obtained at the trunk, i.e., the fourth lumbar vertebra level (L4), and one scan at the forearm, i.e., the midpart of the m. brachioradialis level. The images were transferred to a separate UNIX-based analyzing unit. Tissue areas were determined as previously described (22), with the following precision errors calculated from double determinations: 0.5% subcutaneous adipose tissue, 1.2% visceral adipose tissue, 0.3% muscle tissue, and 3.4% bone tissue. The total adipose tissue and visceral adipose tissue volumes were calculated from predictive equations according to Kvist et al. (23). Estimated mass is obtained by multiplying tissue volumes by the density of adipose tissue, 0.923 g/cm³. Lean body mass can then be determined as body weight − adipose tissue (24).

Calculations

Insulin and glucose uptake rates. Fick’s principle was used to estimate the regional rate of glucose and insulin uptake. During steady state, the formula (A-V) was applied.

\[ A-V = (A - I) \times (1 - e^{-\text{mo}V}) \]

where A is the arterial plasma concentration, V is the deep venous plasma concentration, I is the interstitial concentration, ln is the natural logarithm, and Q is the plasma flow.

Analytical methods. Glucose and urea concentrations in plasma and in the dialysate fractions were determined with a colorimetric method (glucose) and a UV method (urea), on a CMA 600 microdialysis analyzer. Blood glucose during the clamp was analyzed enzymatically on a YSI 2700 select biochemical analyzer (Yellow Springs Instrument, Yellow Springs, OH). Plasma insulin was determined with an enzymatic immunoassay (Insulin ELISA; Mercodia, Uppsala, Sweden), and the concentration of insulin in the microdialysates was determined with an ultrasensitive assay (Mercodia Ultra sensitive Insulin ELISA). Inulin concentrations in plasma and dialysates were determined photometrically (25).

![FIG. 1. Study protocol.](image-url)
INSULIN KINETICS IN OBESITY

TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Arterial insulin</th>
<th>Diallysis insulin</th>
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<tr>
<td></td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
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<tr>
<td>Obese subjects</td>
<td>8 ± 0.4</td>
<td>54 ± 7</td>
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<tr>
<td>Control subjects</td>
<td>9 ± 0.7</td>
<td>56 ± 2</td>
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<td></td>
<td>72 ± 6</td>
<td>148 ± 8</td>
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<tr>
<td>Control subjects</td>
<td>46 ± 6*</td>
<td>98 ± 9†</td>
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<td></td>
<td>35 ± 2</td>
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<td>Arterial insulin</td>
<td>39 ± 3</td>
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<tr>
<td>Diallysis insulin</td>
<td>83 ± 3</td>
<td>153 ± 7</td>
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<tr>
<td>Control subjects</td>
<td>53 ± 7†</td>
<td>123 ± 8*</td>
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Data are means ± SE. *P < 0.05, †P < 0.01 for obese subjects versus control subjects.

Statistics. T<sub>1/2</sub> and T<sub>max</sub> for the increase of diallysis insulin and inulin indicate the time to achieve half-maximal and maximal concentrations, respectively. In vitro, it takes 20 min to detect a stable change in diallysis levels of insulin and inulin after the concentration in the surrounding medium has been changed (data not shown). Thus, 20 min were subtracted when presenting T<sub>1/2</sub> and T<sub>max</sub> of interstitial insulin and inulin, as shown in Table 2. Kinetic analyses were done individually, and the means of T<sub>1/2</sub> and T<sub>max</sub> are presented. For calculation of interstitial concentrations, the mean of four samples collected during the last clamp hour was used. The results are expressed as means ± SE. Significance of difference was tested with Student’s t test for paired and unpaired observations. When data were nonparametrically distributed, the Mann-Whitney U test was applied for unpaired data. P < 0.05 was considered statistically significant. Simple regression analysis was also used, and the Stat-View program was applied.

RESULTS

Glucose infusion rate. Glucose infusion rates (GIRs) achieved at 180–240 min of the clamp were reduced in obese subjects as compared with control subjects when calculated as either per body weight (8.9 ± 0.5 vs. 12.5 ± 0.7 mg · kg<sup>−1</sup> · min<sup>−1</sup>, P < 0.05) or per lean body mass (13.1 ± 0.6 vs. 15.4 ± 0.8, P < 0.05). The obese subjects showed a marked delay in onset of the insulin-mediated increase of glucose disposal rate. The initiation phase of insulin activation of glucose metabolism was expressed as T<sub>1/2</sub>, adapting the GIR during the last hour of the clamp as 100%. In addition, the slope of the tangent to the initial activation curve was characterized as recently suggested in a study by Nolan et al. (9). Figure 2A illustrates the time curves for GIR in the two groups. T<sub>1/2</sub>, calculated from the mean of each individual curve of GIR, was 70 ± 9 min in obese subjects and 45 ± 5 min in control subjects (P < 0.05). The initial activation slopes were reduced by ~25% in the obese group as compared with the control group (Fig. 2B).

Insulin. The steady-state arterial plasma concentration of insulin was 1,960 ± 153 and 2,025 ± 236 pmol/l (NS) and in deep venous plasma was 1,701 ± 206 and 1,911 ± 198 pmol/l (NS) in lean and obese subjects, respectively. Arterial and deep venous levels of insulin are depicted in Fig. 3.

The A-V concentration difference of insulin in the basal state was 8.5 ± 4 vs. 22 ± 11 pmol/l (NS) and during steady-state hyperinsulinemia was 124 ± 37 vs. 139 ± 44 pmol/l (NS) in lean and obese subjects, respectively. Interstitial insulin levels during steady state were 1,199 ± 140 and 916 ± 100 pmol/l in obese and control subjects, respectively (NS). No difference in T<sub>1/2</sub> or T<sub>max</sub> for plasma

FIG. 2. A: Time course of whole-body GIR in lean and obese subjects during a euglycemic-hyperinsulinemic clamp (120 mU · m<sup>−2</sup> · min<sup>−1</sup>). B: Whole-body GIR in lean and obese subjects, plotted as percent of maximal GIR at the last hour of the clamp. Data are means ± SE. ●, lean subjects; ○, obese subjects.

FIG. 3. Arterial insulin (○), venous insulin (▲), arterial insulin (●), and venous insulin (●) in forearm during insulin infusion (120 mU · m<sup>−2</sup> · min<sup>−1</sup>) and insulin infusion (24 ml/h) in all subjects. Data are means ± SE (n = 20).
insulin was seen between obese and control subjects (Table 2). \(T_{1/2}\) and \(T_{\text{max}}\) of insulin in arterial plasma were achieved at 16 ± 1 and 55 ± 3 min (n = 20), respectively (Fig. 3). However, the \(T_{1/2}\) and \(T_{\text{max}}\) of insulin in microdialysates was delayed in obese subjects \((P < 0.05)\) (Table 2 and Fig. 4).

Calculated insulin uptake was 199 ± 55 and 143 ± 30 fmol·100 g\(^{-1}\)·min\(^{-1}\) in lean and obese subjects (NS). Estimated PS for insulin during steady-state clamp was 0.5 ± 0.3 vs. 0.3 ± 0.1 ml·100 g\(^{-1}\)·min\(^{-1}\) in lean and obese subjects, respectively (NS).

**Inulin.** Steady-state concentrations of inulin in arterial plasma were 221 ± 16 and 215 ± 8 mg/l and in deep venous plasma were 222 ± 15 and 209 ± 8 mg/l in lean and obese subjects, respectively (NS). Arterial and deep venous levels of inulin for all subjects are shown in Fig. 3. The \(T_{1/2}\) of inulin in dialysate was significantly longer than in plasma (68 ± 5 vs. 34 ± 2 min; \(P < 0.01\), \(n = 20\)) and was further extended in obese as compared with lean subjects \((P < 0.05)\) (Table 2 and Fig. 5).

**Glucose.** Arterial and venous plasma glucose in the fasting state were 5.4 ± 0.2 and 5.3 ± 0.2 vs. 5.6 ± 0.2 and 5.4 ± 0.1 mmol/l in lean and obese subjects, respectively (NS). During steady-state clamping at 210–240 min, arterial and venous glucose levels were 6.4 ± 0.2 and 5.0 ± 0.4 vs. 6.4 ± 0.1 and 4.9 ± 0.3 mmol/l in the lean and obese groups, respectively (NS). At the end of the clamp, A-V concentration difference of glucose was significant in both groups \((P < 0.01)\). Interstitial glucose in the fasting state was 3.5 ± 0.2 vs. 3.7 ± 0.3 mmol/l and during steady-state clamp was 4.0 ± 0.3 vs. 4.3 ± 0.3 mmol/l in lean and obese subjects, respectively (NS). The calculated glucose uptake tended to be higher in the lean group in the fasting state \((0.6 ± 0.2 vs. 0.3 ± 0.1 \mu\text{mol·100 g}^{-1}·\text{min}^{-1}, P = 0.07)\) and was significantly higher during steady-state clamping \((5.1 ± 1.2 vs. 2.1 ± 0.5, P < 0.05)\) in lean and obese subjects, respectively. The glucose uptake rate correlated positively with the GIR \((r^2 = 0.32, P < 0.05)\). Estimated PS during steady-state clamp was 2 ± 1 vs. 2 ± 1 ml·100 g\(^{-1}\)·min\(^{-1}\) in lean and obese subjects, respectively (NS).

**Blood flow.** Forearm blood flow was lower in the obese group than in the control group, both in the postabsorptive state \((1.6 ± 0.2 vs. 2.2 ± 0.2 ml·100 g^{-1}·min^{-1}, P < 0.05)\) and during steady-state hyperinsulinemia \((1.9 ± 0.2 vs. 3.1 ± 0.3, P < 0.05)\). Blood flow rate increased significantly during the hyperinsulinemic-euglycemic clamp in lean versus obese subjects \((P < 0.05)\) (Fig. 6).

**DISCUSSION**

This study demonstrates that the time kinetics of insulin in muscle tissue are slower than in plasma in both obese and lean subjects. This is in accordance with previous studies in lymph (1) and in subcutaneous adipose tissue in humans (2). Importantly, activation of glucose disposal is also slower than changes in plasma insulin but fits kinetically with insulin in lymph (20). The present data, obtained in the interstitial fluid, confirm the earlier finding of an endothelial barrier for insulin, with a 40–60% lower interstitial insulin level and slower kinetics than in plasma (2,4).

The main finding in this study, reported for the first time, is the marked delay of insulin delivery to the muscle interstitial fluid demonstrated in obese subjects. Earlier studies have shown a kinetic defect in the insulin-medi-
ated activation of glucose uptake in obese subjects (9,27). Insulin-stimulated glucose uptake is the result of the insulin signal, including insulin receptor binding and activation of tyrosine kinase, propagation of the intracellular signal, and translocation and activation of glucose transporters. The relative contribution of a delayed transcapillary transport of insulin in addition to the insulin resistance produced by tentative defects in the insulin signaling system is not clear. Mostly, insulin sensitivity is measured at steady state, and a kinetic defect of insulin action is not taken into account. However, delays in insulin action, as produced by rightward shifts of the dose-effect curve of insulin and by slow transcapillary delivery of insulin, should both make important contributions to the postprandial hyperglycemia in insulin-resistant subjects.

In contrast to a present study by Mokshagundam et al. (28), no delay of transcapillary insulin transport in adipose tissue has been found in either obese or lean individuals. Apart from the fact that different tissues were studied, a possible explanation for the diverging results might be that Mokshagundam et al. administered a bolus infusion of insulin that raised the interstitial insulin more rapidly, whereas we used a continuous infusion. Nolan et al. (9) found no delay in the activation of insulin receptor tyrosine kinase in either obese or type 2 diabetic subjects. This would indicate that the distribution of insulin and binding to the receptor were not delayed and that the kinetic defect in insulin action was located posterior to the receptor. However, because the muscle biopsies for analyzing insulin receptor tyrosine kinase activation were taken in 30-min intervals, a kinetic defect in activation might have been difficult to detect. In contrast, delayed insulin transport was shown in perfused heart from insulin-resistant rats (10) as well as in vivo in rat muscle (5). In the latter study, exercise was shown to reverse the slow onset of insulin action in oophorectomized testosterone-resistant rats (10) as well as in vivo in rat muscle (5). In the latter study, exercise was shown to reverse the slow onset of insulin action in oophorectomized testosterone-treated rats. This finding is in harmony with another microdialysis study of muscle in insulin-resistant rats in which a slow insulin distribution in muscle was combined with a delayed onset of insulin action (11). Our present data demonstrate a delayed appearance of insulin to the muscle interstitial fluid in obese subjects. A reduced clearance of insulin in the skeletal muscle may also influence the appearance time of insulin in the muscle interstitial fluid. However, since insulin and the inert substance inulin are equally delayed in obese subjects, we do not believe the elimination of insulin is altered. Also, a change in distribution space would not affect time of appearance but rather the maximum concentration. Therefore, we suggest a delayed transcapillary transport of insulin in the obese group.

In the present study, we cannot rule out that the delay in GIR is affected by a decreased inhibition of hepatic glucose production (HGP) in the obese group. However, the rate of suppression of HGP is reported to be similar in lean and obese subjects during insulin infusion rates comparable with those used in the present study (27). Also, the delay in GIR activation is of the same magnitude and in the same time interval as the delay in increase of muscle insulin.

Thus, we suggest that the rightward shift of the insulin time-effect curve found in obesity might not only be explained by receptor or postreceptor defects and the resulting high EC50 (half-maximal effective concentration) values, but also by a delayed transport of insulin over the capillary wall.

The muscle interstitial insulin concentrations measured during steady-state hyperinsulinemia did not differ between obese and lean subjects. In a previous study of type 2 diabetic patients, we reported levels of muscle interstitial insulin similar to those in control subjects (29). Increased interstitial insulin levels were also reported in obese Zucker rats (30) and in lymph in obese humans (8). In addition, in this as well as a previous report (8), both insulin uptake and capillary permeability for insulin were normal in obese subjects. Therefore, it may be concluded that insulin levels in the interstitial fluid are normal at steady state in obese subjects and that the reduced GIR presently demonstrated at steady state is not due to failing capillary delivery of insulin.

Inulin is an inert water-soluble substance transported from plasma to peripheral tissue by passive diffusion and is eliminated through glomerular filtration. In this study, time of appearance of inulin in the muscle interstitial fluid was of the same magnitude as insulin. Because insulin and inulin have similar molecular weights, this indirectly supports the theory that insulin and inulin are transported by the same mechanism (diffusion) over the capillary wall. Also, in rat skeletal muscle time kinetics of insulin did not seem to differ markedly from those of inulin (31). In vitro, a transendothelial receptor-mediated pathway for insulin transport has been demonstrated. Labeled insulin can be transported through the endothelial cells, and this transport route can be inhibited by unlabeled insulin and by antibody against the insulin receptor (12). In contrast, in vivo studies of lymph indicate a nonsaturable non–receptor-mediated transport, such as diffusion (14). In muscle of lean rats, the plasma/interstitial concentration ratio increases in higher physiological concentration ranges that might be compatible with a saturable transport system (30). However, this was not evident in obese Zucker rats (30) or in human muscle (29). The present data, indicating that insulin and inulin are transported by the same mode of action (according to their similar kinetics in muscle microdialysates), further suggest that a non–receptor-mediated mechanism, such as diffusion, constitutes a major transport route of insulin.

The delay of transcapillary delivery of both inulin and insulin to the muscle interstitial fluid in obese subjects may depend on their having a lower capillary density (32) or a defective vasodilating response to insulin (33). A low capillary density is believed to constitute a mechanism behind insulin resistance in the muscle (34–36). Furthermore, a longer diffusion distance between capillaries and muscle cells in insulin-resistant subjects has been suggested (34).

The blunted increase in forearm blood flow in the obese subjects during hyperinsulinemia in this study is consistent with earlier reports (33) that also demonstrate an impaired insulin-induced vasodilation in obesity.

Muscle perfusion correlates positively with insulin-mediated glucose uptake in muscle (33,37,38). However, during an insulin infusion, the increase in blood flow
appears later and is relatively lower than the increase of GIR, which is why a casual relationship between blood flow and glucose uptake may not be clear (39). The importance of this late vasodilatory effect of insulin relative to the activation of the insulin-mediated glucose uptake in the muscle has not been entirely defined, but earlier data have suggested that the insulin-mediated increase in blood flow accounts for ~15–30% of insulin’s overall action to stimulate muscle glucose uptake (19,40). Additionally, an increase in muscle perfusion seems to be more important for the insulin effect as insulin sensitivity and A-V difference of glucose increase (41).

It should be noted in this context, however, that in insulin-resistant muscle, blood flow is not rate limiting and vasodilation leads to increased interstitial glucose levels without increasing the glucose transport rate (42,43). The present study, in contrast, shows that insulin-induced vasodilation might be important for the time of onset of insulin action under non–steady-state conditions.

Estimation of the glucose uptake rate in forearm by application of Fick’s principle may be hazardous when the blood flow is not stable (44). Therefore, kinetic analyses of forearm glucose uptake rates were not performed. As both activation of GIR and delivery of insulin to muscle interstitial fluid were delayed in the obese group, this delay should also be expected for muscle glucose uptake. In this context, it is important to note that forearm glucose uptake calculated by Fick’s formula correlates closely with GIR under steady-state but not non–steady-state conditions. It is reasonable to believe that forearm muscle glucose uptake correlates with GIR, even under non–steady-state conditions, and that a lack of correlation might be due to the above difficulties involved with calculations when blood flow changes.

In this study, interstitial glucose was ~35% lower than in plasma at steady-state hyperinsulinemia, confirming earlier reports (29,42). The estimated PS values were similar in obese and lean subjects during stable hyperinsulinemia. Nevertheless, a difference in PS between obese and lean subjects in the fasting state cannot be excluded. However, it seems unlikely because forearm blood flow did not change dramatically in either group after insulin infusion.

The HGP is expected to be shut off at the insulin levels presently used (45), which is why we believe that the GIRs observed in this study mainly represent muscle glucose uptake. This proposal was further supported by the finding that GIR and muscle glucose uptake were correlated.

Obese humans may have an increased first phase of insulin secretion (46), presumably to compensate for peripheral insulin resistance. This increase could also serve to compensate for a tentatively delayed delivery of insulin to the target tissue. In dogs, the interstitial insulin level increased more quickly after a biphasic insulin infusion than after a continuous infusion (47). In patients with early stages of type 2 diabetes, first-phase insulin release is lost despite the concomitant enhancement of second-phase secretion, which may lead to high postprandial glucose levels (48,49). It is possible that a delayed peripheral insulin action in type 2 diabetic subjects could further prolong the hyperglycemia after meals. Epidemiological studies have indicated that plasma glucose levels 2 h after a glucose load are strongly associated with all-cause and cardiovascular relative mortality risk (50).

In summary, the present data show for the first time that obese humans have a delayed distribution of insulin-to-muscle interstitial fluid as well as a slower activation of the glucose uptake rate. These data suggest that a delayed delivery of insulin may contribute to muscle insulin resistance in obesity.

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