Obese subjects exhibit a delay in insulin action and delivery of insulin to muscle interstitial fluid during glucose/insulin infusion. The aim of the present study was to follow the distribution of insulin to skeletal muscle after an oral glucose load in obese subjects. We conducted an oral glucose tolerance test (OGTT) in 10 lean and 10 obese subjects (BMI 23 ± 0.6 vs. 33 ± 1.2 kg/m²; P < 0.001). Insulin measurements in muscle interstitial fluid were combined with forearm arteriovenous catheterization and blood flow measurements. In the obese group, interstitial insulin was significantly (35–55%) lower than plasma insulin (P < 0.05) during the 1st h after the OGTT, whereas in lean subjects, no significant difference was found between interstitial and plasma insulin levels during the same time period. The permeability surface area product for glucose, representing capillary recruitment, increased in the lean group (P < 0.05) but not in the obese group (NS). Obese subjects had a significantly higher plasma insulin level at 90–120 min after oral glucose (398 ± 57 vs. 224 ± 37 pmol/l in control subjects; P < 0.05). The significant gradient between plasma insulin and muscle interstitial insulin during the first hour after OGTT suggests a slow delivery of insulin in obese subjects. The hindered transcapillary transport of insulin may be attributable to a defect in insulin-mediated capillary recruitment.

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Insulin has to traverse the capillary endothelium to reach the target cell in peripheral tissue. At steady-state insulin infusion, interstitial insulin is ~40% lower than plasma insulin (1,2). Insulin-resistant obese subjects, however, have supranormal interstitial insulin levels as a result of the insulin resistance in the target cell (3).

In vivo studies have shown that insulin action or the glucose disposal rate lags after an increase in plasma insulin (4,5). As well, during insulin infusion, most studies, but not all (6), have shown that interstitial insulin lags after plasma insulin (1,4,7), thereby demonstrating that the endothelial wall may delay the transcapillary transport of insulin. Furthermore, the dynamics of glucose uptake correlate closely with changes in interstitial insulin rather than plasma insulin, suggesting that interstitial insulin levels determine the uptake rate of glucose (3,8). A further delay in insulin action has been demonstrated in insulin-resistant obese and type 2 diabetic subjects (9,10), 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 is markedly delayed in obese, insulin-resistant animals (11,12) as well as in obese humans (13) during insulin/glucose infusion. It has been suggested that the slow rate of insulin delivery in insulin-resistant states might be due to reduced capillary density (14) or capillary recruitment (15,16) or the diminished vasodilative response of insulin (17,18). This study was designed to study the distribution of insulin from plasma to the interstitial fluid in skeletal muscle in obese subjects after a physiological increase of insulin during an oral glucose load.

The time course of changes in plasma and muscle interstitial insulin was assessed by means of microdialysis during an oral glucose tolerance test (OGTT). Measurements of blood flow and arteriovenous concentration gradients were conducted in parallel to evaluate the permeability surface area product (PS) and glucose uptake rates.

**RESEARCH DESIGN AND METHODS**

The study subjects were 10 obese and 10 lean control subjects, none of whom were taking any regular medication. Subjects’ clinical characteristics are listed in Table 1. All subjects gave informed consent, and the study was approved by the ethical committee of the University of Göteborg.

The investigations started at 8:00 A.M. after an overnight fast in a room kept at 25°C. The subjects were investigated in a semisupine position. Glucose (75 mg) was dissolved in 250 ml of chilled lemon-flavored water. Measurements were performed after the OGTT.

Three microdialysis catheters (CMA, Microdialysis AB, Stockholm, Sweden) were inserted through the steel mandarin of a 20-gauge cannula into the brachioradialis muscle in the forearm. For insulin and inulin measurements, two catheters with a 12 × 0.5 mm dialysis membrane and a 100-kDa molecular cutoff were used, and for glucose and lactate measurements, a 16 × 0.5 mm catheter and 20-kDa molecular cutoff was applied. Microdialysate sampling for insulin, glucose, and lactate measurements was done at 15-min intervals for 30 min in the postabsorptive state and continued after the start of the OGTT for 120 min, in parallel with forearm blood flow measurements and arterial and deep venous blood samples for insulin, glucose, and lactate. Each sample was stored at −18°C before analysis. The principle of muscle microdialysis has been previously described in detail (2,19). The inlets of the catheters were connected to a microinjection pump (CMA 100; CMA). The perfusion fluid consisted of isotonic saline to which was added 2.0 mmol/l...
**Results**

**Insulin.** In the obese group, interstitial insulin was significantly lower than plasma insulin at 15, 30, 45, and 60 min after the OGTT (Fig. 2B), whereas in lean subjects, no significant difference between interstitial and plasma insulin levels was found during the first hour after the oral glucose load (Fig. 2A). The ratio of interstitial to plasma insulin was therefore higher in lean compared with obese subjects 60 min after glucose ingestion (Fig. 2A and B). At the end of the OGTT (90–120 min), the interstitial insulin was ~60% of the plasma insulin level in both lean (P < 0.05) and obese (P < 0.05) subjects (Fig. 2A and B). Thus, at the last part of the OGTT, the interstitial to plasma insulin ratio was similar in the two groups.

The obese subjects had a significantly higher plasma insulin level at 90–120 min after oral glucose (398 ± 57 vs. 224 ± 37 pmol/l in control subjects; P < 0.05) (Fig. 3). In addition, interstitial insulin was higher in obese subjects (230 ± 35 vs. 146 ± 21 in lean control subjects; P < 0.05) at 90–120 min. Insulin uptake rates in both groups are presented in Fig. 4. The insulin uptake increased significantly (P < 0.05) in both groups compared with basal values: 96 ± 27 in the obese group and 41 ± 6.5 fmol/100 g−1·min−1 in the lean group (NS) at 60 min.

**Glucose.** Arterial plasma glucose in the fasting state was 5.1 ± 0.1 vs. 5.2 ± 0.1 mmol/l, and venous glucose was 5.0 ± 0.1 vs. 5.1 ± 0.1 mmol/l in lean and obese subjects, respectively (NS) (Table 2). During OGTT, the arterial glucose level was 7.6 ± 0.7 vs. 8.3 ± 0.7 (NS) at 120 min, and venous glucose was 6.8 ± 0.4 vs. 7.8 ± 0.8 (NS) in lean and obese subjects, respectively. In the fasting state,
interstitial glucose was 3.4 ± 0.4 vs. 4.1 ± 0.3 (NS) in lean and obese subjects, and at 120 min, it was 5.5 ± 0.6 vs. 6.3 ± 0.6 (NS), respectively. Glucose uptake increased significantly in both groups during the 1st h after oral glucose administration (Table 2).

**Blood flow.** Forearm blood flow was similar in the lean and obese groups in both the postabsorptive state (1.6 ± 0.2 vs. 1.7 ± 0.2 ml·100 g⁻¹·min⁻¹; NS) and at 90–120 min (1.9 ± 0.2 vs. 1.6 ± 0.2 ml·100 g⁻¹·min⁻¹; NS). Blood flow had a tendency to increase during the OGTT in lean subjects (P = 0.07), but not in obese ones.

**DISCUSSION**

This study demonstrated that obese subjects exhibit a significant gradient between plasma insulin and muscle interstitial insulin during the 1st h after an oral glucose load that was not found in lean control subjects. It is suggested that this significant gradient demonstrates a delayed transcapillary transport of insulin in obese subjects. Thus, the ratio of interstitial to plasma insulin was lower in obese than in lean subjects at the beginning of the OGTT. However, by the end of the OGTT, the interstitial-to-plasma insulin ratio was similar in the two groups (~60%), as was previously demonstrated (2,5).

Most earlier studies have investigated insulin action at steady-state insulin levels, and cellular studies from skeletal muscle have shown that intracellular insulin signaling is defective in obese subjects (24). However, another aspect of insulin resistance is a delay in insulin action. Previously, it has been reported that the time of onset of insulin action is delayed in obese subjects during insulin/glucose infusion (10,13). A delayed transcapillary insulin transport in insulin-resistant states has also been reported from in vitro studies (11) and some (1,12,25,26), but not all (6,27), in vivo studies. In a recent study from our laboratory (13), the delay in insulin action was accompanied by a slow delivery of insulin to the muscle interstitial fluid during insulin/glucose infusion in the obese state. However, the distribution of insulin from blood to muscle tissue during more physiological conditions, represented by an OGTT in the present study, has not previously been reported in obese subjects.

During high insulin levels in steady-state conditions, capillary delivery of insulin is sufficient in insulin-resistant muscle (2,3,28). In this study, interstitial muscle insulin was even higher in obese than in lean subjects at the end of the OGTT, confirming earlier data of interstitial insulin...
levels in obese rats (28) and humans (3) at the end of insulin infusion. The insulin resistance associated with obesity that is observed after prolonged insulin stimulation thus does not seem to be caused by a deficient transcapillary delivery of insulin and glucose but rather by cellular insulin resistance. However, during non–steady-state conditions, exemplified by an OGTT in the present study, a hindered insulin distribution is observed in obese, insulin-resistant subjects. The reason for the sluggish insulin distribution may be decreased capillary density, blood flow, capillary recruitment, or permeability in the muscle tissue of obese subjects. Capillary density is negatively correlated with obesity (14); further, it is proposed that low capillary density would prolong the distance along which insulin must be diffused and thus delay insulin action (14).

The issue of whether insulin-mediated vasodilation can modulate glucose uptake has been previously discussed. Muscle blood flow correlates positively with insulin-mediated glucose uptake during insulin infusion (17,29,30). However, the increase in glucose uptake is relatively higher and appears earlier than the increase in blood flow, which would suggest that increased blood flow is not the source of the augmented glucose uptake during the clamp procedure (31). Instead it has been suggested that an increased glucose uptake may stimulate blood flow. Supporting this view are the results of two studies in which insulin administered together with glucose locally in the forearm induced an increase in blood flow (32), whereas insulin infused with a metabolically inactive isomer of glucose did not (33). In a clamp study with lean, obese, and type 2 diabetic subjects, all three groups exhibited similar blood flow when a comparable glucose disposal rate was achieved in all groups (34).

In the present study, no clear difference in blood flow rate was detected between obese and lean subjects during the OGTT. In accordance with the above-mentioned studies (32,34), the higher insulin and glucose levels in the obese group may have compensated for the conjectured diminished blood flow in the obese group. As well, the physiological insulin levels achieved during the OGTT may not have been high enough to increase total limb flow.

Recent work by Vincent et al. (35) has suggested that physiological insulin levels can mediate capillary recruitment, even in the absence of a total blood flow increment. The increased capillary recruitment (35) may be of importance for the muscle glucose uptake. In addition, the PS for glucose was increased in healthy humans during an OGTT without a concomitant increase in blood flow (36). One interesting finding has been that in insulin-resistant states, insulin-mediated capillary recruitment (15,37) seems to be impaired. In the current study, there was a significant difference in interstitial versus plasma insulin in the first hour after the glucose load in the obese group. It may be speculated that decreased capillary recruitment in the obese group impaired the delivery of insulin in the beginning of the OGTT.

In the present study, the PS for glucose increased 1 h after glucose ingestion in the lean but not in the obese group, which may suggest a diminished capillary recruitment in obese subjects. It should be noted that the formula for determining the PS is not equivalent to measurements of capillary recruitment but rather a sum product of vasodilation/vasoconstriction and permeability over the tissue bed. However, a change in capillary recruitment influences the PS value. In addition, calculations of PS (which assumes homogeneity) may be weakened by the presence of heterogeneity of blood flow distribution in muscle (38). It may be assumed that this heterogeneity exists in both lean and obese subjects. Hence, it is reasonable to believe that the change in PS that is found in lean but not in obese subjects corresponds to a difference in change of permeability; that is, the capillary permeability area. Insulin, as well as inulin and glucose, pass through the capillary wall by means of passive diffusion; hence, the blunted increase in PS for glucose found in obese subjects may be relevant for the sluggish increase in interstitial insulin in these subjects.

The present data confirm the well-known observation that obese subjects have a higher insulin response after oral glucose, (39). Similarly, a brisk rise in plasma insulin level with an average peak at 30 min has been demonstrated in nondiabetic subjects in all weight classes (39).

Obese subjects have a high first-phase insulin response (40), which may be an attempt to compensate for the cellular insulin resistance in obesity (24). It has also been shown that a two-phase insulin infusion increases interstitial insulin levels more rapidly than a continuous insulin infusion, suggesting that a loss of the first insulin response may delay transcapillary delivery of insulin (41). In prediabetic states, the first insulin response is diminished (42), which may further deter the distribution of insulin to peripheral tissues. One previous interesting finding is that pulsatile insulin infusion in healthy lean individuals enhances glucose uptake in peripheral tissues more than a continuous insulin infusion (43).

In this study, the insulin response after OGTT showed considered variability in both groups (data not shown).
and not all subjects had a biphasic insulin response. This finding concurs with earlier reports on a wide plasma insulin response after OGTT in healthy individuals (44). In the current study, the insulin uptake rate seemed to be delayed in the obese group, even though direct evidence for this cannot be provided from the present data as the variable (often two-phase) plasma insulin response after oral glucose does not allow calculations of the time to reach half-maximal concentrations. Instead, we suggest that the delayed insulin distribution in obese subjects was demonstrated by the significant gradient concentration between plasma and muscle interstitial insulin seen in the beginning of the OGTT. In the lean group, on the other hand, no significant gradient was found between plasma and interstitial insulin in the beginning of the OGTT, suggesting no major hindrance of insulin transport over the capillary wall. The presence of a minor gradient cannot be excluded in this relatively small group of lean subjects. However, the main finding is the major gradient found in the obese subjects as the result of a significant group difference. The present data agree with those from another recent microdialysis study of transcapillary insulin transport in muscle in lean subjects, where a significant gradient between plasma and interstitial insulin was observed at the peak but not in the beginning of the OGTT (45).

In summary, it appears that obese subjects need a higher plasma insulin response than lean subjects to achieve a similar time curve for muscle interstitial insulin. Also, an increased interstitial muscle insulin level at the end of the OGTT may be of pathogenetic importance for insulin resistance in muscle, as high ambient insulin levels may further desensitize the cells to insulin (46).

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