Involuntary leg movements affect interstitial nutrient gradients and blood flow in rat skeletal muscle

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Holmäng, Agneta, Kazuo Mimura, and Peter Lönnroth. Involuntary leg movements affect interstitial nutrient gradients and blood flow in rat skeletal muscle. J Appl Physiol 92: 982–988, 2002.—To evaluate the effect of passive muscle shortening and lengthening (PSL) on the transcapillary exchange of glucose, lactate, and insulin in the insulin-stimulated state, microdialysis was performed in rat quadriceps muscle. Electrical pulsatile stimulation (0.1 ms, 0.3–0.6 V, 1 Hz) was performed on the sciatic nerve in one leg to induce passive tension on the quadriceps during a hyperinsulinemic-euglycemic clamp (10 mU·kg⁻¹·min⁻¹). In the non-insulin-stimulated (basal) state, the muscle arterial-interstitial (A-I) concentration difference of glucose was 1.6 ± 0.3 mM (P < 0.01). During insulin infusion, it remained unaltered in resting muscle (1.3 ± 0.3 mM) but diminished during PSL. In the basal state there was no A-I concentration difference of lactate, whereas in the insulin infusion state it increased significantly and was significantly greater in moving (2.8 ± 0.5 mM, P < 0.01) than in resting muscle (0.7 ± 0.4 mM). The A-I concentration difference of insulin was equal in resting and moving muscle: 86 ± 7 and 100 ± 8 μU/ml, respectively. Muscle blood flow estimated by use of radiolabeled microspheres increased during PSL from 17 ± 4 to 34 ± 6 ml·100 g⁻¹·min⁻¹ (P < 0.05). These results confirm that diffusion over the capillary wall is partly rate limiting for the exchange of insulin and glucose and lactate in resting muscle. PSL, in addition to insulin stimulation, increases blood flow and capillary permeability and, as a result, diminishes the A-I concentration gradient of glucose but not that of insulin or lactate.

microdialysis; arterial-interstitial concentration gradient; passive muscle shortening and lengthening

Metabolism of glucose and lactate in muscle tissue is of quantitative importance for body glucose homeostasis, and regulation of this metabolism has been investigated intensively with respect to insulin-resistant conditions such as obesity and non-insulin-dependent diabetes mellitus. Most of these studies have focused on muscle glucose metabolism during resting conditions (15, 36). However, a more complex picture may be obtained by investigating exercising muscle, since contraction of the muscle fibers increases glucose uptake (1) via a signaling pathway that is different from that elicited by insulin (19). Moreover, glucose metabolism may be affected by the increase in blood flow that is produced by muscle exercise (6).

Traditionally, metabolism of glucose in intact muscle was studied by measuring arteriovenous concentration differences in the extremities (15). For further insight into the impact of capillary barriers affecting insulin and glucose, delivery measurements should be performed in the interstitial fluid (7, 24). The existence of such barriers implies that the capillary wall affects the rate of muscle glucose uptake; hence, the glucose uptake rate is dependent not only on the rate of the cellular consumption of glucose but also on the blood flow and the capillary permeability surface area. When blood flow is measured in combination with microdialysis, transport of substrates and hormones from capillaries to the extracellular space can be investigated (13).

In a recent study (22), microdialysis measurements in contracting human skeletal muscle demonstrated that the interstitial concentration of glucose and lactate was increased. However, in the same study, the relative microdialysis recovery was increased during contraction, but concomitant blood flow measurements were not done; hence, a full picture of the uptake-release balance was not achieved. To eliminate a contraction-mediated increase of the water pressure near the microdialysis probe, an alternative approach was used in the present study. In this study, to evaluate whether passive shortening and lengthening (PSL) of muscle affects tissue blood flow and capillary delivery of insulin and glucose, calibrated microdialysis and blood flow measurements were performed in the anesthetized rat during euglycemic clamp conditions. In addition, quadriceps PSL was induced by means of electrical stimulation of the sciatic nerve and contractions were thus activated on the flexor side. The data show that the capillary wall is rate limiting for glucose uptake and lactate release in resting muscle during an insulin infusion. PSL of muscle causes a concomitant increase of the muscle blood flow, which results in a diminished glucose gradient over the capillary wall with a corresponding increase in lactate concentration.

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METHODS

Twelve female Sprague-Dawley rats (BK Universal, Sol- lentuna, Sweden), weighing 267 ± 8 (SE) g, were housed in single cages at 23°C. They were fed rat chow containing 22% protein, 5% fat, 51.5% carbohydrate, and sufficient minerals and vitamins (Ewos, Södertälje, Sweden). The rats also received tap water ad libitum. The animals were housed under these conditions in a 12:12-h dark-light cycle for ≥1 wk before inclusion in the study. The study was approved by the Animal Ethics Committee of Göteborg University.

Study protocol. The study protocol is shown in Fig. 1. Rats were anesthetized with thiobutabarbital sodium (Inactin, RBI, Natick, MA; 12.5 mg/100 g body wt ip) and placed on heating pads to maintain adequate temperature (37°C by rectal probe). Catheters were placed in the left carotid artery for blood sampling and the right jugular vein for infusion of glucose and insulin. The sciatic nerve of each hindlimb was exposed through a lateral incision in the thigh. A bipolar electrode was placed adjacent to the sciatic nerve in one limb, while the exposure of the other nerve served as a sham control. The leg was turned outward in the hip joint, and the knee joint was flexed. The bipolar electrode (Grass Instrument, Quincy, MA) was connected to a stimulator (model S6, Grass Instrument). After incision of the skin and exposure of the quadriceps muscle, a microdialysis catheter (0.5 mm OD, 10 mm long, 50 kDa cutoff; BAS) was inserted into the quadriceps muscle in both legs of the rat. After closure of the skin and connection of the catheter inlet to a pump (Carne- gie, CMA, Stockholm, Sweden), the system was perfused with 1% bovine serum albumin in isotonic saline with 1 mM glucose at 1 μL/min. Glucose (1 mM) was also added to the perfusate to prevent depletion of glucose from the tissue (20). The catheters were calibrated under steady-state basal conditions to estimate glucose and lactate concentrations in the interstitial fluid (see Microdialysis calibration).

The euglycemic-hyperinsulinemic glucose clamp technique has been described in detail previously (10). Catheters were inserted into the left carotid artery for blood sampling and into the right jugular vein for infusion of glucose and insulin. Body temperature was maintained at 37°C with a heating blanket. After a bolus injection, insulin (100 U/ml; Human Actrapid, Novo, Copenhagen, Denmark) was continuously infused at 10 mU·kg⁻¹·min⁻¹. Briefly, insulin was continuously infused at 10 mU·kg⁻¹·min⁻¹. A 20% solution of glucose in isotonic saline was also infused to maintain the blood glucose level at 7.0 mM. The insulin infusion was continued for 100 min, from minute 80 to minute 180. During steady-state clamping conditions, i.e., from minute 120 to minute 180, samples of the muscle interstitial fluid were collected every 30 min and analyzed for glucose, lactate, and insulin concentrations. Blood used for the determinations (<2 ml) was compensated for by the infusion volumes. The data are presented as mean values obtained during steady-state conditions.

Electrical stimulation. Electrical stimulation of peripheral efferent nerves may lead to activation of sympathetic fibers and vasodilation (2). The goal of the present study was to investigate the influence of PSL without interference of a putative sympathetic nervous activation. Therefore, the sciatic nerve was utilized for electrical stimulation, and the microdialysis measurements were performed in the non-stimulated passively stretching and contracting quadriceps muscle not innervated by the sciatic nerve.

During the last 60 min of the clamp, the sciatic nerve of one hindlimb was stimulated electrically by using square-wave pulses of 0.1-ms duration at a frequency of 1 Hz. The voltage was adjusted (0.3–0.6 V) to maintain the same amplitude of dorsal extension of the foot from the horizontal position to an angle of ~30°.

Microdialysis calibration. In vivo probe recovery was assessed in situ according to the equilibrium technique (20) and the internal reference calibration technique (21). After steady-state basal conditions were reached (45 min), the equilibrium calibration was carried out as described previously in detail (20). Briefly, known concentrations of glucose and lactate were added to the perfusate in a nonconsecutive order, and the net increase of glucose and lactate concentration in the dialysate was measured. The linear relationship between the perfusate glucose/lactate and the increase in dialysate concentration was established, and the point of no net influx (indicating the interstitial glucose/lactate concentra- tion) was estimated by means of linear regression.

The microdialysis catheters were also calibrated in situ according to the internal reference technique (21) to attain the interstitial glucose and lactate concentrations. Data obtained by internal reference and equilibrium calibration in the same subject have shown similar results (8, 21). For an internal reference calibration, 0.5 mM [³H]glucose (0.1 mCi/
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ml; Amersham) and 0.3 mM [14C]lactate (0.2 mCi/ml; Amersham) were added to the perfusate, and the fractional extraction of radioactivity (relative recovery of the substance of interest) was measured. The interstitial fluid concentrations of lactate and insulin were obtained by the use of a reference calibration technique, which has recently been validated (31). The recovery (dialysate/interstitial concentrations) of both substances was calculated as follows

\[
\frac{\text{recovery of glucose}}{\text{recovery of lactate}} = R_1, \quad \frac{\text{recovery of glucose}}{\text{recovery of insulin}} = R_2, \quad \frac{\text{recovery of lactate}}{\text{recovery of insulin}} = R_3
\]

where the values for \(R_1 - R_3\) were calculated from 68 previous consecutive measurements that were made under the conditions used in this study (31). The use of endogenous references where interstitial concentrations of multiple substances can be calculated from knowledge of the dialysate recovery of one of these substances was recently validated (31). The mean calculated recovery of insulin according to the above formula was 0.03 ± 0.01.

During calibration, dialysates were collected for 15 min during perfusion with each calibration solution. Calibration using equilibration and internal reference methods yielded similar results (Table 1). The mean relative outflow of [3H]glucose through the microdialysis catheter in 12 rats (24 hindlimbs) did not change over the 200-min period, indicating that electrical stimulation and passive muscle movements did not change the relative recovery of interstitial glucose in dialysates (data not shown).

**Measurements of blood flow.** Immediately before termination of the electrical stimulation (180 min), the blood flow in the individual muscles was estimated by using the radioactive microsphere technique (5). The microsphere suspension with specific activity of 11.5 mCi/g (52Co-labeled microspheres in 0.9% saline with 0.01% Tween 80; New England Nuclear, Boston, MA) was roughly mixed and sonicated to avoid aggregation of the microspheres. The mean size of the microspheres was 15.5 μm, which is approximately twice the size of red blood cells and slightly larger than capillaries, which means that the microspheres could approximate the distribution of red blood cells until just before they impacted in the capillary bed (23). The microspheres (\(~5 \times 10^8\)) were immediately injected into the circulation, in the left ventricle via the catheter placed in the left carotid artery, with the catheter tip placed inside the ventricle, followed by a flush of 0.3 ml of saline. A reference blood sample was drawn from the caudal artery with a Minipuls 3 peristaltic pump (Gilson France, Villiers-level, France). After the injection, the kidneys as well as the quadriceps muscle and the muscles of the lower limb (tibialis anterior, extensor digitorum longus, white and red gastrocnemius, soleus, and plantaris) were immediately excised, and their radioactivity was measured. Injections that resulted in a >10% difference in blood flow between the kidneys were excluded, inasmuch as differences this large indicate an inadequate distribution of microspheres (5). By the reference sample technique, the blood flow in each individual muscle could be accurately determined, provided the reference sample contained >200 microspheres (12). Regional blood flow to the lower leg was then calculated as the average radioactivity of all the muscles and was expressed as ml·100 g tissue⁻¹·min⁻¹.

**Analytic methods.** Glucose and lactate concentrations in the plasma and in the dialysate fractions were determined enzymatically by using 10-μl samples for the simultaneous analyses of glucose and lactate in a select biochemical analyzer (model 2700, Yellow Springs Instrument, Yellow Springs, OH). Rat (endogenous) and human (exogenous) insulin were measured with equal efficiency by using a double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden). Radioactivity was counted by using a liquid scintillation counter with a quench-corrected (external standards), double-isotope program (1217 Rackbeta, LKB, Uppsala, Sweden). Internal standards for [14C] and [3H] were used initially to check tissue samples for quenching interferences.

**Statistics.** Values are means ± SE. Linear regression analyses were performed according to the least-squares method. The significance of differences was tested with Student’s t-test for paired or unpaired observations. Nonparametric tests were done by means of the Wilcoxon signed rank test for paired comparisons of blood flow, glucose uptake, and lactate production. \(P < 0.05\) (2-tailed) was considered statistically significant. When multiple comparisons were performed, analysis of variance was used. The StatView (version 4.0) program was used in the Macintosh system for all analyses.

**RESULTS**

**Resting basal non-insulin-stimulated state.** The arterial plasma glucose concentration in the basal state (7.7 ± 0.2 mM) was significantly greater than the estimated interstitial glucose level in muscle (6.1 ± 0.2 mM, \(P < 0.001\)). However, the mean plasma lactate concentration in the basal state did not differ from the estimated interstitial lactate concentration (Table 1). The estimated interstitial concentrations of glucose and lactate were determined by using the equilibrium (20) and internal reference calibration techniques (21) and were found to be similar (Table 1). The mean basal plasma insulin concentration was determined to be 19.8 ± 1.5 μU/ml. The microdialysate levels of insulin were below the detectable limit (2 μU/ml of dialysate insulin or ~10 μU/ml of interstitial insulin) of the analytic methods that were used.

**Effects of insulin infusion and electrical stimulation.** During the steady-state (90 min) hyperinsulenic clamping plasma conditions, insulin concentrations

<table>
<thead>
<tr>
<th>Table 1. Calibration of microdialysis catheters by “equilibration” and “internal reference” techniques</th>
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<td><strong>Glucose</strong></td>
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<tr>
<td><strong>Equilibration technique</strong></td>
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<tr>
<td>Recovery</td>
</tr>
<tr>
<td>Estimated interstitial concentration, mM</td>
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<tr>
<td>Plasma concentration, mM</td>
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Values are means ± SE from 12 rats (24 legs). *P < 0.01, †P < 0.001 vs. interstitial concentration.

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were kept at 247 ± 21 μU/ml. The mean glucose infusion rate during the last 60 min of the insulin infusion was 0.7 ± 0.1 mmol·kg⁻¹·min⁻¹, whereas the plasma glucose concentration during the clamp was 7.1 ± 0.1 mM. Although the interstitial glucose concentration during PSL (6.7 ± 0.3 mM) did not differ from the average plasma concentration, the interstitial glucose concentration of the resting leg (5.8 ± 0.2 mM) was significantly lower than the plasma concentration (P < 0.05; Fig. 2A).

In the basal state, the arterial-interstitial (A-I) concentration difference of glucose was 1.6 ± 0.3 mM (P < 0.01). During insulin infusion, the A-I concentration difference of glucose decreased and became statistically nonsignificant in PSL muscles (0.4 ± 0.6 mM) but was unaltered in resting muscles (1.3 ± 0.3 mM, P < 0.05; Fig. 2A).

The interstitial lactate concentrations of the PSL (P < 0.001) and resting (P < 0.05) muscles were significantly greater than the average plasma lactate concentration (Fig. 2B) during insulin infusion. Moreover, the interstitial lactate concentration in PSL muscle (4.6 ± 0.39 mM) was roughly twice that in the resting muscle (2.5 ± 0.5 mM, P < 0.05).

In the basal state, no significant A-I concentration differences of lactate were found. However, during insulin infusion, the A-I concentration differences of lactate increased significantly in both legs, the amplitude of the change being higher (2.8 ± 0.5 mM, P < 0.01) in PSL than in resting legs (0.7 ± 0.4 mM, P < 0.05; Fig. 2B).

The interstitial insulin concentrations were roughly equal in the PSL and resting muscles (161 ± 22 and 148 ± 14 μU/ml, not significantly different; Fig. 2C). The A-I concentration difference of insulin during the insulin infusion did not differ between PSL (86 ± 7 μU/ml) and resting muscles (100 ± 8 μU/ml; Fig. 2C). Relative microdialysis recovery monitored according to the internal standard technique was unchanged throughout the study (not shown).

Blood flow. Blood flow was significantly increased in all the moving muscles, including the PSL quadriceps muscle, that were studied during the hyperinsulinemic-euglycemic clamp relative to resting muscles. The mean blood flow in quadriceps muscle was 17 ± 4 and 34 ± 6 ml·100 g⁻¹·min⁻¹ (P < 0.05) in control and electrically stimulated legs, respectively (Table 2).

![Fig. 2](image-url)

Fig. 2. A: glucose concentration in plasma and interstitial fluid in medial femoral muscles during basal and insulin infusion conditions (euglycemic-hyperinsulinemic clamp, 10 mU·kg⁻¹·min⁻¹) and during passive shortening and lengthening (PSL). Values are means ± SE; n = 8–12. *P < 0.05, **P < 0.01 vs. plasma. B: lactate measurements in experiments depicted in A. Values are means ± SE; n = 8–12. *P < 0.05, **P < 0.01 vs. plasma. †P < 0.05 vs. right leg. C: insulin concentrations in plasma and interstitial fluid. Values are means ± SE; n = 8–12. ***P < 0.001 vs. plasma.
DISCUSSION

The data presented here demonstrate, for the first time, reciprocal changes in lactate and glucose concentration gradients over the capillary wall during PSL. Furthermore, measurement of insulin in dialysates showed no evidence of changes in insulin delivery to the interstitial fluid during these movements.

The microdialysis technique used in this study was calibrated by using two different techniques: the equilibrium calibration method (20) and the internal calibration method (21). Values obtained from both of these methods were similar, and regression analyses indicated a strong correlation between data generated by the two techniques (Table 1). Furthermore, the fractional outflow of an internal standard (not shown) and the recovery data (Table 1) indicated that the microdialysis technique did not affect the interstitial concentration or the blood flow in muscle tissue during the study. Thus it may be concluded that the concentration gradients that were studied during insulin infusion and electrical stimulation were not affected by any factors other than the rate of cellular uptake/release, capillary diffusion capacity, and blood flow.

Data from previous studies involving subcutaneous adipose tissue have shown that microdialysis calibration with an internal reference may lead to an overestimation of the interstitial concentration of glucose because of an accumulation of reference compound near the catheter (21). However, the present finding of the same results from microdialysis calibration with an internal reference and equilibration calibration indicates that microcirculation near the catheter was sufficient to prevent reference accumulation, thus justifying the use of the internal reference calibration technique in rat muscle tissue.

Resting state. The data obtained from resting muscle confirm that glucose concentration is lower in the interstitial muscle than in arterial plasma (7, 24) (Fig. 2A). The capillary wall thus constitutes a functional diffusion barrier for glucose uptake in muscle during fasting and after oral glucose (24) and also during insulin infusion (the present study). The insulin-stimulated increase of blood flow in the skeletal muscle could be brought about by an increase in the flow rate without a concomitant change in muscle blood volume and/or by recruitment of capillaries (25). In a previous microdialysis study (24), we showed that the glucose utilization in muscle is enhanced and the muscle blood flow is increased after an oral glucose load. Despite this increase in blood flow, the arterial interstitial glucose concentration difference is increased. This implies that the increased glucose consumption in the muscle cells after oral glucose leads to an increased glucose gradient over the capillary wall as a result of the enhanced cellular uptake and the metabolism of glucose.

The presence of an A-I concentration difference allows for calculation of the rate of glucose uptake according to Fick’s principle (13, 24): 

$$\text{GU} = (1 - A) \times (1 - e^{-PS/PS}) \times BF$$

where GU is glucose uptake rate, A is arterial blood glucose concentration, I is interstitial glucose concentration, PS is permeability-surface area product (a marker for the number of recruited capillaries), Q is plasma flow rate, and BF is blood flow. PS is assumed to be 5 ml·100 g⁻¹·min⁻¹ for glucose in the resting state (4) and ~10 ml·100 g⁻¹·min⁻¹ in the contracting muscle (27). Application of the above formula then gives an estimated glucose uptake rate of ~10 μmol·100 g⁻¹·min⁻¹ in the femoral muscles during insulin infusion, in agreement with earlier data obtained in arteriovenous difference and perfusion studies in the leg (29, 30).

In the resting state, the muscular, interstitial lactate concentration in the femoral muscle was not different from the arterial lactate concentration (Fig. 2B). In contrast to the present data, the interstitial lactate concentration has been demonstrated to be higher than the arterial lactate concentration in resting gastrocnemius muscle (3). However, results presented by Okuda et al. (26) from the medial thigh muscles indicated that interstitial and arterial lactate were equal in the basal state. Data from different muscle groups may differ in this respect because of regional differences in muscle fiber composition and blood flow as well as in capillary diffusion capacity. In the present work, lactate production could not be estimated by using the above equation, because the capillary diffusion was not rate limiting for lactate release from muscle in the basal state (24).

Stimulation by insulin increased lactate production, which resulted in a significant increase in the interstitial lactate concentration compared with the plasma concentration, which is in accordance with previous data (32). In this insulin-stimulated state, then, capillary diffusion should be regarded as partly rate limiting for lactate release.

PSL. This study was designed to investigate the effects of PSL in the quadriceps muscle through stimulation of the sciatic nerve, which induces active contractions of the flexor groups. By using this approach, the observed changes in glucose metabolism should be regarded as resulting from the activation of the non-

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### Table 2. Blood flow in skeletal muscles during hyperinsulinemic-euglycemic clamp

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<tr>
<th></th>
<th>Tibialis Anterior</th>
<th>EDL</th>
<th>Gastrocnemius</th>
<th>Soleus</th>
<th>Plantaris</th>
<th>Quadriceps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Red</td>
<td></td>
<td></td>
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<tr>
<td>PSL</td>
<td>115 ± 22†</td>
<td>127 ± 33†</td>
<td>52 ± 7†</td>
<td>61 ± 11*</td>
<td>68 ± 14*</td>
<td>70 ± 8‡</td>
</tr>
<tr>
<td>Resting leg</td>
<td>30 ± 7</td>
<td>32 ± 10</td>
<td>19 ± 5</td>
<td>24 ± 7</td>
<td>33 ± 9</td>
<td>23 ± 6</td>
</tr>
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</table>

Values are means ± SE in ml·100 g⁻¹·min⁻¹; n = 6. For hyperinsulinemic-euglycemic clamp, insulin was infused at 10 mU·kg⁻¹·min⁻¹. PSL, passive shortening and lengthening; EDL, extensor digitorum longus. †P < 0.05, ‡P < 0.01, §P < 0.001 vs. resting leg. 

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interstitial glucose, lactate, and insulin concentration

insulin-dependent signaling pathway as a means for stimulating glucose transport and metabolism (19) without direct interference from electrical stimulation or from increasing interstitial water pressure gradients induced by active contractions.

The interstitial muscle glucose concentration was higher in the PSL quadriceps muscle than in the quadriceps muscle of the control leg. This finding suggests that, in moving muscles, capillary recruitment, blood flow, and/or the permeability surface (27) was increased to a magnitude that was high enough to compensate for the increase in cellular glucose uptake and high enough to allow glucose to equilibrate over the capillary wall. In this situation, the capillary wall is no longer rate limiting for muscle glucose uptake. Instead, a maximum concentration gradient of glucose was applied over the plasma membrane to drive glucose transport through facilitated diffusion.

Earlier studies (16, 30) demonstrated that increasing plasma glucose concentrations may enhance the blood flow, while the arteriovenous concentration difference of glucose remains constant, which may indicate that the increase in blood flow could explain the total increase in muscle glucose consumption in these subjects (16). In the present study, PSL produced a substantial increase in muscle blood flow that was enough to compensate for the increased tissue glucose uptake and to diminish the A-I concentration difference. In contrast, the interstitial lactate concentration in the PSL muscle was significantly higher than the concentration that was measured during the insulin infusion in the control resting leg or the plasma lactate concentration (Fig. 2B). It is thus clear that the increase in blood flow, which blunts the glucose gradient over the capillary wall during electrical stimulation and PSL movements, is not enough to prevent a concomitant increase in the lactate A-I concentration gradient. This indicates that the PSL of muscle partly switches the glucose metabolism to enhance glycolysis. Furthermore, this change in glucose metabolism is compatible with the theory that the increase in blood flow may be mediated by the accumulation of lactate or other vasoactive glucose metabolites. According to this theory, the increase in blood flow is regulated such that reciprocal changes in glucose and lactate concentration gradients over the capillary wall allow for autoregulation of glucose A-I concentration differences (8, 9).

Previous investigations, including measurements in lymph (35) and interstitial fluid (7, 31, 32), have shown that the interstitial concentration of insulin is 40–60% lower than the plasma concentration. Thus the capillary wall is rate limiting for the delivery of insulin to the muscle cells. The delivery rate per se is dependent on the blood flow rate and on the permeability of the capillaries. The capillary permeability is a function of the number of open capillary beds as well as the permeability of each capillary. The existence of a transendoctytic and regulated pathway for insulin has been demonstrated (14), but its physiological significance for the transcapillary insulin delivery is unclear (33). The interstitial concentration of insulin in muscle was not affected by the PSL (Fig. 2C). This finding is consistent with previous data which demonstrated that muscle contraction and the concomitant increase of blood flow only provide for an increase in the interstitial concentration of insulin in the presence of nonphysiologically high plasma insulin concentrations and when the transcapillary concentration gradient of insulin is high (7). Insulin delivery over the capillary wall is not readily increased by changes in blood flow due to the poor capillary permeability (4, 27, 31).

The design of the present investigation does not permit us to fully differentiate the effect of PSL movements from effects of insulin or other humoral factors. For obvious technical reasons, an insulin-free experiment could not be performed, and, furthermore, we wanted to study the transcapillary delivery of insulin during PSL. Therefore, passive muscle movements were induced in the insulin-stimulated state, and the effect should be considered as additional to insulin and other hormones.

In summary, the present data demonstrate that the capillary wall is rate limiting for glucose uptake in resting muscle during euglycemic clamp conditions but is not rate limiting for lactate release under these conditions. PSL results in elevated blood flow and glucose consumption with a shift in rate-limiting steps and an increase in lactate production. These data suggest that in PSL the capillary wall is rate limiting for delivery of lactate to the plasma but not for uptake of glucose into the muscle cell.

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