IGF-I increases forearm blood flow without increasing forearm glucose uptake

MERRI PENDERGRASS, ELISA FAZIONI, DARLENE COLLINS, AND RALPH A. DEFRONZO

Diabetes Division, Department of Medicine, University of Texas
Health Science Center, San Antonio, Texas 78284

Pendergrass, Merri, Elisa Fazioni, Darlene Collins, and Ralph A. DeFronzo. IGF-I increases forearm blood flow without increasing forearm glucose uptake. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E345–E350, 1998.—Decreased insulin-mediated muscle glucose uptake is a characteristic feature of non-insulin-dependent diabetes mellitus and other insulin-resistant states. It has been suggested that an impairment in the ability of insulin to augment limb blood flow, resulting in diminished glucose delivery to muscle, may contribute to this abnormality. In this study, we used human insulin-like growth factor (IGF) I in conjunction with the forearm balance technique to determine whether forearm glucose uptake could be stimulated by increasing blood flow without directly stimulating the intrinsic ability of the muscle to extract glucose. IGF-I was infused intra-arterially in healthy controls at a rate of either 0.4 µg·kg⁻¹·min⁻¹ (high IGF) or 0.04 µg·kg⁻¹·min⁻¹ (low IGF) for 140 min. With high IGF, forearm blood flow increased approximately twofold (34 ± 3 vs. 64 ± 8 ml·min⁻¹·l forearm volume⁻¹, P < 0.01), and arteriovenous glucose concentration difference (a-v difference) increased modestly (0.19 ± 0.05 vs. 0.31 ± 0.08 mM, P = 0.32), resulting in an increased forearm glucose uptake (6.4 ± 1.7 vs. 21.7 ± 7.4 µmol·min⁻¹·l forearm volume⁻¹, P = 0.09 vs. basal). With low IGF, forearm blood flow increased by 59% (29 ± 4 vs. 46 ± 9 ml·min⁻¹·l forearm volume⁻¹, P < 0.05) and was associated with a proportional decrease in the a-v difference (0.29 ± 0.04 vs. 0.18 ± 0.05 mM, P < 0.05). Forearm glucose uptake therefore was not significantly different from basal values (7.6 ± 0.6 vs. 6.9 ± 1.8 µmol·min⁻¹·kg⁻¹). These data demonstrate that increasing blood flow without increasing the intrinsic ability of the muscle to extract glucose does not increase forearm muscle glucose uptake.

insulin-like growth factor I; insulin resistance

DECREASED INSULIN-MEDIATED glucose uptake by skeletal muscle is a characteristic feature of type 2 diabetes mellitus and other insulin-resistant states (14). Theoretically, reduced glucose uptake could result from defects in either one or both of its components, glucose extraction and/or glucose delivery (48). Impaired glucose extraction consistently has been demonstrated in type 2 diabetes mellitus and obesity (8, 14, 17). At the cellular level, multiple defects in insulin-mediated glucose metabolism have been described, including impaired insulin receptor signal transduction and decreased glucose transport, glucose phosphorylation, glycogen synthesis, glycolysis, and glucose oxidation (14). More recently, it has been suggested that an impairment in the ability of insulin to augment limb blood flow, resulting in diminished glucose delivery, may contribute to the insulin resistance of type 2 diabetes mellitus (33), obesity (5, 32, 44), type 1 diabetes (4), and hypertension (3). However, this position has been challenged for a number of reasons. First, many studies have failed to demonstrate a vasodilatory effect of insulin on limb (6, 7, 11, 29, 31, 47), splanchnic (16), or renal (15, 43) blood flow. Moreover, when a vasodilatory effect of insulin has been demonstrated, it usually has been observed after prolonged insulin infusion (3–4 h) or with pharmacological doses of insulin (>100 µU/ml) (reviewed in Refs. 38 and 42). These results suggest that blood flow is not a primary regulator of insulin-stimulated muscle glucose uptake under physiological conditions. Second, impaired insulin-stimulated glucose uptake without corresponding impairments in blood flow has been demonstrated (7, 46). Third, some studies have demonstrated a normal increase in limb blood flow in insulin-resistant obese subjects even though insulin-mediated glucose uptake remained severely impaired (39, 19). Fourth, severe defects in insulin-stimulated glucose disposal persist when muscle tissues from obese and diabetic subjects are studied in vitro (23). Last, it is very difficult to conceptualize how vasodilatation (without recruitment of new capillary beds) could augment glucose uptake in the absence of any change in the energy needs of the cell.

One way to examine whether an increase in blood flow, per se, contributes to the insulin-mediated stimulation of glucose uptake is to increase blood flow to the muscle without enhancing its intrinsic ability to extract glucose. If an insulin-mediated increase in glucose delivery (accomplished solely by augmenting blood flow) contributes to muscle glucose utilization, other manipulations that increase glucose delivery (by augmenting blood flow) also should stimulate glucose uptake. In this study, we used human insulin-like growth factor (IGF) I in conjunction with the forearm balance technique to examine the separate effect of increased glucose delivery, independent of any change in the intrinsic ability of the muscle to extract glucose, on glucose uptake in healthy nondiabetic subjects. IGF-I is a polypeptide hormone that has dose structural and functional homology to insulin and has been shown to stimulate glucose uptake (9), although it is 10–15 times less potent than insulin in promoting glucose transport (22, 34, 40). IGF-I is also a potent stimulator of muscle blood flow (13, 26), having a much more pronounced effect than insulin on this parameter. Because of the differential dose-related action of IGF-I to enhance glucose uptake and to stimulate blood flow, we were able to augment blood flow by 60%, an increase comparable to that reported with insulin in some studies (2), without significantly affecting muscle glucose extraction, i.e., intrinsic activity. This study design allowed us directly to assess the effect of increased
blood flow on forearm muscle glucose uptake. Although IGF-I increased blood flow up to twofold, forearm glucose uptake did not increase, indicating that enhanced blood flow, per se, is not an independent regulator of muscle glucose uptake.

SUBJECTS AND METHODS

Subjects. Fourteen healthy volunteers each participated in one of two protocols. Clinical characteristics of the subjects are shown in Table 1. None of the volunteers had a family history of diabetes or clinical or laboratory evidence of systemic disease or were taking any medications. Subjects were instructed not to exercise on the day before the study and to eat a diet containing at least 200 g of carbohydrate for at least 3 days preceding the study. Body weight was stable in all subjects for at least 3 mo before the study. The purpose, nature, and potential risks of the study were explained to all subjects, and informed, written consent was obtained before their participation. The protocol was reviewed and approved by the Human Investigation Committee of the University of Texas Health Science Center in San Antonio, Texas.

Experimental design. All studies took place at the Clinical Research Center of the Audie L. Murphy Memorial Veterans Administration Hospital and began at 0800 after a 10- to 12-h overnight fast. After subjects arrived at the research unit, catheters were introduced percutaneously into the brachial artery and retrogradely into an ipsilateral deep forearm vein draining forearm muscle. All blood samples were obtained through these two catheters. The tip of the deep forearm vein catheter was advanced for a distance of 2 in. from the puncture site and could not be palpated in any of the subjects. Previous studies have documented that such catheter placement allows sampling of the muscle bed perfused by either the radial or the ulnar artery (12). Catheter patency was maintained by a slow infusion of normal saline. To exclude blood flow from the hand, a pediatric pharyngomonometric cuff was inflated around the wrist to 100 mmHg above the systolic pressure for 2 min before and during each venous sampling period. A third catheter was inserted into a contralateral arm vein for infusion of glucose.

After a 70-min basal period, IGF-I (Genentech, South San Francisco, CA) was infused locally into the brachial artery at a rate of 0.4 µg·kg⁻¹·min⁻¹ (low IGF, n = 7) or 0.04 µg·kg⁻¹·min⁻¹ (low IGF, n = 7) for 140 min. Arterial plasma glucose concentration was clamped at the basal level by a variable infusion of 20% glucose determined by a 5- to 10-min sample taken during the clamp according to the following formula:

\[ \text{blood glucose concentration} = \frac{\text{plasma glucose concentration} \times (1 - 0.3 \text{Hct})}{\text{Hct}} \]

where blood glucose concentration was estimated from plasma glucose concentration and the hematocrit (Hct) according to the following formula:

\[ \text{Blood concn} = (\text{plasma concn}) \times (1 - 0.3 \text{Hct}) \]

Forearm blood flow was measured by indocyanine green dye dilution in the deep vein according to the following formula:

\[ \text{Blood flow rate} = \frac{\text{dye infusion rate}}{(\text{deep vein dye concn})/(1 - \text{Hct})} \]

For forearm blood flow is expressed per liter forearm volume. Statistical analysis. All data are presented as means ± SE. All basal values are reported as means of the samples taken at the time points −70, −30, and −15 min. Test-period values for insulin and IGF-I levels are reported as the means of all samples taken during the IGF-I infusions. Test-period values for FFA levels are reported as the means of samples taken during the last hour of each study (time points 80, 100, and 140 min). Differences between the basal and test-period values were tested by the paired Student’s t-test.

RESULTS

Plasma IGF-I, insulin, and FFA concentrations. The effects of IGF-I infusion on plasma IGF-I, insulin, and FFA concentrations are shown in Table 2. The deep venous total IGF-I concentration increased from 117 ± 17 to 451 ± 68 ng/ml (P < 0.01) during high IGF and from 93 ± 9 to 136 ± 11 ng/ml (P < 0.001) during low IGF. Free IGF-I levels increased from undetectable in the basal state to 143 ± 42 ng/ml during high IGF and 8 ± 3 ng/ml during low IGF. Plasma insulin levels were unchanged in response to both high IGF and low IGF infusions. During high IGF, plasma arterial FFA concentration fell significantly (P < 0.01) but remained unchanged during the low IGF infusion.
Whole body glucose uptake and forearm blood flow, arterial venous glucose concentration difference, and glucose uptake. The glucose infusion rate required to maintain euglycemia was $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during high IGF and $1.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during low IGF.

Forearm blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{l forearm volume}^{-1}$), arterial venous glucose concentration difference, and forearm glucose uptake ($\text{mmol} \cdot \text{min}^{-1} \cdot \text{l forearm volume}^{-1}$) are shown in Figs. 1 (high IGF) and 2 (low IGF). Forearm blood flow increased approximately twofold after 140 min of the high IGF infusion ($34 \pm 6$ vs. $64 \pm 8 \text{ ml} \cdot \text{min}^{-1} \cdot \text{l forearm volume}^{-1}$, $P < 0.01$; Fig. 1). In response to high IGF, the arterial venous glucose concentration difference increased slightly in four subjects and decreased in three subjects. On average, the arterial venous glucose concentration difference increased slightly, although not significantly ($0.19 \pm 0.05$ vs. $0.31 \pm 0.08 \text{ mM}$, $P = 0.32$). Forearm glucose uptake rose notably from $6.4 \pm 1.7$ to $21.7 \pm 7.4 \text{ µmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{l forearm volume}^{-1}$ ($P = 0.09$ vs. basal).

Forearm blood flow increased by $\sim 59\%$ during the low IGF infusion ($29 \pm 4$ vs. $46 \pm 9 \text{ ml} \cdot \text{min}^{-1} \cdot \text{l forearm volume}^{-1}$, $P < 0.05$; Fig. 2). This increase in blood flow was associated with a $38\%$ decrease in arterial venous glucose concentration difference ($0.29 \pm 0.04$ vs. $0.18 \pm 0.05 \text{ mM}$, $P < 0.05$; Fig. 2). Because the increase in forearm blood flow was associated with a proportional decrease in arterial venous glucose concentration difference, forearm glucose uptake was not significantly different from basal values ($7.6 \pm 0.6$ vs. $6.9 \pm 1.8 \text{ µmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$).

**DISCUSSION**

We have shown that IGF-I, infused locally into the brachial artery at doses that increase blood flow by $59\%$, does not stimulate forearm muscle glucose uptake because of a proportional decrease in glucose extraction. Thus the average forearm glucose uptake after 140 min was not significantly increased from basal values. Thus the low-dose IGF-I infusion allowed us to completely dissociate the effects of IGF-I on blood flow and glucose metabolism in forearm tissues. In response to an isolated increase in forearm blood flow of $59\%$, a value similar to that reported for insulin (2), glucose extraction was not stimulated in any subject. The arterial venous glucose concentration difference fell in five subjects and remained unchanged in two subjects ($P < 0.05$). This resulted in no change in forearm blood flow.

**Table 2. IGF-I, insulin, and FFA concentrations**

<table>
<thead>
<tr>
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<th>High IGF</th>
<th>Low IGF</th>
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<tr>
<td></td>
<td>Basal</td>
<td>$0.04 \text{ µg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>Total IGF-I, ng/ml</td>
<td>$117 \pm 17$</td>
<td>$451 \pm 68^*$</td>
</tr>
<tr>
<td>Free IGF-I, ng/ml</td>
<td>$143 \pm 42^*$</td>
<td>$8 \pm 3^*$</td>
</tr>
<tr>
<td>Plasma insulin, pM</td>
<td>$22 \pm 6$</td>
<td>$42 \pm 7$</td>
</tr>
<tr>
<td>Arterial FFA, mM</td>
<td>$795 \pm 96$</td>
<td>$819 \pm 63$</td>
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Values are means $\pm$ SE. Where no value is given, concentration was undetectable. IGF-I, insulin-like growth factor I; FFA, free fatty acid. $^*P < 0.01$ vs. basal.

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**Fig. 1. Forearm blood flow, arterial venous glucose concentration difference (a-v difference), and forearm glucose uptake (FGU) during high insulin-like growth factor (IGF) infusion ($0.40 \text{ µg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ IGF-I). Data are presented as means $\pm$ SE.**

**Fig. 2. Forearm blood flow, a-v difference, and FGU during low IGF ($0.04 \text{ µg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ IGF-I). Data are presented as means $\pm$ SE.**
glucose uptake from basal values. These data demonstrate that increasing blood flow without increasing the intrinsic ability of the muscle to extract glucose does not increase forearm muscle glucose uptake. We therefore conclude that increased blood flow, per se, is not a primary regulator of glucose uptake.

Seven subjects received a brachial arterial IGF-I infusion that was 10-fold greater than during the low-dose IGF-I infusion. This infusion rate was chosen because it produces plasma free IGF-I levels that are known to increase the intrinsic activity of the muscle to extract glucose (26). Even at these high infusion rates, we failed to observe a significant rise (P = 0.09) in forearm glucose uptake because the marked vasodilatation (forearm blood flow increased 2.5-fold) offset the intrinsic ability of muscle to extract glucose and a consistent increase in arteriovenous glucose concentration difference did not occur. In fact, in three subjects, the arteriovenous glucose concentration difference actually decreased. Thus both the high- and the lode-dose IGF-I infusion studies are consistent and demonstrate that an increase in blood flow alone is not sufficient to augment forearm muscle glucose uptake.

The results of this study are in agreement with results reported by Fryburg (26), who primarily was interested in the effect of IGF-I on amino acid metabolism. This investigator infused IGF-I at 0.03 µg·kg⁻¹·min⁻¹, a dose similar to the low dose used in our study. Although blood flow increased by 44% (similar to the increase in our study) after 3 h of IGF-I infusion and by 76% after 6 h, glucose extraction was unchanged and there was no change in forearm glucose uptake. Our study more specifically addresses the issue of whether increased blood flow contributes to insulin-mediated glucose uptake. First, measurements were made after 140 min, which is a more physiological period of time (38, 42) than the study of Fryburg. Second, blood flow was raised by 59%, an amount comparable to that reported for insulin in some studies (2).

Several recent studies have also used vasodilators to examine whether muscle glucose uptake can be increased simply by increasing blood flow (36, 38, 41). Pöyry et al. (41) stimulated forearm blood flow 4.5-fold with the use of acetylcholine. Increased blood flow was associated with a decrease in arteriovenous glucose concentration difference of ~73%, and, as a result, glucose uptake remained unchanged. Pöyry et al. also noted reciprocal decreases in glucose extraction when blood flow was increased by sodium nitroprusside. Neither acetylcholine nor sodium nitroprusside is believed to have any effects on glucose metabolism. Similar results have been provided by Natali et al. (36), who used adenosine to increase blood flow by 100% yet observed no rise in forearm glucose uptake. The study of Nuutila et al. (38) is of particular interest. Leg blood flow and leg glucose uptake were measured using positron emission tomography. They found that when blood flow was increased 60% with the use of bradykinin, leg glucose uptake remained unchanged. Taken collectively, these studies are consistent with the findings we report here for IGF-I. When muscle blood flow is increased with vasodilators, there is a reciprocal decrease in glucose extraction. Consequently, muscle glucose uptake remains unchanged. Thus increasing blood flow without simultaneously increasing the intrinsic ability of the muscle to extract glucose does not stimulate muscle glucose uptake.

Some investigators have suggested that the overall action of insulin to enhance muscle glucose disposal is related specifically to its vasodilatory effect (2). In addition to the findings of our study and the evidence reviewed above (38, 41, 46), several lines of evidence indicate that, under physiological conditions, blood flow is not a regulator of muscle glucose uptake. First, increased glucose uptake in response to insulin infusions that result in physiological levels of hyperinsulinemia has consistently been demonstrated without any increase in muscle blood flow (6, 7, 11, 29, 31, 47). Under more physiological conditions, i.e., ingestion of a mixed meal, leg blood flow in healthy volunteers is not significantly increased over basal values, even though muscle glucose uptake is increased four- to fivefold in response to the accompanying hyperinsulinemia (35). A normal increase in forearm glucose uptake also has been demonstrated during the oral glucose tolerance test without any change in blood flow from baseline (25, 30). Conversely, the blood flow responses to an oral glucose load in obese subjects have been reported to be increased relative to controls (25). Further evidence that blood flow does not regulate glucose uptake under physiological conditions is provided by studies examining glucose uptake in insulin-resistant individuals. Impaired insulin-mediated glucose uptake in these studies repeatedly has been shown to occur without any impairment in muscle blood flow (6, 7, 16, 19, 39, 46). Nevertheless, it is possible that in some specific situations, such as during exercise (20, 45) and in aerobically trained athletes (21, 24, 28), fuel requirements of the muscle are provided by increases in both glucose extraction and glucose delivery.

In conclusion, our results demonstrate that when IGF-I is infused at a dose that is sufficient to increase forearm blood flow by 59%, an amount comparable to that reported for insulin in some studies, there is a reciprocal decrease in glucose extraction. The result is no net increase in glucose uptake. Glucose uptake is increased only when IGF-I is infused at a high enough dose to stimulate glucose extraction as well as delivery. Thus blood flow, per se, does not appear to be a primary regulator of muscle glucose uptake.

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Address for reprint requests and present address of M. Pendergrass: Tulane Univ., School of Medicine, Dept. of Medicine SL53, 1430 Tulane Ave., New Orleans, LA 70112-2699.

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