Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans

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Baron, A. D., G. Brechtel, P. Wallace, and S. V. Edelman. Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. Am. J. Physiol. 255 (Endocrinol. Metab. 18): E769-E774, 1988.—In vivo glucose uptake can occur via two mechanisms, namely, insulin-mediated glucose uptake (IMGU) and non-insulin-mediated glucose uptake (NIMGU). Although the principal tissue sites for IMGU are skeletal muscle, the tissue sites for NIMGU at a given serum glucose concentration are not known. To examine this issue, rates of whole body glucose uptake (Rd) were measured at basal and during glucose clamp studies performed at euglycemia (~90 mg/dl) and hyperglycemia (~220 mg/dl) in six lean healthy men. Studies were performed during hyperinsulinemia (~70 μU/ml) and during somatostatin-induced insulinopenia to measure IMGU and NIMGU, respectively. During each study, leg glucose balance (arteriovenous catheter technique) was also measured. With this approach, rates of whole body skeletal muscle IMGU and NIMGU can be estimated, and the difference between overall Rd and skeletal muscle glucose uptake represents non-skeletal muscle Rd. The results indicate that ~20% of basal Rd is into skeletal muscle. During insulinopenia ~86% of body NIMGU occurs in non-skeletal muscle tissues at euglycemia. When hyperglycemia was created, whole body NIMGU increased from 128 ± 6 to 213 ± 18 mg/min (P < 0.01); NIMGU into non-skeletal muscle tissues was 134 ± 11 and 111 ± 6 mg/min at hyperglycemia and euglycemia, respectively, P = NS. Therefore, virtually all the hyperglycemia induced increment in NIMGU occurred in skeletal muscle. During hyperinsulinemia, IMGU in skeletal muscle represented 75 and 95% of body Rd at euglycemia and hyperglycemia, respectively. In conclusion, the great majority of basal Rd is non-insulin mediated and occurs in non-skeletal muscle tissues, chiefly the central nervous system (CNS). Since CNS Rd saturates at physiological glucose levels, hyperglycemia increases NIMGU in skeletal muscle but not in the CNS.

MATERIALS AND METHODS

Materials

Porcine monocomponent insulin was generously supplied by Dr. Ronald Chance of Eli Lilly (Indianapolis, IN); 125I-labeled insulin and D-[3-3H]glucose were purchased from New England Nuclear (Boston, MA); bovine serum albumin (BSA; fraction V) was obtained from Armour Pharmaceutical (Chicago, IL); guinea pig anti-insulin antibody was kindly supplied by Dr. Edward Arquilla (Irvine, CA); and somatostatin (SRIF; cyclic form) was purchased from Bachem (Torrance, CA).

Subjects

The study group consisted of six healthy nonobese men. All had a normal 75 g load oral glucose tolerance test, as defined by the criteria of the National Diabetes Data Group (22). The mean ± SD age of the study group was 31 ± 5 yr and the mean ± SD weight and body mass index was 70 ± 3 kg and 22 ± 1, respectively. The study protocol was reviewed and approved by the Committee on Human Investigation of the University of California.
at San Diego. After informed consent was obtained, all subjects were admitted to the Veterans Administration Medical Center's Special Diagnostic and Treatment Unit (La Jolla, CA). While hospitalized they remained active to approximate their prehospital exercise level. All subjects were chemically euthyroid, and no subject had a concurrent disease or was ingesting pharmacological agents known to affect carbohydrate or insulin metabolism.

Diet

All subjects were fed a weight maintenance (−32 kcal·kg\(^{-1}\)·day\(^{-1}\)) diet with three divided feedings containing one-, two-, and two-fifths of the total daily calories, given at 0800, 1200, and 1700, respectively. The diet contained 50% carbohydrate, 20% fat, and 30% protein. All subjects ate this diet for at least 48 h before any studies were performed.

Protocol

Each subject underwent two randomly sequenced studies, each performed approximately a month apart after an overnight fast. **Study 1** was designed to measure basal whole body glucose turnover \((d-[3^3H]glucose)\) and basal leg glucose uptake (arteriovenous femoral catheterization technique) as well as whole body and leg NIMGU at euglycemia and hyperglycemia (−220 mg/dl). To accomplish this \(d-[3^3H]glucose\) was infused through a catheter placed in an antecubital vein starting at 6:30 A.M. At ~8:00 A.M. catheters were inserted in the right femoral artery and vein (see technique below). At least 30 min after the femoral catheters were inserted, arterial blood was obtained at 5-min intervals over a 20-min period for the determination of serum glucose, plasma specific activity, and serum insulin and C-peptide levels. Simultaneously femoral venous blood was obtained for the determination of serum glucose levels. Basal leg blood flow was also determined (see technique below). After the basal measurements were obtained, an infusion of somatostatin (SRIF), 0.16 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\), was started at time 0 to suppress endogenous insulin secretion, and the arterial serum glucose level was held at the basal level utilizing the glucose clamp technique (10). Since the biological effect of insulin to stimulate \(R_d\) decays with an apparent half time \((t_{1/2})\) of 40 min (15), it follows that after 120 min of severe SRIF-induced insulinopenia iso-topically determined \(R_d\) and leg glucose uptake represent NIMGU. Therefore, NIMGU at euglycemia was measured from 120 to 160 min; subsequently the SRIF infusion rate was gradually raised to 0.29 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\); the serum glucose level was raised to a mean level of ~220 mg/dl, clamped at that level for an additional 40 min and NIMGU measurements were repeated.

**Study 2** was designed to measure whole body and leg IMGU. To accomplish this, insulin (40 mU·m\(^{-2}\)·min\(^{-1}\)) was infused starting at 7:00 A.M. through a catheter inserted in an antecubital vein, and the serum glucose was clamped at the basal level. Because the biological effect of insulin to fully activate glucose disposal occurs with a \(t_{1/2}\) of ~40 min in normal humans (23), the hyperinsulinemic euglycemic clamp was maintained for at least 160 min before any measurements were performed. Steady-state insulin action was considered achieved when the exogenous glucose infusion rate and the arterial difference for glucose were stable over 30 min. All subjects achieved steady-state insulin action by 160 min of insulin infusion. Therefore, glucose turnover data were obtained from 160 to 200 min at euglycemia and from 260 to 300 min at hyperglycemia. In this condition infusion of \(d-[3^3H]glucose\) was not necessary since hepatic glucose production is completely suppressed during the combination of hyperinsulinemia and somatostatin-induced glucagon deficiency. Thus whole body glucose disposal was taken as the exogenous infusion rate corrected for the change in glucose mass in a distribution volume of 19% body weight. Rates of IMGU were calculated as the difference between the rate of insulin-stimu-lated \(R_d\) and the rate of NIMGU measured at the same serum glucose level (i.e., IMGU equals \(R_d\) minus NIMGU).

**Leg Glucose Balance Technique**

With this technique a 16-gauge Teflon catheter is inserted percutaneously (modified Seldinger technique) in the femoral artery 2.3 cm below the inguinal ligament and advanced in a retrograde fashion 4–6 cm for the sampling of arterial blood. Similarly, in the ipsilateral leg a double-lumen 5-French thermodilution catheter for the measurement of leg blood flow and blood drawing is advanced in a cephalad direction through a 5-French sheath inserted in the femoral vein into the external iliac vein with the tip of the catheter peripheral to the end of the internal iliac vein. The thermodilution catheter (American Edwards, Santa Ana, CA), the design of which has been previously validated (13, 14), is constructed in such a way that the indicator (cold saline) achieves instantaneous mixing (13, 14) and therefore able to measure flow in a single vessel. An Edwards cardiac output computer (model 9510) was connected to the thermistor wire to integrate indicator dilution curves and thus provide a virtually instantaneous bedside measure of leg blood flow. Leg glucose uptake was calculated by the Fick principle (27) as the product of the arteriovenous difference for plasma glucose and the leg plasma flow \((\text{plasma flow} = \text{blood flow} \times \left(1 - \text{hematocrit}\right))\).

Measurements of blood flow (5 determinations) were performed at the beginning and end of the euglycemic and hyperglycemia plateaus. The mean of 10 flow measurements at each glycemic plateau was taken as the representative value. At each glycemic plateau, simultaneous determinations of arteriovenous serum glucose concentration were obtained at 5-min intervals during the period between blood flow measurements; these values were meaned, and the mean value was taken as the representative arteriovenous difference. Leg volume was measured by the water displacement technique (8, 9) by inserting the leg into a water-filled cylinder up to the ischial tuberosity. Leg muscle mass was calculated assuming that ~65% of leg volume is muscle (17), and glucose uptake into whole body muscle was calculated with the assumptions that in a lean 70-kg man the muscle...
mass is \( \sim 30 \) kg \((1)\) and that glucose uptake in leg muscle is representative of \( R_d \) in the whole body muscle. The mean leg muscle mass for the study group was \( 7.0 \pm 0.2 \) kg.

Rates of Glucose Appearance \((R_a)\) and \( R_d \)

\( R_a \) and \( R_d \) were measured in the basal state and during each of the glucose clamp studies by infusion of D-[\( 3^3\text{H}\)]glucose in a primed continuous manner. With this technique, \( 60 \mu\text{Ci} \) of tracer was injected as a bolus dose, followed by a continuous infusion at the rate of \( 0.60 \mu\text{Ci}/\text{min} \). The tracer was allowed to equilibrate for 120 min, and glucose specific activity was measured for the subsequent 20-min period at 5- to 10-min intervals. \( R_a \) and \( R_d \) were calculated using the Steele equation \((26)\) assuming steady-state conditions. In the basal state \( R_a \) equals \( R_b \), and \( R_a \) represents the rate of hepatic glucose output \((HGO)\). During the clamp studies, blood samples were obtained at 10-min intervals for determination of both the serum glucose concentration and plasma specific activity. \( R_a \) and \( R_d \) were calculated with the Steele equations in their modified derivative form, since the tracer exhibits non-steady-state kinetics under these conditions \((7)\). Since the studies were performed at a serum glucose level of \( \sim 200 \) mg/dl, the values for \( R_d \) were corrected for urinary glucose loss to reflect the actual rate of endogenous glucose disposal. Rates of HGO were calculated by subtracting the rate of exogenous glucose infused from the isotopically measured \( R_a \).

**Analytical Methods**

Blood for serum glucose determinations was drawn, put in untreated polypropylene tubes, and centrifuged using a Beckman microfuge (Beckman Instruments, Spinco Division, Palo Alto, CA). The glucose concentration of the supernatant was then measured by the glucose oxidase method using a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Blood for determination of serum insulin levels and plasma glucose specific activity was collected in untreated and treated tubes, respectively, and allowed to clot. The specimens were spun, and the supernatant was removed and stored at \(-20^\circ\text{C}\). Serum insulin levels were measured by double-antibody radioimmunoassay \((RIA)\) \((11)\); the detection limits of the insulin assay was \( 4 \mu\text{U}/\text{ml} \). All values reported as \( < 4 \mu\text{U}/\text{ml} \) were treated as representing \( 4 \mu\text{U}/\text{ml} \). Blood for determination of plasma C-peptide levels was collected in tubes containing EDTA and aprotinin \((\text{Trasylol} \times 500 \text{ KIU/ml}) \) and chilled, and the plasma was separated and frozen. The C-protein \( RIA \) \((20)\) was kindly performed in Dr. Arthur Rubenstein’s laboratory \((\text{Chicago, IL})\). Plasma free fatty acids \((FFA)\) levels were measured by the method of Itaya and \( Vi \) \((18)\).

**Data Analysis**

All calculations and analyses were performed using the CLINFO data base management and analysis program \((\text{Bolt, Beranek, and Newman, Cambridge, MA})\) operational at the University of California, San Diego, General Clinical Research Center. The data are presented as the mean \( \pm \) SE unless otherwise indicated. Statistical analysis was done using Student's two-tailed \( t \) test for paired and unpaired data as indicated.

**RESULTS**

**Studies of NIMGU**

**Hormone and metabolic data** \((Table 1)\). The basal serum glucose level was \( 94 \pm 2 \) mg/dl; during euglycemic insulinopenia the serum glucose level was \( 88 \pm 2 \) mg/dl and not different from basal, \( P = \text{NS} \). During SRIF infusion the basal serum insulin level fell from \( 6.3 \pm 1.1 \mu\text{U}/\text{ml} \) to below the detection limits of the assay; similarly the basal plasma C-peptide level was suppressed by 90% at both euglycemia and hyperglycemia. The basal leg plasma flow was \( 2.4 \pm 0.3 \) dl/min and was not changed during insulinopenia at both glucose levels. The serum FFA level rose from a basal value of \( 0.45 \pm 0.03 \) to 0.81 \pm 0.07 mM, \( P < 0.001 \) during SRIF-induced insulinopenia.

\( R_d \) \((Table 1)\). Whole body basal \( R_d \) was \( 146 \pm 5 \) mg/min. Whole body \( R_d \) during euglycemic insulinopenia was \( 128 \pm 6 \mu\text{g} / \text{min} \) \((P < 0.05 \text{ vs. basal} R_d)\); thus \( \sim 83 \% \) of basal \( R_d \) is non insulin mediated. Under basal conditions \((6 \mu\text{U}/\text{ml} \text{insulin present})\) the arteriovenous difference for glucose across the leg was \( 2.6 \pm 0.4 \) mg/dl; since basal leg plasma flow was \( 2.4 \pm 0.3 \) dl/min, leg muscle mass was \( 7.0 \pm 0.2 \) kg, and whole body muscle mass was \( 30 \) kg, this resulted in an estimate of basal glucose uptake into muscle of \( 29 \pm 8 \mu\text{g} / \text{min} \) or \( 20 \% \) of overall basal \( R_d \). Under euglycemic insulinopenia the arteriovenous difference fell from the basal value in all but one subject to a mean level of \( 1.6 \pm 0.3 \mu\text{g} / \text{dl} \) \((P = \text{NS} \text{ vs. basal})\) and resulted in only \( 17 \pm 3.5 \mu\text{g} / \text{min} \) \((P = \text{NS} \text{ vs. basal})\) or \( \sim 13 \% \) of whole body NIMGU into muscle. Therefore, roughly half of basal glucose uptake into muscle is non insulin mediated and half is insulin mediated. Conversely \( \sim 87 \% \) of NIMGU at euglycemia or \( 128 \pm 6 \mu\text{g} / \text{min} \) is occurring in tissue other than muscle. When the prevailing serum glucose level was increased to \( \sim 200 \) mg/dl, the glucose arteriovenous difference increased to \( 7.35 \pm 0.83 \mu\text{g} / \text{dl} \) \((P < 0.01 \text{ vs. euglycemia})\), and this resulted in an increase in whole body NIMGU to \( 213 \pm 18 \mu\text{g} / \text{min} \) \((P < 0.01 \text{ vs. euglycemia})\) and about a fivefold increase in whole body muscle NIMGU from \( 17 \pm 3.5 \) to \( 81 \pm 12 \mu\text{g} / \text{min} \), \( P < 0.01 \). NIMGU into nonmuscle tissue at hyperglycemia was \( 134 \pm 11 \mu\text{g} / \text{min} \), a value not different from nonmuscle NIMGU at euglycemia \((111 \pm 6 \mu\text{g} / \text{min})\). Therefore, increasing the prevailing serum glucose concentration from euglycemia to hyperglycemia had no effect to increase NIMGU in nonmuscle tissues but a marked effect to increase NIMGU in skeletal muscle.

**Studies of IMGU**

**Hormone and metabolic data** \((Table 2)\). During insulin infusion the steady-state serum insulin level was \( \sim 70 \mu\text{U}/\text{ml} \) at both serum glucose levels. The serum glucose level was clamped at \( 81 \pm 1 \mu\text{g} / \text{dl} \), which is a level slightly lower than during euglycemic insulinopenia, \( P <
TABLE 1. Hormone and metabolic data, leg plasma flow, and glucose uptake rates during basal and insulinopenia (NIMGU) at euglycemia and hyperglycemia

<table>
<thead>
<tr>
<th></th>
<th>Arterial Serum Glucose, mg/dl</th>
<th>Serum Insulin, μU/ml</th>
<th>Plasma C-Peptide, pmol/ml</th>
<th>Leg Plasma Flow, dl/min</th>
<th>Femoral Arteriovenous Glucose Difference, μg/dl</th>
<th>Leg Muscle Glucose Uptake, mg·kg⁻¹·min⁻¹</th>
<th>Whole Body Glucose Uptake, mg/min</th>
<th>Whole Body Muscle Glucose Uptake, mg/min</th>
<th>Whole Body Glucose Uptake Into Skeletal Muscle, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>94±2</td>
<td>6.3±1</td>
<td>0.36±0.04</td>
<td>2.4±0.3</td>
<td>2.6±0.4</td>
<td>0.97±0.27</td>
<td>146±5</td>
<td>29±8</td>
<td>20±5</td>
</tr>
<tr>
<td>Euglycemic hypoinsulinemia</td>
<td>88±2</td>
<td>&lt;4†</td>
<td>0.37±0.005†</td>
<td>2.4±0.3</td>
<td>1.6±0.3</td>
<td>0.56±0.11†</td>
<td>128±6*</td>
<td>17±5†</td>
<td>13.2±3*</td>
</tr>
<tr>
<td>Hyperglycemic hypoinsulinemia</td>
<td>207±8</td>
<td>&lt;4†</td>
<td>0.030±0.000†</td>
<td>2.6±0.3</td>
<td>7.4±0.8†</td>
<td>2.74±0.35†</td>
<td>213±18†</td>
<td>81±12†</td>
<td>38±3†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6 subjects. NIMGU, non-insulin-mediated glucose uptake. * P < 0.05, † P < 0.01 vs. basal; § P < 0.01 vs. insulinopenia.

TABLE 2. Hormone and metabolic data, leg plasma flow, and glucose uptake rates during hyperinsulinemia (IMGU) at euglycemia and hyperglycemia

<table>
<thead>
<tr>
<th></th>
<th>Arterial Serum Glucose, mg/dl</th>
<th>Serum Insulin, μU/ml</th>
<th>Leg Plasma Flow, dl/min</th>
<th>Femoral Arteriovenous Glucose Difference, μg/dl</th>
<th>Leg Muscle Glucose Uptake, mg·kg⁻¹·min⁻¹</th>
<th>Whole Body Glucose Uptake, mg/min</th>
<th>Whole Body Muscle Glucose Uptake, mg/min</th>
<th>Whole Body Glucose Uptake Into Skeletal Muscle, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycemic hyperinsulinemia</td>
<td>81±1</td>
<td>80±3</td>
<td>3.7±1.0</td>
<td>25±2</td>
<td>13.8±4.2</td>
<td>536±49</td>
<td>409±122</td>
<td>74±15</td>
</tr>
<tr>
<td>Hyperglycemic hyperinsulinemia</td>
<td>219±9†</td>
<td>69±3</td>
<td>5.7±1.2†</td>
<td>60±7†</td>
<td>47.4±9.8†</td>
<td>1,518±152</td>
<td>1,395±281</td>
<td>95±17†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6 subjects. IMGU, insulin-mediated glucose uptake. † P < 0.01 vs. euglycemia.

DISCUSSION

The present study was undertaken to examine the relative proportion of NIMGU and IMGU into body skeletal muscle vs. non-skeletal muscle tissues. The results indicate that under basal conditions ~20% of whole body Rd occurs in skeletal muscle and that about one-half of basal skeletal muscle glucose uptake is NIMGU and about one-half IMGU. Thus at euglycemia 74± 15% of whole body IMGU is into muscle. During hyperglycemic hyperinsulinemia the glucose disposal rate was 1,518± 152 mg/min in whole body and 1,395± 281 in whole body muscle. Therefore, at hyperglycemia 95± 17% of whole body IMGU is into muscle.

FIG. 1. Absolute and relative rates of non-insulin-mediated glucose uptake (NIMGU) at euglycemia (left) and hyperglycemia (right). Calculated rates of skeletal muscle (♂) and non-skeletal muscle (♀) NIMGU are shown. ----, Probable values of NIMGU into central nervous system (CNS) and into non-CNS, non-skeletal muscle tissues.

NIMGU. Furthermore, whole body skeletal muscle accounted for 75% of the increment in whole body NIMGU observed when the prevailing serum glucose level was increased from euglycemia to hyperglycemia. Thus at euglycemia virtually all NIMGU occurs in non-skeletal muscle tissue; as the prevailing serum glucose level is raised, the resultant increment in NIMGU is small (25%) in non-skeletal muscle but relatively large (75%) in skeletal muscle (Fig. 1). We have previously reported that rates of NIMGU are elevated in hyperglycemic type 2 diabetic subjects (2), the current data support the notion that these elevated rates of NIMGU can be accounted for by increased rates of NIMGU in skeletal muscle. A number of studies (6, 16, 25) have estimated that...
CNS glucose uptake represents 50–80% of basal whole body glucose disposal after an overnight fast. Since NIMGU accounts for ~80% of basal whole body $R_d$, if one assumes that basal CNS glucose uptake is 65% of basal whole body $R_d$ it follows that the CNS accounts for ~80% of basal whole body NIMGU. Therefore 20% of basal NIMGU occurs in tissues other than the CNS, such as blood cells, peripheral nerves, and other non insulin-sensitive tissues, but a small amount (~13%) is also likely to occur in skeletal muscle, an insulin-sensitive tissue. We have noted that a large proportion (75%) of the increment in NIMGU that occurs as a result of a rise in the prevailing serum glucose level occurs in skeletal muscle. Two possible mechanisms exist for this observation, 1) that non-skeletal muscle tissues have a glucose uptake system with a high capacity for glucose uptake relative to skeletal muscle, or 2) that non-skeletal muscle tissues (chiefly the CNS) have a $R_d$ system with a high affinity for glucose (i.e., low $K_m$). If the first possibility were operative one would expect that at euglycemia, body skeletal muscle, which receives approximately the same proportion of cardiac output as the CNS (12), would uptake more glucose than nonmuscle tissues. Since we have shown that 80% of NIMGU at euglycemia is into nonmuscle tissues, the present and published (6, 6, 16, 25) data are most consistent with the formulation that under insulinopenic conditions the CNS glucose uptake system has a high affinity (low $K_m$) for glucose relative to skeletal muscle, so that as one raises the prevailing serum glucose level and exceeds the CNS $K_m$, relatively less glucose uptake occurs in the CNS (saturation) and more occurs in non-CNS tissues (chiefly skeletal muscle).

These findings have an impact on the interpretation of rates of whole body IMGU. For example, $R_d$ obtained during hyperinsulinenic glucose clamp studies include a component of $R_d$ that is non-insulin mediated. Therefore, to obtain true rates of IMGU it is necessary to subtract the NIMGU component from the overall rate of glucose disposal [IMGU equals ($R_d$ minus NIMGU)]. The rate of NIMGU is ~130 mg/min at euglycemia and ~210 mg/min at hyperglycemia. Although this correction appears small, it can have a significant impact on the calculation of the 50% effective dose (ED$_{50}$) for IMGU. For example, uncorrected for NIMGU the ED$_{50}$ for insulin’s effect to stimulate $R_d$ would be ~20–30 μU/ml lower than if the NIMGU component were factored out (19, 24). Similarly, if a perturbation decreases insulin’s action to stimulate glucose uptake in peripheral tissue but has no effect on NIMGU, the effect of the perturbation to decrease IMGU will be underestimated if NIMGU is not factored out. For example, we have reported that epinephrine decreases rates of insulin-stimulated glucose disposal by 46%, but when the effect of epinephrine on IMGU ($R_d$ – NIMGU) was examined, the inhibitory effect of epinephrine was more potent, as indicated by a 61% decrease in IMGU (4).

We have noted that the current data suggest that NIMGU at physiological glucose levels occurs almost exclusively in the CNS and that increments in the prevailing serum glucose level increase NIMGU almost exclusively in skeletal muscle. One can take advantage of this to study NIMGU in skeletal muscle vs. NIMGU in the CNS. To this point, we have recently reported the effect of a prolonged fast on NIMGU measured at euglycemia (CNS glucose uptake) and at hyperglycemia (CNS plus skeletal muscle NIMGU) (3). The results indicate no effect of fasting to modulate NIMGU at euglycemia (CNS glucose uptake) but a marked effect of fasting to decrease rates of NIMGU at hyperglycemia. Since CNS glucose uptake saturates at physiological glucose concentrations, NIMGU in skeletal muscle can be calculated by subtracting the rate of CNS glucose uptake (NIMGU measured at euglycemia) from the rate of NIMGU measured at hyperglycemia (CNS plus skeletal muscle NIMGU).

With respect to IMGU, the results indicate that in the presence of ~70 μU/ml of insulin under euglycemic conditions, ~75% of whole body $R_d$ is into muscle. This finding is in good agreement with those of DeFronzo et al. (8, 9), who found that ~85% of IMGU is in skeletal muscle at an insulin concentration of ~100 μU/ml. In addition, we found that at a prevailing serum glucose level of ~220 mg/dl, 95% of whole body IMGU is into skeletal muscle. This is consistent with our formulation that at hyperglycemia relatively more glucose is driven into muscle and less is driven into nonmuscle tissues.

The interpretation of the present data are dependent on a number of assumptions that deserve comment, including 1) validity of the muscle mass estimates. The estimates of muscle mass were made by assuming that a liter of leg volume is equal to 650 g of leg muscle and that a lean 70 kg male has 30 kg of skeletal muscle. These assumptions are likely to result in rough estimates of skeletal muscle mass and although they may not result in accurate absolute rates of skeletal muscle glucose uptake, the proportional differences in the rates of basal $R_d$, IMGU, and NIMGU at the different glucose levels remain valid. Therefore the conclusion regarding the relative rates of $R_d$ under the various conditions are not altered by these assumptions. 2) Leg muscle must reflect whole body skeletal muscle. Although this cannot be ascertained by the available data, the leg represents a composite of functionally heterogenous muscle groups of all fiber types (21) and therefore is likely to be representative of whole body skeletal muscle. 3) We have assumed that the proportion of leg blood flow to skeletal muscle is similar to the proportion of skeletal muscle in the leg. Unfortunately, data do not exist to support this assumption. Therefore, if the proportion of blood flow to leg muscle was greater than the proportion of muscle in the leg this would have lead us to underestimate rates of whole body muscle glucose uptake. If the proportion of blood flow to leg muscle was less than the assumed proportion of muscle in leg we would have overestimated rates of whole body $R_d$. 4) Insulin action must be absent during measurements of NIMGU. In this regard SRIF suppressed basal C-peptide levels by >90%, which would result in an estimated circulating insulin level of <1 μU/ml. Given the ED$_{50}$ for insulin’s effect to stimulate $R_d$ of ~100 μU/ml, it is unlikely that any insulin action was
These findings support the notion that a large portion of IMGU occurs in muscle at all glucose levels. In contrast, euaglycemia the great majority of NIMGU occurs in nonmuscle tissue (chiefly the CNS), and at hyperglycemia roughly half of overall NIMGU is into muscle. These findings support the notion that a large portion of the elevated rates of NIMGU observed in type II diabetic subjects occur in skeletal muscle.

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