Rates and Tissue Sites of Noninsulin- and Insulin-Mediated Glucose Uptake in Diabetic Rats (43333)

CHARLES H. LANG[1]
Department of Physiology, Louisiana State University Medical Center, New Orleans, Louisiana 70112

Abstract. **The purpose of the present study was to determine whether streptozotocin-induced diabetes alters the rates and tissue distribution of insulin-mediated glucose uptake (IMGU) and noninsulin-mediated glucose uptake (NIMGU). *In vivo* glucose disposal was assessed using the tracer [U-^{14}C]-2-deoxyglucose technique in chronically catheterized conscious rats. For nondiabetic animals, rates of NIMGU were determined during severe insulinopenia (<5 μU/ml), induced by the infusion of somatostatin, under both euglycemic (6 m*M*) and hyperglycemic (17 m*M*) conditions. In diabetic rats, in which a severe insulin deficiency already existed, NIMGU was determined under basal hyperglycemic conditions and during euglycemic conditions produced by inhibiting hepatic glucose output. IMGU was determined in both groups using the euglycemic-hyperinsulinemic clamp technique. Glucose uptake was consistently higher (50–280%) in all tissues removed from diabetic rats under basal conditions, compared with tissues from control animals in the basal state. When control animals were rendered insulinopenic, glucose uptake by the skeletal muscle, heart, and diaphragm was reduced 30–60%, indicating that the uptake by these tissues occurred by both insulin- and noninsulin-mediated mechanisms. Glucose disposal by the other tissues sampled was entirely due to NIMGU under basal conditions. When blood glucose levels were elevated from 6 to 17 m*M* in control animals, NIMGU increased in all tissues (60–280%) except the brain. Rates of NIMGU were essentially identical between control and diabetic animals, under either euglycemic or hyperglycemic conditions, when glucose uptake was determined under the same steady-state plasma glucose levels. In contrast to the normal rate of NIMGU by muscle, IMGU by the skeletal muscle and heart from diabetic rats were reduced under mild hyperinsulinemic conditions (100 μU/ml), compared with control animals. Furthermore, in response to a maximal, stimulating dose of insulin (5000 μU/ml), IMGU was impaired in the diaphragm, liver, lung, spleen, skin, and kidney removed from diabetic animals. These results indicate that the majority of glucose disposal under basal postabsorptive conditions occurs by NIMGU in both control and diabetic rats. Furthermore, while IMGU was selectively impaired in this model of insulin-dependent diabetes, the rates and tissue distribution of NIMGU were unaltered when glucose uptake was determined under similar plasma glucose levels.** [P.S.E.B.M. 1992, Vol 199]

Whole body glucose disposal results from both insulin- and noninsulin-mediated glucose uptake (1, 2). Insulin-mediated glucose uptake (IMGU) occurs primarily in insulin-sensitive tissues, such as muscle, whereas noninsulin-mediated glucose uptake (NIMGU) occurs to varying degrees in all tissues, regardless of their sensitivity to insulin. Several studies have indicated that under postabsorptive conditions, NIMGU accounts for 75% to 85% of the total whole body glucose disposal (1–3). These two pathways for glucose uptake appear to be regulated independently, as evidenced by the impairment in IMGU, but not in NIMGU, during the infusion of epinephrine or cortisol (4, 5). Furthermore, individuals with noninsulin-dependent diabetes exhibit severe peripheral insulin resistance without a concomitant alteration in the rate of NIMGU by the whole body (6). While skeletal muscle is primarily responsible for the diabetes-induced impairment of whole body insulin-stimulated glucose

[1] To whom correspondence and requests for reprints should be addressed at Department of Physiology, Louisiana State University Medical Center, 1901 Perdido Street, New Orleans, LA 70112.

Received March 22, 1991. [P.S.E.B.M. 1992, Vol 199]
Accepted July 30, 1991.

0037-9727/92/1991-0081$3.00/0

uptake (1, 7), the rates and tissue sites for disposal of glucose by noninsulin-mediated mechanisms are poorly defined. Data in this area would extend previous measurements of whole body glucose disposal which represent a composite of multiple glucose uptake systems with different kinetic parameters in different tissues (8). Therefore, the current studies were performed to quantitate alterations in the rate and tissue distribution of insulin- and noninsulin-mediated glucose uptake in streptozotocin-induced diabetic rats, a commonly used animal model of Type 1 (insulin-dependent) diabetes. To accomplish this aim, IMGU was assessed under euglycemic conditions and at various plasma insulin levels in diabetic and nondiabetic animals. To study NIMGU, a severe insulinopenia was produced and glucose disposal was determined under both euglycemic and hyperglycemic conditions in diabetic and nondiabetic rats. In all studies, *in vivo* glucose uptake by individual tissues was determined using the tracer 2-deoxyglucose technique.

Materials and Methods

Male Sprague–Dawley rats (325–350 g; Charles River, Wilmington, MA) were lightly anesthetized with ether, and diabetes was induced in fed rats by injection (tail vein) of 70 mg/kg of streptozotocin (Upjohn) dissolved in 50 m*M* citrate buffer (pH 4.5). Three weeks after the injection of streptozotocin, blood (25 μl) was obtained via tail snip from fed animals and the glucose concentration was determined with the use of the YSI glucose analyzer (YSI, Yellow Springs, OH). Diabetic animals that did not have blood glucose concentrations >200 mg/dl were excluded from the study. We have previously characterized this model of diabetes and demonstrated that these rats have an impaired glucose tolerance and are insulin resistant (9, 10). Control animals in this study were weight-matched animals that received an equal volume of citrate buffer instead of streptozotocin. On the day prior to the experiment, animals were anesthetized with a mixture of ketamine and xylazine (90 and 9 mg/kg, respectively) and sterile surgery was performed. A catheter was implanted in the left carotid artery and advanced to the arch of the aorta and two catheters were placed in the right jugular vein (9). Following surgery, animals were returned to individual cages and fasted overnight, with water provided. All animals were conscious and unrestrained during the remainder of the experimental protocol.

Glucose uptake was determined under various experimental conditions in which the plasma glucose and insulin concentrations were matched in diabetic and nondiabetic animals. There were three groups of diabetic and nondiabetic rats: (i) euglycemic insulinopenic, (ii) hyperglycemic insulinopenic, and (iii) euglycemic hyperinsulinemic. In the first group, noninsulin-mediated glucose uptake was determined under euglycemic conditions by producing a severe insulin deficiency (<5 μU/ml; Ref. 2). In nondiabetic rats, insulinopenia was produced by a primed constant intravenous infusion of somatostatin (SRIF; Bachem, Torrance, CA), 60 μg/kg + 3 μg/kg/min, which suppressed endogenous insulin secretion. In the rat, the infusion of SRIF does not significantly reduce the plasma glucose concentration; therefore, these animals remain euglycemic (2). In diabetic rats, which were rendered insulinopenic by the prior administration of streptozotocin, euglycemia was achieved by the intraperitoneal injection of 3-mercaptopicolinic acid (3-MP; 20 mg/100 g body wt). The 3-MP is an inhibitor of phosphoenolypyruvate carboxykinase and has been shown to suppress endogenous glucose production in rats (11, 12). After 140 min of SRIF or 3-MP, a tracer amount of 2-[U-^{14}C]deoxy-D-glucose (8 μCi/rat; Amersham, Arlington Heights, IL, sp act 310 mCi/mmol) was injected through the second venous catheter so as to not interrupt the infusion of SRIF. Serial arterial blood samples (0.3 ml) were withdrawn during the 40-min *in vivo* labeling period, plasma was deproteinized with perchloric acid, and radioactivity was determined as described previously (2). An aliquot of the perchloric acid supernatant for each sample was neutralized and the glucose concentration was determined. Animals were sacrificed with sodium pentobarbital 180 min after the start of the SRIF infusion or the administration of 3-MP (i.e., 40 min after injection of 2-deoxyglucose), and the accumulation of phosphorylated metabolites of 2-deoxyglucose (dGlc) was measured in selected tissues using the Somogyi reagent (2).

In the second group of rats, NIMGU was determined under hyperglycemic conditions. Nondiabetic animals in this group (hyperglycemic insulinopenic) were administered a primed constant intravenous infusion of SRIF (60 μg/kg + 3 μg/kg/min) and mannoheptulose (100 mg + 100 mg/h), and the arterial glucose concentration was increased to ~17 m*M* by a variable infusion of 15% glucose. Mannoheptulose was used because previous studies demonstrated that this compound, but not SRIF, was capable of completely preventing glucose-stimulated insulin secretion in rats (2). Neither SRIF nor mannoheptulose has been shown to significantly alter whole body glucose utilization (13, 14). Diabetic rats were hyperglycemic and insulinopenic in the basal state; therefore, they were infused with an equal volume of saline. Tracer dGlc was injected at 140 min, and blood samples were obtained as described above.

In the third group of rats, a euglycemic hyperinsulinemic clamp was performed, as described previously (9), to determine insulin-stimulated glucose uptake. Briefly, porcine insulin (Eli Lilly, Indianapolis, IN) was infused intravenously to rapidly raise the plasma insulin concentration to the desired level. The

insulin infusion rate was 0, 1.4, and 20 mU/min in nondiabetic rats and 0.3, 1.4, and 20 mU/min in diabetic animals. These infusion rates produced circulating insulin levels of approximately 30, 100, and 5000 μU/ml, respectively, in both groups of animals. The highest insulin concentration has been shown to produce maximum rates of glucose uptake in the rat (9, 15). The insulin infusion was continued for a total of 180 min and each animal received only one infusion rate. In order to maintain euglycemia during the hyperinsulinemic clamp, an intravenous glucose infusion containing 30% D-glucose was started after initiating the insulin infusion. Arterial blood glucose concentrations were determined every 10 min using a YSI glucose analyzer, and the glucose infusion rate was adjusted empirically to maintain euglycemia. Steady-state plasma glucose values were obtained by 120 min and tracer dGlc was injected at 140 min after the start of the insulin clamp to determine glucose uptake by individual tissues.

Blood glucose concentrations were determined enzymatically (16). Plasma immunoreactive insulin and glucagon concentrations were determined by radioimmunoassay (ICN/Micromedic, Horsham, PA) using porcine standards. Glucose uptake (referred to as the glucose metabolic rate; Rg) for each tissue was calculated on the basis of the concentration of the phosphorylated-2-dGlc concentration in the tissue and the integrated [dGlc] to [glucose] ratio in the plasma during the 40-min *in vivo* labeling period (2). Data were analyzed using analysis of variance followed by Newman-Keuls to determine treatment effect. Statistical significance was set at $P < 0.05$.

The studies described in this report were reviewed and approved by the Institutional Animal Care and Use Committee at Louisiana State University Medical Center. In conducting the research described, the investigators adhered to the Guide for the Care and Use of Laboratory Animals (DHEW Publication (NIH) 85-23).

Results

Steady-State Glucose, Insulin, and Glucagon Concentrations. The values for the diabetic rats in Group 2 (hyperglycemic insulinopenic) and the control animals in Group 3 (euglycemic hyperinsulinemic) represent the basal postabsorptive metabolic characteristics of these two groups of animals (Table I). It is evident that under basal conditions, streptozotocin-induced diabetes decreased plasma insulin levels by 80% and increased the glucose (233%) and glucagon (98%) concentrations, compared with levels in nondiabetic control animals. The infusion of SRIF reduced the plasma insulin concentration in control animals by 88%, when compared with basal control values, and these levels were not different from those seen in diabetic animals. When diabetic animals were treated with 3-MP, which inhibited the enhanced rate of gluconeogenesis, steady-state plasma glucose levels were achieved that were comparable to those in euglycemic insulinopenic control animals. However, the glucagon concentrations in diabetic rats were still elevated approximately 4-fold, compared with those in euglycemic insulinopenic control animals. In both diabetic and nondiabetic rats, under hyperglycemic insulinopenic conditions, the insulin levels were ≤5 μU/ml and the plasma glucose concentrations were ~17 m*M*. Despite the prevailing hyperglycemia, glucagon levels remained elevated in diabetic rats compared with hyperglycemic nondiabetic control values. During the euglycemic hyperinsulinemic clamp, plasma insulin levels were approximately 30, 100, and 5000 μU/ml. There were no differences between the insulin concentrations of control and diabetic rats at any given insulin infusion rate. The steady-state plasma glucose concentrations during the euglycemic clamp were similar between diabetic and control animals, and the hyperglucagonemia seen in diabetic animals was still evident under hyperinsulinemic conditions (average increase, 115%).

Glucose Uptake by Individual Tissues. Glucose uptake was consistently higher in all tissues removed from diabetic rats under basal conditions (20 m*M* glucose and 5 μU/ml of insulin) compared with uptake in tissues isolated from control animals in the basal state (6 m*M* glucose and 30 μU/ml of insulin). Under basal conditions, Rg was elevated by 48%, 53%, and 103% in the gastrocnemius, heart (P = NS), and diaphragm obtained from diabetic rats (Fig. 1). Glucose uptake was increased by immunocompetent tissues, such as the liver, lung, and spleen, removed from diabetic rats (285%, 74%, and 65%; Fig. 2). Of the four other tissues examined (skin, ileum, kidney, and brain), only the first three showed a significant elevation in Rg (151%, 56%, and 120%, Fig. 3). Under basal postabsorptive conditions, the cerebral glucose uptake for diabetic rats (397 ± 35 nmol/min/g) tended to be lower than that in control animals (466 ± 43 nmol/min/g), but this difference was not statistically significant.

When the circulating insulin levels were reduced from basal to ~5 μU/ml in control animals, Rg fell in the gastrocnemius, heart, and diaphragm (32%, 61%, and 50%, respectively; Fig. 1). Glucose uptake under these severe insulinopenic conditions provides an estimate of NIMGU (1, 2). None of the other tissues sampled from control animals demonstrated a significant decrease in glucose uptake under insulinopenic conditions. Raising the blood glucose concentration from 6 to 17 m*M* in control animals increased NIMGU in all tissues sampled. For the gastrocnemius, heart, and diaphragm, NIMGU was increased by 121%, 278%, and 242%, respectively, compared with that in euglycemic insulinopenic animals (Fig. 1). The Rg of the liver, lung, and spleen were also elevated (147%,

Table I. Steady-State Plasma Glucose, Insulin, and Glucagon Concentrations in Control and Diabetic Rats[a]

Group	Treatment	Steady-state insulin (μU/ml)	Steady-state glucose (mM)	Steady-state glucagon (pg/ml)
Euglycemic insulinopenic	Control	5 ± 2[b]	5.8 ± 0.4	105 ± 12[b]
	Diabetic[c]	4 ± 3[b]	6.1 ± 0.8	421 ± 37[d]
Hyperglycemic insulinopenic	Control	3 ± 2	17.4 ± 2.1[e]	129 ± 18
	Diabetic	5 ± 3	19.7 ± 1.6[e]	387 ± 26[d]
Euglycemic hyperinsulinemic	Control[c]	25 ± 3	5.9 ± 0.3	195 ± 22
	Diabetic	31 ± 4	6.0 ± 0.4	454 ± 65[d]
	Control	95 ± 7[b]	6.1 ± 0.5	210 ± 15
	Diabetic	100 ± 9[b]	5.9 ± 0.4	423 ± 29[d]
	Control	4550 ± 250[b]	5.9 ± 0.5	187 ± 25
	Diabetic	4725 ± 495[b]	6.0 ± 0.3	396 ± 42[d]

[a] Values are means ± SE; n = 6–7 rats per group. Steady-state insulin and glucagon values were determined at 120 and 180 min after the start of the respective infusion. Steady-state glucose values were determined at 20 min intervals between 120 and 180 min of the respective infusion.
[b] $P < 0.05$, compared with euglycemic values at 30 μU/ml of insulin for the same treatment group (control or diabetic).
[c] The values for these two groups represent the basal postabsorptive metabolic characteristics for diabetic and nondiabetic control rats, respectively.
[d] $P < 0.05$, compared with control values at the same glucose and insulin levels.
[e] $P < 0.05$, compared with euglycemic insulinopenic values of the same treatment group.

141%, and 106%; Fig. 2). Of the remaining tissues, the Rg of the skin was increased 109%, the ileum by 105%, and the kidney by 62% (Fig. 3). The brain was the only tissue sampled from control animals in which hyperglycemia did not increase tissue Rg (data not shown). Under hyperglycemic insulinopenic conditions, there were no statistically significant differences in the rates of NIMGU for individual tissues obtained from diabetic and control animals (Figs. 1–3). When the blood glucose concentration was decreased from 20 mM to 6 mM in diabetic animals, NIMGU fell in all tissues examined except the brain. Under euglycemic insulinopenic conditions, there was no significant difference in NIMGU for individual tissues obtained from diabetic and control animals, with the exception of the spleen (Figs. 1–3).

Under euglycemic conditions and with steady-state plasma insulin levels of ~30 μU/ml, Rg tended to be lower in the three muscles sampled from diabetic animals, compared with Rg from control rats. However, only the 51% reduction in myocardial glucose uptake was statistically significant (Fig. 1). When the circulating insulin levels were increased to 100 and 5000 μU/ml, muscle Rg increased in a dose-dependent manner in both control and diabetic animals. Under these two hyperinsulinemic conditions, Rg was lower in the gastrocnemius muscle (36% and 55%) and heart (48% and 73%) obtained from diabetic animals than in muscle isolated from control rats. The glucose uptake by the diaphragm from diabetic animals was also reduced by 48% at the highest insulin infusion rate. Although muscle showed the largest increment in IMGU, insulin also enhanced glucose uptake in other tissues, albeit to a lesser degree. In nondiabetic animals, compared with their own basal values, the Rg was elevated by 100% and 59% in skin and kidney at plasma insulin levels of 100 μU/ml. In addition, Rg was elevated in the liver, lung, spleen, skin, and kidney (108%, 45%, 40%, 351%, and 65%, respectively) when insulin levels were raised to 5000 μU/ml. In diabetic rats, the only tissue besides muscle to respond to insulin was the skin. IMGU in this tissue was dose-dependent and increased by 40% and 134% under hyperinsulinemic conditions (Fig. 3).

Discussion

In nondiabetic rats, under basal postabsorptive conditions (glucose, 6 mM; insulin, 30 μU/ml), whole body glucose disposal occurred by both insulin- and noninsulin-mediated mechanisms. Since Rg by the various nonmuscle tissues is not reduced under euglycemic insulinopenic conditions, NIMGU appears to account for essentially all of the basal glucose uptake by these tissues. In contrast, the three different muscles examined in this study showed a significant fall in glucose uptake when plasma insulin levels were reduced. These data indicate that 68%, 39%, and 50% of the basal glucose uptake by the gastrocnemius, heart, and diaphragm is also mediated by noninsulin-dependent mechanisms. The relative contribution of the two pathways to total tissue glucose uptake in the gastrocnemius is comparable to that reported previously for skeletal muscle in humans (1). Since the muscle mass represents a large fraction of the total body weight, these data are consistent with earlier reports indicating that NIMGU accounts for 75% to 85% of the whole body glucose disposal in nondiabetic subjects under basal conditions (1–3). These results clearly demonstrate that although NIMGU by muscle represents a substantial fraction of

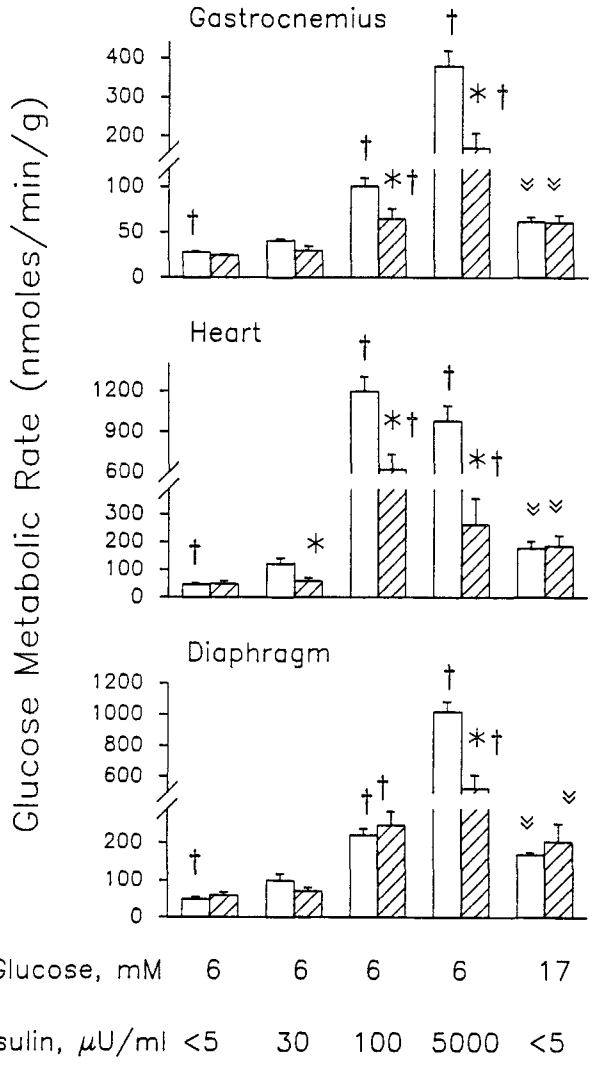

Figure 1. The glucose metabolic rate (Rg) of various muscles removed from nondiabetic (open bars) and streptozotocin-diabetic (hatched bars) rats. Noninsulin-mediated glucose uptake and insulin-stimulated glucose uptake were determined *in vivo* under different conditions in which the plasma glucose and insulin levels were matched in diabetic and nondiabetic rats. Values are means ± SE; n = 6–7 rats per group. * $P < 0.05$, compared with nondiabetic values at the same plasma glucose and insulin level. † $P < 0.05$, compared with euglycemic (6 m*M*) values at 30 μU/ml of insulin for the same treatment group (nondiabetic or diabetic). ⁑ $P < 0.05$, compared with euglycemic insulinopenic (<5 μU/ml of insulin) values for the same group.

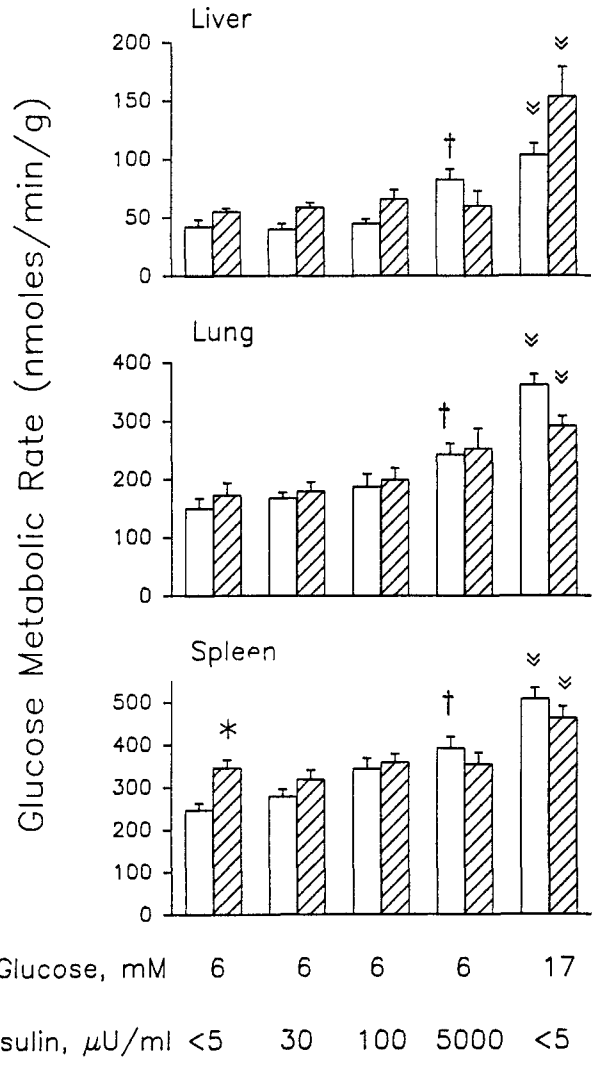

Figure 2. Glucose metabolic rate for liver, lung, and spleen from nondiabetic (open bars) and diabetic (hatched bars) rats. Values are means ± SE; n = 6–7 rats per group. * $P < 0.05$, compared with nondiabetic values at the same plasma glucose and insulin levels. † $P < 0.05$, compared with euglycemic (6 m*M*) values at 30 μU/ml of insulin for the same treatment group. ⁑ $P < 0.05$, compared with euglycemic insulinopenic (< 5 μU/ml of insulin) values for the same group.

the whole body glucose disposal, NIMGU by nonmuscle tissues accounts for the majority of the whole body glucose utilization in rats. Furthermore, when plasma glucose levels are elevated, the rate of NIMGU by all tissues examined (except brain) was increased, as a result of the mass action effect. It should be noted that the percentage of contribution of NIMGU by the brain to whole body glucose disposal decreases under hyperglycemic conditions in both humans and rats (1, 2). However, the contribution by the central nervous system appears to be markedly greater in humans (40–70%) than in rats (5–10%). This difference appears to result from the higher rate of whole body glucose turnover and the smaller contribution of the central nervous system to total body weight in the rat, as compared with humans.

The basal postabsorptive state in diabetic rats is characterized by insulin deficiency (<5μU/ml of insulin) and hyperglycemia (~20 m*M*)). Therefore, under these conditions, glucose uptake by all tissues occurs predominantly by noninsulin-mediated mechanisms. When the basal diabetic state is compared with the basal nondiabetic condition, glucose uptake is elevated in all tissues (except brain) obtained from diabetic rats. This is consistent with previous reports indicating that whole body glucose utilization is elevated in streptozotocin-diabetic rats (9). Moreover, these data indicate

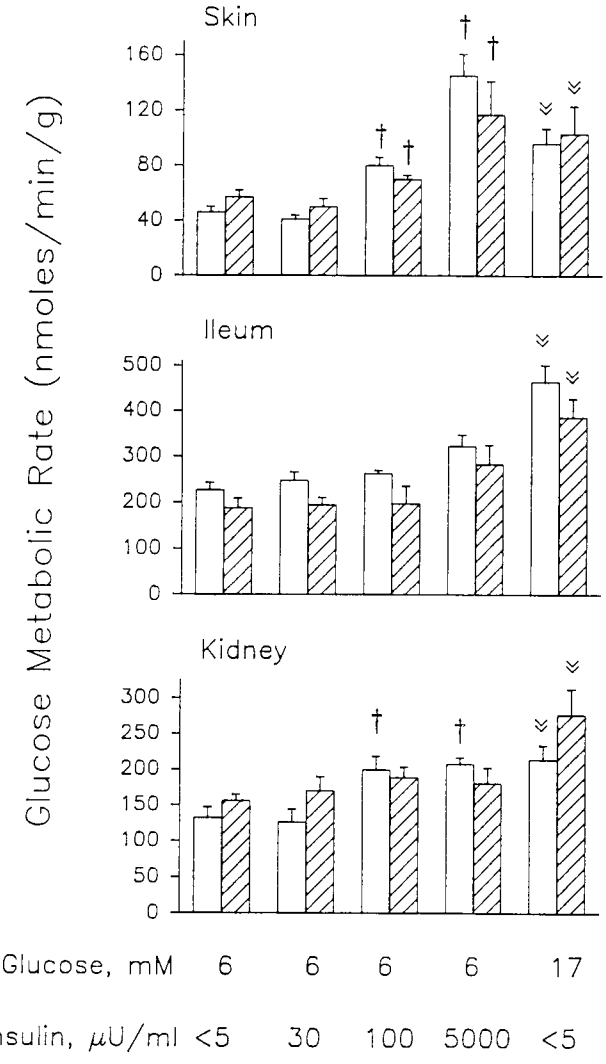

Figure 3. Glucose metabolic rate of skin, ileum, and kidney from nondiabetic (open bars) and diabetic (hatched bars) rats. Values are means ± SE; n = 6–7 rats per group. $^{\dagger}P < 0.05$, compared with euglycemic (6 m*M*) values at 30 μU/ml of insulin for the same treatment group. $^{\ddagger}P < 0.05$, compared with euglycemic insulinopenic (< 5 μU/ml of insulin) values for the same group.

that NIMGU is increased in tissues from diabetic rats as a result of the mass action effect of glucose. Conversely, NIMGU was reduced in all tissues from diabetic rats when the prevailing hyperglycemia was reduced to nondiabetic control levels by inhibiting hepatic glucose production. Under euglycemic insulinopenic conditions, there is no difference in NIMGU by tissues obtained from either control or diabetic rats. Likewise, when the plasma glucose concentration was elevated in nondiabetics to match that observed in diabetic rats under basal conditions, NIMGU was similar in the two groups. These findings are consistent with the results of Hansen *et al.* (17), who demonstrated that, in patients with insulin dependent diabetes, the ability of an increase in glucose concentration to enhance whole body glucose utilization did not differ from that in nondiabetic subjects. Therefore, the tissue sites and the rates of NIMGU in diabetic and nondiabetic rats are essentially identical when the plasma glucose levels are the same. These data on NIMGU by individual tissues extend previous findings, which indicate that diabetes does not alter whole body noninsulin-mediated glucose disposal in humans (6).

The ability of elevated levels of glucose or insulin to suppress glucagon secretion is well established (18). However, in the present study, neither hyperglycemia or hyperinsulinemia significantly reduced the plasma glucagon levels in either diabetic or nondiabetic rats. Although the reason why these stimuli failed to reduced glucagon levels is not known, previous studies in rats have produced similar results (2, 9, 15). However, it seems unlikely that the difference in glucagon concentrations between control and diabetic rats would significantly affect rates of NIMGU, since elevations in other stress hormones (epinephrine and cortisol) do not alter NIMGU (4, 5) and glucagon is not reported to have a direct effect on glucose uptake by muscle (19).

In contrast to the relatively normal rates of NIMGU, insulin-stimulated glucose disposal is markedly impaired in a number of tissues from diabetic rats. As expected, IMGU is most severely blunted in the various muscle tissues. In diabetic rats, IMGU by the skeletal muscle and heart is depressed at plasma insulin levels of 100 and 5000 μU/ml. Although complete insulin-dose response curves were not generated in the present study, these data suggest that diabetes decreased both insulin sensitivity and responsiveness in these tissues (20). Similar changes in IMGU for whole body and muscle have been reported for Type I diabetes in humans (21).

Although IMGU was highest in muscle, other tissues did demonstrate modest increases in glucose uptake in response to hyperinsulinemia in nondiabetic rats. Insulin enhanced glucose uptake in the skin and kidney at both low (100 μU/ml) and high (5000 μU/ml) plasma insulin levels, whereas IMGU was elevated in the liver, lung, and spleen at only the highest insulin concentration. In contrast to these findings, hyperinsulinemia failed to increase IMGU in any tissue obtained from diabetic animals, with the exception of muscle and skin. Many cell types possess receptors for both insulin and insulin-like growth factor I (IGF-1) (22). Since these receptors have a high degree of homology, it is possible that some of the insulin-stimulated increase in glucose uptake that occurred under hyperinsulinemic conditions is mediated by binding of insulin to receptors for IGF-I. Furthermore, resistance to both insulin and IGF-1 has been demonstrated in muscle strips from obese patients (23) and in denervated muscle (24); therefore, it is possible that the impairment of IMGU observed under hyperinsulinemic

conditions in diabetic rats is due in part to IGF-1 resistance.

Diabetic animals have a basal rate of glucose disposal that is higher than that seen in nondiabetic control animals. This is a generalized response that is observed in both muscle and nonmuscle tissues from diabetic animals, and results from hyperglycemia-induced increases in NIMGU. The postabsorptive hyperglycemia seen in diabetic rats appears to overcompensate for the decreased rate of insulin-stimulated glucose uptake observed in these animals. However, when plasma glucose levels are matched in the two groups, the disposition of NIMGU by individual tissues does not appear to be substantially altered by diabetes. In contrast, the present studies indicate that IMGU is markedly impaired in streptozotocin-induced diabetic rats, and the insulin-resistant state is attributed primarily to the decreased insulin-stimulated glucose uptake by various muscle tissues. Collectively, these data support the hypothesis that NIMGU and IMGU are independently regulated and functionally distinct (4, 5).

Supported by National Institutes of Health Grant GM 38032. The excellent technical assistance of Janet Gunter is gratefully acknowledged. Streptozotocin was a generous gift of the Upjohn Company.

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