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Research Article

Tissue sensitivity to insulin was examined with the euglycemic insulin clamp technique in 17 chronically uremic and 36 control subjects. The plasma insulin concentration was raised by approximately 100 microU/ml and the plasma glucose concentration was maintained at the basal level with a variable glucose infusion. Under these steady-state conditions of euglycemia, the glucose infusion rate is a measure of the amount of glucose taken up by the entire body. In uremic subjects insulin-mediated glucose metabolism was reduced by 47% compared with controls (3.71 ± 0.20 vs. 7.38 ± 0.26 mg/kg . min; P less than 0.001). Basal hepatic glucose production (measured with $[3H]$ -3-glucose) was normal in uremic subjects (2.17 ± 0.04 mg/kg . min) and suppressed normally by $94 \pm 2\%$ following insulin administration. In six uremic and six control subjects, net splanchnic glucose balance was also measured directly by the hepatic venous catheterization technique. In the postabsorptive state splanchnic glucose production was similar in uremics (1.57 ± 0.03 mg/kg . min) and controls (1.79 ± 0.20 mg/kg . min). After 90 min of sustained hyperinsulinemia, splanchnic glucose balance reverted to a net uptake which was similar in uremics (0.42 ± 0.11 mg/kg . min) and controls (0.53 ± 0.12 mg/kg . min). In contrast, glucose uptake by the leg was reduced by 60% in the uremic group (21 [...])

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Insulin Resistance in Uremia

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ABSTRACT Tissue sensitivity to insulin was examined with the euglycemic insulin clamp technique in 17 chronically uremic and 36 control subjects. The plasma insulin concentration was raised by $\sim 100 \mu\text{U/ml}$ and the plasma glucose concentration was maintained at the basal level with a variable glucose infusion. Under these steady-state conditions of euglycemia, the glucose infusion rate is a measure of the amount of glucose taken up by the entire body. In uremic subjects insulin-mediated glucose metabolism was reduced by 47% compared with controls (3.71 ± 0.20 vs. $7.38 \pm 0.26 \text{ mg/kg} \cdot \text{min}$; $P < 0.001$). Basal hepatic glucose production (measured with $[^3\text{H}]\text{-3-glucose}$) was normal in uremic subjects ($2.17 \pm 0.04 \text{ mg/kg} \cdot \text{min}$) and suppressed normally by $94 \pm 2\%$ following insulin administration. In six uremic and six control subjects, net splanchnic glucose balance was also measured directly by the hepatic venous catheterization technique. In the postabsorptive state splanchnic glucose production was similar in uremics ($1.57 \pm 0.03 \text{ mg/kg} \cdot \text{min}$) and controls ($1.79 \pm 0.20 \text{ mg/kg} \cdot \text{min}$). After 90 min of sustained hyperinsulinemia, splanchnic glucose balance reverted to a net uptake which was similar in uremics ($0.42 \pm 0.11 \text{ mg/kg} \cdot \text{min}$) and controls ($0.53 \pm 0.12 \text{ mg/kg} \cdot \text{min}$). In contrast, glucose uptake by the leg was reduced by 60% in the uremic group (21 ± 1 vs. $52 \pm 8 \mu\text{mol/min} \cdot \text{kg}$ of leg wt; $P < 0.005$) and this decrease closely paralleled the decrease in total glucose metabolism by the entire body. These results indicate that: (a) suppression of hepatic glucose production by physiologic hyperinsulinemia is not impaired by uremia, (b) insulin-mediated glucose uptake by the liver is normal in uremic subjects, and (c) tissue insensitivity to insulin is the primary cause of insulin resistance in uremia.

INTRODUCTION

Previous studies using the glucose clamp technique have demonstrated that tissue insensitivity to insulin is

the primary cause of glucose intolerance in patients with chronic renal failure (1). This observation is consistent with previous results documenting a delayed and diminished glucose response after exogenous insulin (2–9) and tolbutamide (3, 5, 8–11). However, in none of these previous studies (1–11) was the site of insulin resistance defined. Impaired insulin action could result from one of three abnormalities: (a) impaired glucose uptake by peripheral tissues; (b) impaired glucose uptake by the liver; or (c) impaired ability of insulin to inhibit hepatic glucose production. In the present study we have used the euglycemic insulin clamp technique in combination with tritiated glucose and hepatic venous and femoral venous catheterization to examine the contribution of the liver vs. peripheral tissues to the impaired insulin action observed in uremia.

METHODS

Subjects. 17 ambulatory volunteers with chronic (>3 yr) renal disease of diverse etiology were studied. There were 12 males and 5 females ranging in age from 23–57 yr (mean = 37 ± 2). All uremic (mean = $106 \pm 2\%$) and control (mean = $105 \pm 2\%$) subjects were within 19% of ideal body weight based on Metropolitan Life Insurance Tables (1959), and were consuming a weight-maintaining diet containing at least 200–300 g of carbohydrate/d for 3 d prior to study. Although none of the subjects were instructed to limit the amount of protein in their diet, a low serum urea nitrogen to creatinine ratio was observed in four uremic individuals, suggesting that they may have self imposed a limitation on protein intake. Other than Amphogel and sodium bicarbonate, subjects consumed no medications for at least 5 d prior to study. The mean serum urea nitrogen and serum creatinine concentrations were 92 ± 7 and $10.2 \pm 0.9 \text{ mg/dl}$, respectively. Serum bicarbonate (23 ± 1), potassium (4.6 ± 0.1), calcium (9.1 ± 0.2), and phosphate (4.2 ± 0.3) concentrations, and blood pH (7.40 ± 0.01) were normal or only slightly reduced. Liver-function studies were within normal limits. There was no family history of diabetes mellitus; clinical evidence of diabetic retinopathy and neuropathy were absent; renal histology, available for nine patients, revealed no lesions suggestive of diabetic nephropathy.

The control population consisted of 36 healthy, ambulatory volunteers, ranging in age from 21–59 yr (mean = 35 ± 2) and in percent ideal body weight from 96–113% (mean = $105 \pm 2\%$). There were 24 males and 12 females. All tests were performed in the postabsorptive state at 8 a.m. following a

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12-h overnight fast. The purpose and potential risks of the study were carefully explained to all subjects and their written voluntary consent was obtained before their participation. The study protocols were approved by the ethical committees of the Karolinska Institute and Huddinge Hospital and the Yale University School of Medicine.

Euglycemic insulin clamp. Polyethylene catheters were inserted into a forearm vein and an antecubital vein as described (12). Following the collection of at least four base-line samples, a prime-continuous ($42.6 \text{ mU/m}^2 \cdot \text{min}$) infusion of crystalline porcine insulin (Eli Lilly and Co., Indianapolis, Ind.) was administered to acutely raise and maintain the plasma insulin concentration at $\sim 100 \text{ } \mu\text{U/ml}$ above basal levels (13). The plasma glucose concentration was maintained at basal preinfusion levels by determination of the plasma glucose concentration every 5 min and the periodic adjustment of a variable 20% glucose solution as described (13). Under these steady-state conditions of constant euglycemia, all of the infused glucose is taken up by cells and, when added to the rate of endogenous glucose production, serves as a measure of the body's sensitivity to the infused insulin.

Endogenous glucose production. During all insulin clamp studies the effect of hyperinsulinemia on hepatic glucose production was quantitated by infusing [^3H]-3-glucose as previously described (14). For 180 min before initiating the insulin infusion, each subject's glucose pool was labeled by a primed-continuous infusion of tritiated glucose (New England Nuclear, Boston, Mass.). The labeled glucose was administered as a priming ($25 \text{ } \mu\text{Ci}$) plus continuous ($0.25 \text{ } \mu\text{Ci/min}$) infusion of [^3H]-3-glucose. Plasma samples for determination of glucose specific activity were taken at 30-min intervals for the first 2 h and at 10–15-min intervals for the subsequent hour. A steady-state plateau of glucose specific activity was achieved in all subjects during the third hour of [^3H]-3-glucose infusion and this plateau value was used to calculate basal hepatic glucose production. After 3 h of continuous tritiated glucose infusion, the insulin infusion was begun and the tritiated glucose was continued at the same rate. During the insulin infusion plasma samples for glucose specific activity were drawn every 15 min for the first 90 min and every 5–10 min thereafter.

Hepatic venous catheterization. In six uremic subjects (mean serum urea nitrogen and creatinine = 83 ± 6 and $10.9 \pm 1.3 \text{ mg/dl}$, respectively) and in six controls, the insulin clamp and tritiated glucose studies were performed in combination with hepatic and femoral venous catheterization to quantitate splanchnic and leg uptake of glucose after insulin administration. In these studies a catheter was also inserted into the brachial artery to allow quantitation of arteriohepatic and arterio-femoral venous blood glucose concentration differences. The duration of the insulin clamp study was 90 min. Hepatic blood flow was determined by the continuous infusion technique using indocyanine green dye as previously described (15). Leg blood flow was measured using the indicator-dilution procedure described by Jorfeldt and Wahren (16).

Analytical procedures. Plasma and whole-blood glucose concentrations were determined with the glucose oxidase method (17). Methods for the determination of immunoreactive insulin (18) and tritiated glucose specific activity (14) have been described previously.

Calculations. During the insulin clamp studies the glucose infusion rate was determined by calculating the mean value observed from 20 to 120 min. The total amount of glucose metabolized by the entire body was calculated by adding the rate of endogenous glucose production (as described below) to the exogenous glucose infusion rate required to maintain euglycemia. Steady-state plasma glucose

and insulin levels were calculated from the mean values from 20 to 120 min. The metabolic clearance rate of insulin was calculated by dividing the continuous insulin infusion rate by the mean increment in plasma insulin concentration above base line.

Glucose production in the basal state was determined by dividing the tritiated glucose infusion rate (counts per minute) by the steady-state plateau of tritiated glucose specific activity achieved during the last hour of the preinsulin infusion control period. After the insulin-glucose administration (euglycemic insulin clamp), a nonsteady-state condition in glucose specific activity exists and hepatic glucose production was calculated by Steele's equations (19) in their derivative form, using a value of 0.65 for the pool fraction (20). The rate of endogenous glucose production was calculated by subtracting the glucose infusion rate from the rate of glucose appearance as determined by the isotopic tracer technique.

Net splanchnic glucose balance was calculated as the product of the arteriohepatic venous difference for blood glucose and the hepatic blood flow which was determined at 10-min intervals. Net splanchnic glucose balance (SGB) represents the result of two simultaneously occurring processes, namely splanchnic glucose uptake (SGU) and hepatic glucose production (HGP), and is given by the equation: $\text{net SGB} = \text{SGU} - \text{HGP}$. From this equation splanchnic glucose uptake can be quantitated from the sum of the net splanchnic glucose balance (which is measured as the product of the arterio-hepatic venous blood-glucose concentration difference \times splanchnic blood flow) and endogenous hepatic glucose production (which is measured with tritiated glucose).

Leg uptake of glucose was calculated as the product of the arterio-femoral venous difference for blood glucose and the leg blood flow which was determined at 30-min intervals.

All data are presented as the mean \pm SEM. All statistical comparisons between uremic and control subjects were performed by the unpaired *t*-test analysis (21). Statistical analyses within groups were performed with the paired *t*-test analysis. Coefficients of correlation were determined by standard procedures (21).

RESULTS

The basal insulin concentration was higher in the uremic subjects ($18 \pm 1 \text{ } \mu\text{U/ml}$) than in the control subjects, ($14 \pm 1 \text{ } \mu\text{U/ml}$, $P < 0.01$). Likewise, the steady-state insulin concentration during insulin infusion was slightly higher in the uremic subjects ($137 \pm 6 \text{ } \mu\text{U/ml}$) compared with controls ($117 \pm 5 \text{ } \mu\text{U/ml}$, Table I). The stability of plasma insulin concentration during the plateau period is reflected by the coefficients of variation of $6 \pm 1\%$ and $5.9 \pm 0.9\%$ in the control and uremic subjects, respectively. The metabolic clearance rate of insulin in uremics ($357 \pm 20 \text{ ml/m}^2 \cdot \text{min}$) was significantly reduced compared to the controls ($414 \pm 25 \text{ ml/m}^2 \cdot \text{min}$, $P < 0.002$).

The basal glucose concentration was similar in the uremic ($90 \pm 2 \text{ mg/dl}$) and the control subjects ($89 \pm 2 \text{ mg/dl}$). The glucose concentration in the uremics was maintained at $89 \pm 2 \text{ mg/dl}$ with a coefficient of variation of $3.5 \pm 0.2\%$ during the insulin-infusion period. The corresponding values in the control subjects were $89 \pm 1 \text{ mg/dl}$ and $4.4 \pm 0.2\%$.

TABLE I
Summary of Glucose Metabolism, Hepatic Glucose Production, and Plasma Insulin
Response in 36 Control and 17 Uremic Subjects

	Amount of glucose metabolized in 20–120 min	Hepatic glucose production		Steady-state plasma insulin concentration	Metabolic clearance rate of insulin in 20–120 min
		Basal	Postinsulin		
	mg/kg·min	mg/kg·min		μU/ml	ml/m ² ·min
Uremics*	3.71±0.20‡	2.17±0.04	0.12±0.03	137±6§	357±20§
Controls	7.38±0.26	2.18±0.06	0.11±0.04	117±5	414±25

* *n* = 17.

‡ Significantly different from controls, *P* < 0.001.

§ Significantly different from controls, *P* < 0.05.

^{||} *n* = 36.

The average rate of glucose utilization from minute 20 to 120 of the study period in the 17 uremic subjects (3.71 ± 0.20 mg/kg·min) was 50% lower than in the 36 controls (7.38 ± 0.26 mg/kg·min, *P* < 0.001, Table I).

Basal hepatic glucose production (measured with [³H]-3-glucose) in the 17 uremic subjects (2.17 ± 0.04 mg/kg·min) was similar to that of the 36 controls (2.18 ± 0.06 mg/kg·min, Fig. 1). After insulin administration, hepatic glucose production was similarly suppressed in the uremic and the control subjects (Fig. 1).

In the six uremic and six control subjects studied with hepatic venous catheterization, basal hepatic glucose production (measured with [³H]-3-glucose) was

2.22 ± 0.09 and 2.36 ± 0.12 mg/kg·min, respectively. Basal splanchnic glucose balance revealed a net output of 1.57 ± 0.03 mg/kg·min in the uremic subjects and net output of 1.79 ± 0.20 mg/kg·min in the controls (Fig. 1). Consequently, there was a net glucose uptake by the splanchnic area in the basal state which averaged 0.60 ± 0.04 mg/kg·min in the uremic subjects and 0.51 ± 0.12 mg/kg·min in the controls (Fig. 1). Within 30 min after starting the insulin infusion, net splanchnic glucose balance in the uremic subjects became slightly positive 0.19 ± 0.14 mg/kg·min, and subsequently increased to 0.42 ± 0.11 mg/kg·min by 90 min (Fig. 1). A similar increase was observed in controls. Splanchnic glucose uptake was not significantly changed from base line in either the uremic (0.50 ± 0.04 mg/kg·min) or control (0.56 ± 0.12) groups after the 90-min period of insulin infusion (Fig. 1).

Basal leg uptake of glucose in the uremic subjects (3.18 ± 1.12 μmol/kg·min) was slightly, although not significantly, less than in the controls, 6.22 ± 0.81 μmol/kg·min, Fig. 2). Following insulin infusion, leg glucose uptake increased in both groups, reaching a plateau value (60–90 min) in the uremics of 21 ± 1 μmol/kg·min, which was 60% lower than in the controls, 52 ± 8 μmol/kg·min (*P* < 0.005, Fig. 2). The total amount of glucose metabolized by the six uremic and six control subjects who were studied with combined hepatic and femoral venous catheterization was 3.36 ± 0.28 and 7.61 ± 0.84 mg/kg·min, respectively (*P* < 0.001). The 56% reduction in total glucose metabolism in the uremic subjects is similar to the 60% decrease in glucose uptake by the leg. Leg blood flow in the basal state was similar in controls (0.56 ± 0.05 liter/min) and uremics (0.68 ± 0.12 liter/min) and remained unchanged during insulin administration.

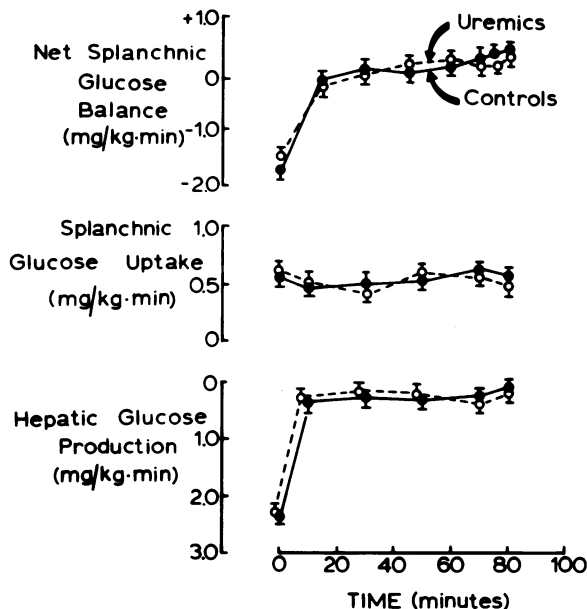


FIGURE 1 Net splanchnic glucose balance (measured by hepatic venous catheterization), hepatic glucose production (measured with tritiated glucose), and splanchnic glucose uptake in six uremic and six control subjects during the post-absorptive state and after euglycemic hyperinsulinemia (insulin clamp technique).

DISCUSSION

Although abnormal glucose metabolism in uremia has been recognized for many years, until recently the mechanisms contributing to this carbohydrate intoler-

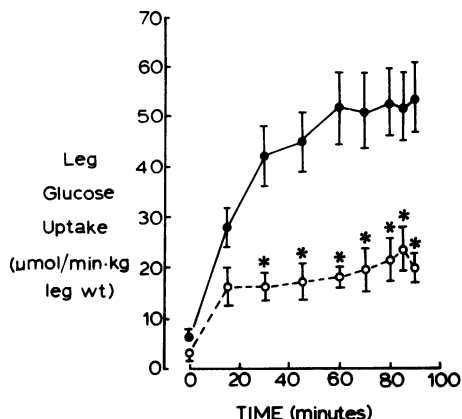


FIGURE 2 Leg glucose uptake in six uremic (○) and six control (●), subjects during the postabsorptive state and following euglycemic hyperinsulinemia (insulin clamp technique). * $P < 0.001$.

ance have remained unclear. Previous studies employing both the oral and intravenous glucose tolerance tests have documented that insulin secretion is not impaired in uremic subjects (1–3, 5, 6, 8–11). In a recent study using the glucose clamp technique (1) we documented that insulin secretion was not impaired in most patients with chronic renal failure. Instead, decreased tissue sensitivity to insulin was responsible for the abnormal glucose metabolism. Tissue insensitivity to insulin could result from any of the following three abnormalities: (a) augmented hepatic glucose production which is not normally suppressed by insulin, (b) impaired hepatic uptake of glucose, or (c) impaired peripheral (muscle and adipose) tissue uptake of glucose.

The present results indicate that neither augmented basal hepatic glucose production, nor incomplete suppression of hepatic glucose production following insulin can account for the marked insulin resistance observed in uremic patients under the present experimental conditions. Basal hepatic glucose production, measured with [^3H]-3-glucose, was 2.17 ± 0.04 mg/kg·min, a value that was nearly identical to controls, 2.18 ± 0.06 mg/kg·min. More important, after insulin, hepatic glucose production was suppressed by >90% in both the uremic and control groups. To provide an independent measure of hepatic glucose production, six uremic and six control subjects were studied simultaneously with tritiated glucose and hepatic venous catheterization. Again, in both uremic and control groups, basal splanchnic glucose production (1.57 ± 0.03 vs. 1.79 ± 0.20 mg/kg·min, respectively) was similar. After 90 min of insulin administration, splanchnic glucose balance reverted to a net uptake that was also similar in both uremics and controls (0.42 ± 0.11 vs.

0.53 ± 0.12 mg/kg·min). Because net splanchnic glucose balance (hepatic venous catheter technique) (SGB), and hepatic glucose production ([^3H]-3-glucose) (HGP) were measured simultaneously splanchnic glucose uptake (SGU) could be calculated from the equation: $\text{SGU} = \text{HGP} + \text{net SGB}$. As can be seen in Fig. 1, splanchnic glucose uptake in the postabsorptive state was similar in uremic and control subjects. After hyperinsulinemia, no significant change in splanchnic glucose uptake was observed in either group. These results indicate that differences in glucose uptake by the liver and extrahepatic splanchnic tissues can not account for the insulin resistance observed in uremic subjects after intravenous insulin and glucose administration. These results are in keeping with our previous observations (22) and indicate that (a) the primary effect of insulin is to suppress hepatic glucose production and (b) insulin has little effect on enhancing hepatic glucose uptake. Thus, the results of both the isotopic dilution studies as well as direct splanchnic arterio-venous glucose measurements are in close agreement, and indicate that neither excessive hepatic glucose production, nor impaired splanchnic glucose uptake can account for the glucose intolerance of uremia observed in the present study. It should be noted, however, that splanchnic glucose uptake following euglycemic hyperinsulinemia is quite small and represents only 5–10% of the total amount of glucose metabolized by the entire body. This is in keeping with our previous observations that splanchnic glucose uptake following intravenous insulin and/or intravenous glucose is small compared to that observed following oral glucose ingestion (22). Thus, although neither diminished splanchnic glucose uptake, nor impaired suppression of hepatic glucose production can account for the insulin resistance observed in the present study, further studies are needed to document whether an abnormality in hepatic glucose metabolism exists in uremic subjects following the ingestion of oral glucose. Studies by Sherwin et al. (23) have shown that the liver of chronically uremic subjects displays enhanced sensitivity to the stimulatory effect of glucagon on hepatic glucose production. In subsequent studies Soman and Felig (24) suggested that this higher sensitivity was due to increased glucagon binding to hepatic membranes with a resultant increase in cyclic AMP generation. Thus, it is possible that during conditions in which glucagon is increased, i.e., pure protein feeding or a mixed protein-carbohydrate meal, the suppression of hepatic glucose production by insulin may be incomplete.

Only one other study has examined hepatic glucose production in subjects with chronic renal failure. Rubenfeld and Garber (25) studied 13 normal-weight, chronically uremic subjects with a mean serum creat-

inine concentration of 10.7 ± 1.2 mg/dl. They found that basal hepatic glucose production in uremic subjects, 2.56 mg/kg·min, was increased by 38% compared to controls, 1.85 mg/kg·min ($P < 0.05$). The ability of insulin to suppress hepatic glucose production was not examined in this study. Several factors may explain the higher basal rates of hepatic glucose production reported by these authors. First, they used tritiated glucose labeled in the two position; this is known to overestimate glucose turnover because of the presence of futile cycles (26). Second, their equilibration curve for tritiated glucose specific activity suggests a failure to reach an equilibrium plateau; this would also tend to overestimate hepatic glucose production.

Because both suppression of hepatic glucose production and stimulation of splanchnic glucose uptake by insulin were similar in uremic and control subjects, the present results suggest that the primary site of insulin resistance in uremia resides in peripheral tissues. That this is indeed the case was confirmed by direct quantitation of insulin-mediated glucose uptake by the leg in uremic subjects. During the euglycemic insulin clamp study, leg uptake of glucose was reduced by 60%; this paralleled closely the 56% decrease in the total amount of glucose metabolized by the entire body.

These results suggest that the major site of insulin resistance in uremia resides in the periphery and are consistent with previous reports using the forearm infusion technique in chronically uremic man (27, 28). Mondon et al. (29) have reported similar results in rats made acutely uremic by bilateral nephrectomy. They found that glucose removal following intravenous glucose was markedly impaired despite higher insulin levels, thereby suggesting the presence of insulin resistance. Basal hepatic glucose production, as well as suppression of glucose production by insulin from isolated perfused livers from uremic rats, was normal. In contrast, the ability of insulin to enhance glucose uptake by the isolated perfused hindlimb of uremic rats was markedly impaired (29).

In summary, the findings of the present study demonstrate that tissue sensitivity to insulin is markedly impaired in uremia and that the primary site of this insulin resistance resides in peripheral tissues. The effect of intravenous insulin on hepatic glucose production and splanchnic glucose uptake are not altered by uremia.

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