The Effect of Graded Doses of Insulin on Total Glucose Uptake, Glucose Oxidation, and Glucose Storage in Man

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SUMMARY

The dose-response relationship between plasma insulin concentration and total glucose uptake, glucose oxidation, and glucose storage was examined in 22 healthy young volunteers by employing the euglycemic insulin clamp technique in combination with indirect calorimetry. Insulin was infused at five rates to achieve steady-state hyperinsulinemic plateaus of 62 ± 4, 103 ± 5, 170 ± 10, 423 ± 16, and 1132 ± 47 μU/ml. With increasing plasma insulin concentrations within the physiologic range, there was a linear increase in glucose uptake with a half maximally effective insulin concentration of 72 μU/ml. Glucose uptake by all tissues of the body reached 80% of its maximum value (12.6 mg/kg · min) at a plasma insulin concentration of ~200 μU/ml. In contrast to total glucose uptake, glucose oxidation plateaued more quickly, achieved a maximum rate of only 4.0 mg/kg · min, and displayed a lower half maximally effective insulin concentration of 40 μU/ml. The increase in glucose uptake with progressively increasing plasma insulin levels was primarily the result of an increase in glucose storage, with a half maximally effective insulin concentration of 105 μU/ml and maximum rate of 8.7 mg/kg · min. Glucose storage represented over 60–70% of total glucose uptake at all insulin concentrations. After achieving maximum rates of insulin-mediated glucose uptake (plasma insulin concentration = 1132 μU/ml), hyperglycemia (+125 mg/dl) was superimposed on hyperinsulinemia to further enhance glucose transport. Under these conditions, total glucose uptake (32.5 mg/kg · min, $P < 0.001$) was markedly augmented but no significant increase in glucose oxidation was observed. These results indicate a true saturation of the glucose oxidation pathway. With progressively increasing doses of insulin, the glucose storage represents the major route of glucose disposal. **DIABETES *31*:957–963, November 1982.**

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Following the infusion of insulin, there is a decline in the plasma glucose concentration which is the result of an inhibition of hepatic glucose production and a stimulation of glucose uptake by tissues. The glucose that is taken up by tissues may have one of two major fates. It can either be oxidized to carbon dioxide and water or it can be stored within the body as glycogen and lipid. Since recent studies by Björntorp et al.[1–3] have shown that adipose tissue is responsible for the disposal of less than 1–2% of both intravenously and orally administered glucose, it is likely that glycogen deposition in muscle and/or liver represents the primary form of glucose storage following glucose infusion or ingestion. Although several previous studies have examined the effect of insulin on suppression of hepatic glucose production[4–8] and total glucose uptake[4,8–10] in normal individuals, little information is available concerning the dose-response relationship between the plasma insulin concentration and insulin-mediated glucose oxidation and glucose storage. In the present study, we have employed the euglycemic insulin clamp technique[11] in combination with indirect calorimetry[12,13] to quantitate the effect of graded doses of insulin on glucose oxidation, glucose storage, and total glucose uptake in young healthy subjects.

METHODS

Study subjects. Twenty-two healthy male volunteers, ranging in age from 21 to 28 yr (mean ± SEM 23 ± 1 yr) were studied. Their ideal body weight (based on medium frame individuals from the Metropolitan Life Insurance Tables, 1959) ranged from 90 to 106% (mean 97 ± 2%). Their mean weight and height were 67 ± 3 kg and 175 ± 3 cm, respectively. No subject had a family history of diabetes mellitus and none was taking any medications. All were consuming

a weight-maintaining diet containing at least 250–300 g of carbohydrate per day for 3 days before each study. Prior to their participation the nature, purpose, and risks of the study were explained to all subjects and their voluntary consent was obtained. The experimental protocol was approved by the human investigation committee of the Department of Medicine of the University of Lausanne, Switzerland.

Experimental protocol. All studies were performed in the recumbent position at 8:00 a.m. following a 10–12-h overnight fast. A teflon catheter (Abbocath) was inserted into an antecubital vein for the infusion of all test substances. For blood sampling, a second catheter was inserted retrogradely into a wrist vein and kept patent with an infusion of isotonic saline. The hand was then inserted into a heated box (70°C) to achieve arterialization of the venous blood.[14] Forty-five minutes before beginning the insulin clamp studies, continuous respiratory exchange measurements were begun and continued throughout the duration of the experimental protocol.

Euglycemic insulin clamp. The effect of progressively increasing levels of hyperinsulinemia at a basal plasma glucose concentration was determined by the insulin clamp technique.[11] After a 60-min equilibration period, a prime-continuous infusion of crystalline porcine insulin was administered. The plasma glucose concentration was maintained constant at basal preinfusion levels by determination of the plasma glucose concentration every 5 min and periodically adjusting a variable 20% glucose solution based on a negative feedback principle.[11] The continuous infusion was given at 0.5, 1, 2, 4, and 10 mU/kg · min to groups A, B, C, D, and E, respectively, to achieve plasma insulin concentrations throughout the physiologic and supraphysiologic range. The number of subjects in each group was 9, 11, 9, 7, and 6, respectively. In all, 22 subjects participated in 42 insulin clamp protocols. All the subjects who received the 0.5- and 1-mU/kg · min insulin clamp study also participated in the 2- or 4-mU/kg · min insulin clamp protocol. Not all of the subjects who participated in the 0.5-mU/kg · min insulin clamp protocols participated in the 1-mU/kg · min insulin clamp studies. Four of the subjects in the 10-mU/kg · min insulin clamp study took part in the lower insulin dose infusion protocols. In subjects who participated in repeated studies, the second study was performed 1–3 wk after the initial one. Each insulin clamp study lasted for 120 min.

Combined hyperinsulinemic hyperglycemic clamp. In the 10-mU/kg · min insulin clamp study, after 120 min of sustained hyperinsulinemia, the plasma glucose concentration was raised by 125 mg/dl for 1 h. In this latter study, when the plasma glucose concentration was raised at 120 min, the insulin infusion rate was concomitantly decreased by 0.5 mU/kg · min every 15 min in an attempt to maintain a constant plateau of hyperinsulinemia.

Respiratory exchange measurements. During the 45-min control period and throughout the 2-h insulin clamp studies, substrate utilization rates were determined by computerized open-circuit indirect calorimetry using a ventilated hood as previously described.[13] Briefly, a transparent plastic ventilated hood is placed over the subject's head and made airtight around the neck. To avoid air loss, a slight negative pressure is maintained in the hood. Ventilation was measured with a massic flowmeter (Setaram, Lyon, France). A constant fraction of the air flowing out of the hood was automatically collected for analysis. The oxygen content was continuously measured by a thermomagnetic analyzer (Hartmann and Braun, Magnos) and carbon dioxide content by an infrared analyzer (Hartmann and Braun, Uras, 2T). The analyzers are calibrated before and after each test using gas mixtures prepared with a proportional pump (Wösthoff, Bochum, Germany). In addition, the whole system of indirect calorimetry can be checked by burning butane in a special hood; the amount of butane burnt is weighed and the corresponding oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are calculated using the stoichiometric equation of butane oxidation. The experimental values of VO_2 and VCO_2 correspond within ±1% to the expected values of VO_2 and VCO_2, respectively, obtained from stoichiometric calculations. The nonprotein respiratory quotient (NPRQ) was calculated from calorimetric values and urinary nitrogen.[15] Determination of carbohydrate (CHO) oxidation rate was obtained by using the table of Lusk[16] for NPRQ which is based on 0.707 R.Q. for 100% fat oxidation and 1.00 for 100% carbohydrate oxidation. The quantity of urinary nitrogen excreted during the study period was used to obtain an index of the amount of protein oxidized assuming that protein oxidation was relatively constant. It should be noted, however, that this assumption does not substantially affect the calculation of carbohydrate oxidation.[17] Lipogenesis from CHO does not invalidate calculation of CHO and lipid oxidation.[13] The coefficients of variation of NPRQ and CHO oxidation rates were measured over 5 consecutive days and were 1.0% and 5%, respectively. In two subjects, a glucose challenge (100-g oral load) was given on two occasions, and the reproducibility of CHO oxidation was witnessed. The amount of glucose stored during the test was calculated by subtracting the amount of glucose oxidized from the total amount of glucose infused.[18] No change was observed in the glucose concentration in the glucose space from the beginning to the end of the study.

Analytical procedures. Plasma glucose concentration was determined in duplicate by the glucose-oxidase method on a Beckman glucose analyzer II (Beckman Instrument, Inc., Fullerton, California). Plasma immunoreactive insulin was determined by radioimmunoassay as described by Herbert et al.[19] Plasma free fatty acids were extracted using the method of Dole and Meinertz[20] and determined according to the method of Heindel et al.[21] Glucagon was determined by radioimmunoassay as described by Aguilar-Parada et al.[22] Urinary nitrogen was measured by the method of Kjeldhal.[23]

Data analysis. During the 120-min insulin clamp study the glucose infusion rate was calculated at 20-min intervals. For data presentation, the mean of the three 20-min values from 60–120 min is given. Hepatic glucose production was not determined in the present studies. However, it has been previously shown that in normal subjects infusion of insulin at a rate of 1 mU/kg · min (plasma insulin levels of 100 μU/ml) or greater suppresses hepatic glucose production by over 90–95%.[4,24] Therefore, under the steady-state conditions of euglycemia employed in the present protocol (1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies), glucose uptake by the entire body must be approximately equal to the rate of exogenous glucose infusion. During the 0.5-mU/kg · min insulin clamp study suppression of hepatic glucose production is slightly less complete, 87%.[4] In the basal state, in young subjects, hepatic glucose produc-

tion has previously been measured (with ^{3}H-3-glucose) and found to be 2.2 ± 0.1 mg/kg · min.[4] Therefore, in the lowest dose insulin clamp study total glucose uptake would be slightly underestimated by about 0.3 mg/kg · min.

The glucose oxidation rate was calculated from calorimetric measurements for 5-min intervals during the basal state and throughout the 120-min insulin clamp period. Glucose storage was calculated by subtracting the rate of glucose oxidation during a given time period from the total rate of glucose uptake during the same time period.[18] Presented values for glucose oxidation and glucose storage represent the mean for the 60–120-min time period. To calculate steady-state plasma glucose and insulin concentrations during the insulin clamp, the mean of values (every 5 min for glucose and every 10 min for insulin) from 60–120 min were employed. The mean values during the 60–120-min time period were chosen to allow insulin to more fully exert its biologic effect.

All data are presented as the mean ± SEM. Statistical comparisons between groups were performed by unpaired *t* test analysis where appropriate. Coefficients of variation were determined by standard formulae.

RESULTS

Plasma glucose, insulin, and glucagon (Table 1). The mean fasting plasma glucose concentration (93 ± 2 mg/dl) was similar in the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies. During the last 60 min of the euglycemic insulin clamp, the steady-state plasma glucose values were 93 ± 2, 92 ± 2, 92 ± 1, 93 ± 1, and 92 ± 2 mg/dl with coefficients of variation of 2.7 ± 1, 3.2 ± 1, 3.1 ± 1, 3.4 ± 1, and 2.6 ± 1%, respectively. The fasting plasma insulin concentrations in the five groups were 13 ± 2, 11 ± 1, 13 ± 2, 14 ± 2, and 11 ± 1 μU/ml. The steady-state plasma insulin levels during the 60–120-min time period were 62 ± 4, 103 ± 5, 170 ± 10, 423 ± 16, and 1132 ± 47 μU/ml with coefficients of variation of 7.4 ± 1, 7.8 ± 1, 10.5 ± 1, 8.2 ± 2, and 8.1 ± 1, respectively. In the 10-mU/kg · min insulin clamp study, when hyperglycemia was superimposed on hyperinsulinemia, the mean plasma insulin and glucose concentrations during the 120–180-min time intervals were 1072 ± 43 μU/ml and 218 ± 5 mg/dl, respectively. The plasma insulin concentration was not significantly different from the 60–120-min time period in euglycemia (1132 ± 47 μU/ml).

Plasma glucagon. The fasting plasma glucagon concentrations in the five groups were 98 ± 3, 96 ± 3, 99 ± 4, 96 ± 3, and 88 ± 4 pg/ml. The steady-state plasma glucagon levels during the 60–120-min time period were significantly decreased: 68 ± 4, 59 ± 4, 52 ± 5, 48 ± 2, and 36 ± 4 pg/ml.

Glucose metabolism (Tables 1 and 2). During the 60–120-min time period, the glucose infusion rates required to maintain euglycemia during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies were 5.9 ± 0.4, 7.3 ± 0.3 ($P < 0.01$), 9.9 ± 0.4 ($P < 0.001$), 11.1 ± 0.4 ($P < 0.05$), and 11.8 ± 0.5 (P = NS) mg/kg · min, respectively. The P values refer to each preceding insulin clamp study (Figures 1 and 2). Basal glucose oxidation was similar in all groups and averaged 1.3 ± 0.1 mg/kg · min (Table 2). Following insulin infusion, glucose oxidation (60–120 min) averaged 2.4 ± 0.1, 3.1 ± 0.2 ($P < 0.005$), 3.4 ± 0.2 (P = NS), 3.7 ± 0.1 (P = NS), and 3.7 ± 0.2 (P = NS) mg/kg · min, respectively (Figure 1). The increment in glucose oxidation above basal was 1.1 ± 0.1, 1.8 ± 0.2 ($P < 0.001$), 2.1 ± 0.2 (P = NS), 2.3 ± 0.1 (P = NS), and 2.4 ± 0.2 (P = NS) mg/kg · min. Again, the P values refer to the immediately preceding period. The total rate of glucose oxidation as well as the increment in oxidation above basal during the 4- and 10-mU/kg · min insulin clamp studies was significantly greater than during the 1-mU/kg · min insulin study. The glucose storage rate during each of the five insulin clamp protocols was 3.6 ± 0.2, 4.2 ± 0.3 ($P < 0.001$), 6.5 ± 0.4 ($P < 0.05$), 7.4 ± 0.3 (P = NS), 8.0 ± 0.4 (P = NS) mg/kg · min, respectively. In the 10-mU/kg · min insulin clamp study, when hyperglycemia was created from 120 to 180 min, total glucose oxidation (4.0 ± 0.2 mg/kg · min) failed to increase significantly above that observed during euglycemic hyperinsulinemic conditions, 3.7 ± 0.2 mg/kg · min. In contrast, glucose storage rose significantly to 28.4 ± 0.8 mg/kg · min ($P < 0.001$) (Figure 2).

The maximum rates in euglycemic conditions of total glucose uptake, glucose oxidation, and glucose storage were

TABLE 1
Summary of plasma glucose and insulin concentrations and total glucose uptake, glucose oxidation, and glucose storage during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies

Insulin infusion rate	N	Steady state plasma glucose (mg/dl)	Steady state plasma insulin (μU/ml)	Total glucose uptake (mg/kg · min)	Total glucose oxidation (mg/kg · min)	Total glucose storage (mg/kg · min)
Euglycemic hyperinsulinemia						
0.5 mU/kg · min	9	93 ± 2	62 ± 4	5.9 ± 0.4	2.4 ± 0.1	3.6 ± 0.2
1.0 mU/kg · min	11	92 ± 2	103 ± 5	7.3 ± 0.3†	3.1 ± 0.2‡	4.2 ± 0.3
2.0 mU/kg · min	9	92 ± 1	170 ± 10	9.9 ± 0.4‡	3.4 ± 0.2	6.5 ± 0.4‡
4.0 mU/kg · min	7	93 ± 2	423 ± 16	11.1 ± 0.4*	3.7 ± 0.1	7.4 ± 0.3*
10 mU/kg · min	6	92 ± 2	1132 ± 47	11.8 ± 0.5	3.7 ± 0.2	8.0 ± 0.4
Hyperglycemic hyperinsulinemia						
10 mU/kg · min	6	218 ± 5‡	1072 ± 43	32.5 ± 0.8‡	4.0 ± 0.2	28.4 ± 0.8

All values represent the mean ± SEM for the basal or 60–120-min time period. N refers to the number of subjects in each group.
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.

TABLE 2
Summary of total oxidation rate, basal and increase above basal carbohydrate oxidation, basal and postinsulin lipid oxidation, and protein oxidation during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies

Insulin infusion rate	Glucose oxidation (mg/kg · min)		Lipid oxidation (mg/kg · min)		Protein oxidation (mg/kg · min)
	Basal	Suprabasal	Basal	Postinsulin	
Euglycemic hyperinsulinemia					
0.5 mU/kg · min	1.3 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.6 ± 0.05	0.9 ± 0.1
1.0 mU/kg · min	1.3 ± 0.1	1.8 ± 0.2*	1.1 ± 0.1	0.3 ± 0.05*	0.8 ± 0.1
2.0 mU/kg · min	1.2 ± 0.1	2.1 ± 0.2	1.1 ± 0.1	0.2 ± 0.03	0.9 ± 0.1
4.0 mU/kg · min	1.3 ± 0.1	2.3 ± 0.1	1.0 ± 0.1	0.1 ± 0.03	0.9 ± 0.1
10 mU/kg · min	1.3 ± 0.1	2.4 ± 0.2	1.0 ± 0.1	0.04 ± 0.04	1.0 ± 0.1
Hyperglycemic hyperinsulinemia					
10 mU/kg · min	1.3 ± 0.1	2.7 ± 0.2	1.0 ± 0.1	0.00 ± 0.05	1.0 ± 0.1

All values represent the mean ± SEM for the basal or 60–120-min time period.
* $P < 0.001$.

12.6, 4.0, and 8.7 mg/kg · min. The half maximally effective insulin concentration was 72, 40, and 105 mU/ml, respectively.

Plasma free fatty acids and lipid oxidation. The mean fasting plasma free fatty acid concentrations in the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies were 389 ± 6, 368 ± 8, 381 ± 5, 385 ± 8, and 371 ± 7 μmol/L, respectively. During the last 60 min of the euglycemic clamp, the plasma free fatty acid concentrations were all significantly decreased: 161 ± 5, 151 ± 3, 149 ± 4, 138 ± 3, and 130 ± 6 μmol/L, respectively. The fall in plasma free fatty acid levels was proportional to the steady-state plasma insulin concentration during the euglycemic clamp ($r = 0.90$, $P < 0.001$). Lipid oxidation during the 60–120-min period was 0.6 ± 0.05, 0.3 ± 0.05, 0.2 ± 0.03, 0.1 ± 0.03, and 0.04 ± 0.04 in the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies (Table 2). The fall in lipid oxidation was also proportional to the steady-state plasma insulin concentration during the euglycemic clamp ($r = 0.92$, $P < 0.001$).

DISCUSSION

Little information is presently available concerning the dose-response relationship between the plasma insulin concentration and the two major routes of glucose disposal, namely glucose oxidation and glucose storage. In the present study, the insulin clamp technique[11] was combined with indirect calorimetry[12,13] to examine these relationships. From Figure 1, it can be appreciated that the total rate of glucose uptake rises very steeply with plasma insulin concentrations within the physiologic range (62–170 μU/ml). It can be estimated that the maximal rate of glucose uptake under euglycemic conditions in postabsorptive man is approximately 12.6 mg/kg · min and that the plasma insulin

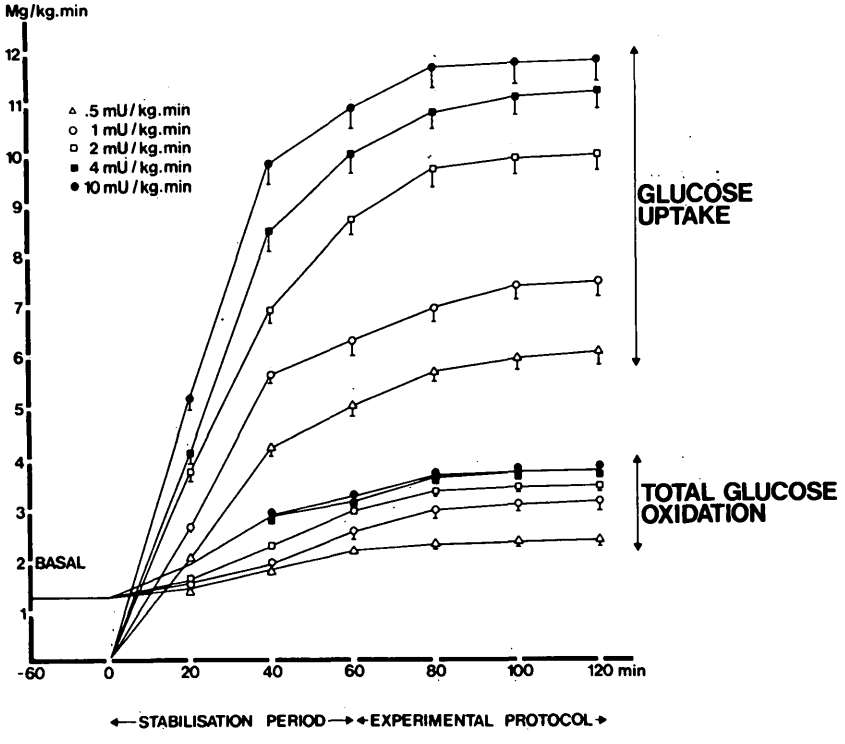

FIGURE 1. Time course of the glucose infusion rate (i.e., glucose uptake) and total glucose oxidation rate during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies. Values from 0 to 60 min represent the stabilization period and those from 60 to 120 min show the experimental protocol time period.

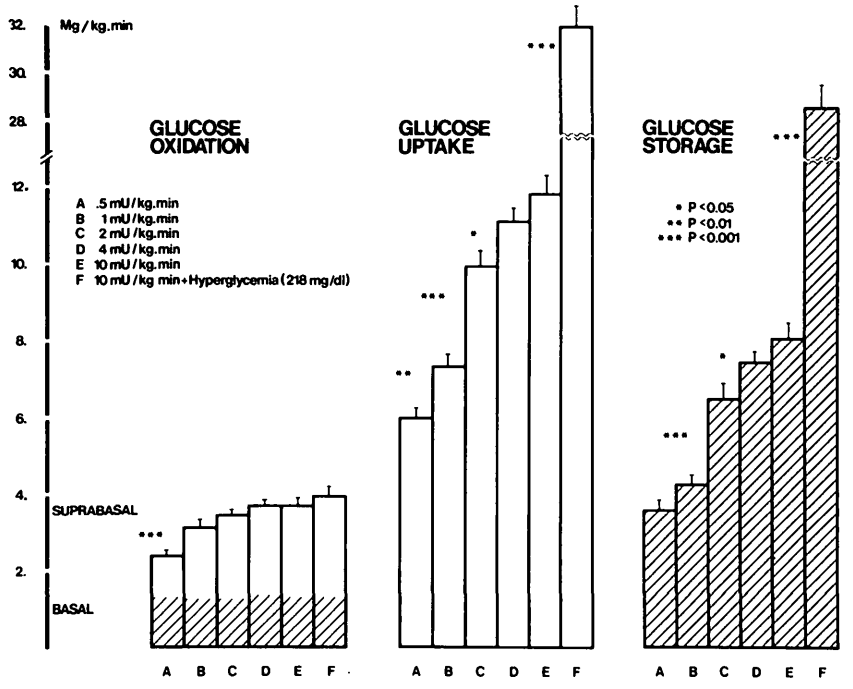

FIGURE 2. Summary of total glucose oxidation (basal in cross-hatched areas and suprabasal in clear areas above basal), total glucose uptake, and glucose storage during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies. The height of each bar represents the mean ± SEM for the 60–120-min time period. The P values above each bar refer to the following insulin clamp study.

concentration at which half-maximal stimulation occurs is 72 μU/ml. In a recent report, Rizza et al.[8] found a somewhat lower Km (55 μU/ml). Part of the difference between their results and present ones can be accounted for by the fact that they found a lower maximal rate of glucose uptake (10 mg/kg · min). Using the maximal uptake rate (12.6 mg/kg · min) obtained in the present study on their curve, one calculates a half maximally effective insulin concentration of approximately 70 μU/ml. This is very similar to the value observed by us (72 μU/ml).

Previous studies demonstrated that under euglycemic conditions, total glucose uptake plateaued at plasma insulin concentrations between 400–1100 μU/ml.[4] Kolterman et al. achieved a plateau between 300–1000 μU/ml.[9] Plasma insulin levels between 100 and 300–400 μU/ml were not examined in these previous studies.[8] From Figure 3, it can be seen that at a plasma insulin concentration of 200 μU/ml, the rate of glucose uptake had achieved 80% of its maximal value. These results are in agreement with the forearm infusion studies of Zierler and Rabinowitz,[24] who found that a plasma insulin concentration of approximately 200 μU/ml elicited a near maximum uptake of glucose by the human forearm.

The present observations may give some insight concerning the successful use of "low" versus "high" dose insulin in the therapy of diabetic ketoacidosis.[25,26] It should be noted that the so-called "low-dose therapy" (6–8-U bolus followed by 6–8 U/h) results in plasma insulin levels in excess of 200 μU/ml.[26] Thus, this "low-dose therapy" actually achieves plasma insulin levels that are maximally effective in stimulating glucose uptake in normal man. They are also well above the insulin levels necessary to maximally inhibit

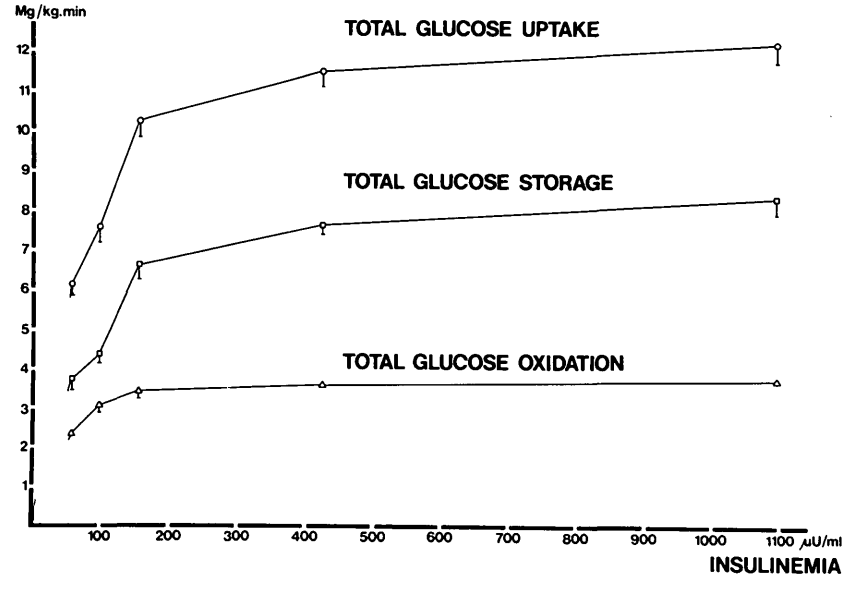

FIGURE 3. Dose-response relationship between the plasma insulin concentration (X axis) and total glucose uptake, glucose oxidation, and glucose storage (Y axis) during the 0.5-, 1-, 2-, 4-, and 10-mU/kg · min insulin clamp studies.

hepatic glucose production[4,8] and lipolysis.[27] Thus, it should not be surprising that "low-dose" insulin therapy has proven as effective as "high-dose" therapy[25,26] in the treatment of diabetic ketoacidosis. However, it should be noted that in some diabetic patients with ketoacidosis, who have particularly high circulating levels of counterregulatory hormones, plasma insulin concentrations in excess of 200 μU/ml may be needed to maximally stimulate glucose metabolism. In the basal state, the rate of glucose oxidation was 1.25 ± 0.1 mg/kg · min. The majority of this represents glucose oxidation by the brain and is presumed to be insulin-independent.[28–32] From Figure 3, it can be seen that the dose-response curve between the plasma insulin concentration and glucose oxidation is very different from the one relating plasma insulin to glucose uptake. The V_{max} for glucose oxidation is 4.0 mg/kg · min, a value only 30% of that for total insulin-mediated glucose uptake. This is also true whether one examines the half maximally effective insulin concentration for total glucose uptake and total glucose oxidation (72 versus 40 μU/ml, $P < 0.001$). It is particularly noteworthy that at all plasma insulin concentrations, the ability of the body to oxidize glucose is limited and that within the physiologic range of plasma insulin concentration, the rate of rise in glucose oxidation is less steep than for glucose storage or total glucose uptake. This relationship predicts that with increasing plasma insulin concentrations, glucose oxidation represents a progressively smaller amount of glucose uptake. Thus, as the plasma insulin concentration is increased from basal to 170 μU/ml, glucose oxidation rose only from 1.25 (basal value) to 3.4 mg/kg · min (Table 1, Figure 2). Consequently, glucose storage, which rose to 6.5 mg/kg · min, quantitatively became the most important route of glucose disposal.[33] To examine whether the plateau in glucose oxidation observed at plasma insulin concentration in excess of 170 μU/ml was due to a limitation in glucose transport or was due to a true saturation of the glucose oxidative pathway, at the end of the 2-h, 10-μU/kg · min insulin clamp the plasma glucose concentration was raised by 125 mg/dl while maintaining the plasma insulin concentration constant at 1072 ± 43 μU/ml. When hyperglycemia was superimposed, the total rate of glucose uptake increased from 11.8 ± 0.5 to 32.5 ± 0.8 mg/kg · min, yet glucose oxidation failed to increase significantly. These results indicate that there is a true saturation of one or more steps involved in glucose oxidation and they further emphasize that at high rates of glucose uptake, glucose storage represents the major fate of glucose disposal.

The maximal rate of glucose oxidation (3.7 mg/kg · min) corresponds to an energy expenditure of 13.7 cal/g · min, or approximately 85% of the total energy expenditure measured, 15% being covered by an obligatory protein oxidation. Thus, suprabasal glucose oxidation completely replaced lipid oxidation (Table 2). On the other hand, for thermogenic reasons, the rate of glucose oxidation cannot exceed the measured values for resting subjects.

It is noteworthy that in the postabsorptive state, there is a significant amount of glucose that is taken up and disposed of by nonoxidative pathways. Assuming that rate of endogenous glucose production is 2.2 mg/kg · min[34] and with a mean measured basal rate of glucose oxidation of 1.25 mg/kg · min (Table 1), then approximately 1.0 mg/kg · min of basal endogenous glucose production is accounted for by nonoxidative glucose metabolism. As discussed in an earlier paper,[35] the apparent glucose "storage" is probably the result of several processes including: (1) glucose uptake and conversion to lactate by extrahepatic splanchnic tissues,[36–39] and by peripheral tissues including muscle,[40–42] erythrocytes,[43] bone marrow elements,[44] and renal medulla;[45] (2) glucose conversion to lipid;[46,47] (3) gluconeogenesis;[48] and (4) re-uptake of glucose by the splanchnic tissues, liver or gastrointestinal.[36] Following the infusion of insulin, there was a marked increase in glucose storage and the time course of increase closely paralleled the increase in total glucose uptake. The site and form in which glucose is stored cannot be determined from the present study. However, previous studies[4,49,50] have shown that the majority of intravenously infused glucose is taken up by peripheral tissues, primarily muscle.[35,51] Since insulin is known to stimulate glycogen synthetase and enhance muscle glycogen formation,[49–59] it is likely that glycogen represents the major storage form of glucose following insulin infusion.

In summary, physiologic increments in the plasma insulin concentration cause a dose-response-related increase in glucose uptake with a maximum rate of ~13 mg/kg · min. At a plasma insulin concentration of 200 μU/ml, 80% of the maximum rate of glucose uptake is achieved. In contrast, the ability of insulin to stimulate glucose oxidation is quite limited, having a maximum rate of only 4.0 mg/kg · min. Thus, with progressively increasing doses of insulin, glucose storage (presumably as glycogen) represents the major route of glucose disposal. Comparing the half maximally effective insulin concentration of total glucose oxidation (40 μU/ml) versus glucose storage (105 mU/ml), it appears that glucose oxidation becomes saturated at lower plasma insulin concentration than glucose storage.

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