Glucose Disposal is Not Proportional to Plasma Glucose Level in Man

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SUMMARY

Metabolic clearance rate (MCR) of glucose has been defined as the rate of glucose utilization divided by the glucose concentration. This model of glucose transport has been widely used as a measure of hormonally regulated glucose disposal, on the assumption that glucose disposal rate is proportional to glucose concentration. To test this assumption, the relationship between glucose concentration and disposal rate was studied in man during infusion of somatostatin ± exogenous insulin to achieve fixed plasma insulin levels of 1, 18, and 46 μU/ml on separate days. When glucose concentration was increased to more than twice basal fasting levels, the glucose disposal rate increased significantly at all three insulin levels. However, the increase was not proportional to the rise in glucose concentration, and MCR fell by 38%, 16%, and 11% at the low, medium, and high insulin levels, respectively. These results are explained by an alternative model of glucose transport in which insulin-independent tissues such as brain have a relatively fixed glucose uptake, while other tissues have glucose transport systems which take up glucose at a rate proportional to its plasma concentration. We conclude that MCR of glucose is not a good measure of hormonally regulated glucose disposal because it is partially dependent on the glucose concentration, particularly at low insulin levels. DIABETES *30*:847–850, October 1981.

Because glucose disposal rate is influenced by the glucose concentration, the ratio of glucose disposal rate to glucose concentration (MCR of glucose) was chosen as a measure of the "overall efficiency" of the removal of glucose.[1] Subsequently, it was assumed that glucose disposal is proportional to glucose concentration, and that MCR of glucose is therefore a measure of hormone-dependent glucose disposal independent of the glucose concentration.[2] Based on this assumption, MCR has been widely used to correct for the effects of experimentally induced hyperglycemia on glucose disposal in order to interpret how glucose disposal is affected by various changes in hormone levels.[2–5] However, non-insulin-dependent tissues such as brain account for most of the glucose utilized in the fasting state,[6] and during hyperglycemia these tissues may not increase their uptake of glucose in proportion to the rise in glucose level.[7] Because this possibility would invalidate MCR as an accurate measure of hormone-dependent glucose disposal, the relationship between glucose concentration and glucose disposal rate was evaluated in man.

MATERIALS AND METHODS

Six healthy, male subjects aged 21–34 yr and all within 10% of their ideal body weight were studied after an overnight fast. A catheter was placed in the cubital fossa vein of one arm for the infusion of isotope, hormones, and glucose. Venous blood samples were obtained through a scalp vein needle in the cubital fossa of the other arm, while "arterialized" venous blood was sampled through a scalp vein needle in a dorsal vein of the ipsilateral hand, which was kept in a heated box (60°C) during the study.

All subjects were infused with cyclic somatostatin 500 μg/h (courtesy of Dr. Jean Rivier, Salk Institute, San Diego, California) in order to suppress endogenous insulin secretion. Arterialized plasma glucose concentration was measured at the bedside (Beckman glucose analyzer) at 5-min intervals throughout the study. A variable-rate glucose infusion was adjusted according to the plasma glucose level in order to "clamp" plasma glucose close to the fasting level for the first measurement of glucose disposal rate (euglycemic clamp), and then at approximately double that level for a second measurement of glucose disposal rate (hypergly-

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cemic clamp). The effect of this change of plasma glucose concentration on glucose disposal rate was studied at three different insulin levels on separate days. All subjects were studied both without insulin replacement and during an insulin infusion rate of 200 μU/kg/min, and five of the six subjects were also studied during an insulin infusion rate of 500 μU/kg/min. Somatostatin and insulin (purified pork insulin, Eli Lilly & Company, Indianapolis, Indiana) were dissolved in 0.9% NaCl containing 0.5% human serum albumin. A primed (15–25 μCi) continuous (0.15–0.25 μCi/min) infusion of 3-^{3}H-glucose (New England Nuclear, Boston, Massachusetts) was used for isotopic determination of glucose disposal rate. The first measurement of glucose disposal was made between 150 and 190 min after somatostatin ± insulin infusion was begun. The measurement at the higher glucose level was made between 90 and 130 min after the first measurement. At the end of each study, urine was collected and glucose content measured to ensure that there was no significant glycosuria.

Blood samples were obtained at 10-min intervals basally and over the two 40-min sampling periods described above. Plasma and urine glucose levels were measured by the Autoanalyzer glucose oxidase method (Technicon Instruments). Plasma insulin (IRI) levels were measured by a modification of the double antibody method of Morgan and Lazarow.[8] Plasma glucagon (IRG) was measured by radioimmunoassay, employing a C-terminal-directed antiserum.[9] To rule out effects of possible changes of catecholamine levels on glucose uptake, plasma norepinephrine and epinephrine were measured by single isotope enzymatic assay.[10] Basal values for glucose, insulin, glucagon, epinephrine, and norepinephrine are the mean of two samples. Values during the euglycemic and hyperglycemic clamps are the mean of two (epinephrine and norepinephrine), three (insulin and glucagon), or five (glucose) samples. Plasma 3-^{3}H-glucose specific activity was determined as described by Rizza et al.[11] The average coefficient of variation for the specific activity of glucose in the five samples during the euglycemic clamp and in the five samples during the hyperglycemic clamp was less than 3%. Glucose disappearance was calculated using the non-steady-state equations of Steele as modified by DeBodo et al.[12] Data are expressed as mean ± SEM. Statistical analysis was by two-tailed paired Student's *t* test.

RESULTS

In the absence of concurrent insulin infusin, somatostatin resulted in suppression of plasma IRI to I μU/ml even when plasma glucose was increased to 195 ± 5 mg/dl (see Table 1). Similarly, when insulin was infused with somatostatin, plasma IRI remained constant despite a doubling of plasma glucose. Plasma IRG was also suppressed by somatostatin, but plasma epinephrine and norepinephrine were unaffected (Table 1).

The effects of different IRI levels and changes of plasma glucose on glucose disposal rate (Rd) and MCR are illustrated in Figure 1. When plasma glucose concentration was increased from 85 ± 4 to 195 ± 5 mg/dl while insulin was suppressed (no insulin infusion), glucose disappearance rate increased from 1.62 ± 0.11 to 2.30 ± 0.13 mg/kg/mln ($P < 0.001$), but MCR fell from 1.90 ± 0.07 to 1.18 ± 0.08 ml/kg/min ($P < 0.001$). When insulin was infused with somatostatin to achieve a plasma IRI level of 18 ± 2 μU/ml, Rd during the euglycemic clamp was greater than when no insulin was infused (2.72 ± 0.24 vs. 1.62 ± 0.11, $P < 0.025$). When plasma glucose concentration was then increased from 89 ± 5 to 193 ± 5 mg/dl, glucose disappearance rate increased further to 5.07 ± 0.65 mg/kg/min ($P < 0.005$), but MCR fell from 3.16 ± 0.37 to 2.65 ± 0.35 ml/kg/min ($P < 0.05$). When plasma IRI levels were raised to 46 ± 5 μU/ml by infusing a higher dose of insulin, Rd during the euglycemic clamp was significantly greater than during the lower

TABLE 1
Concentrations of glucose, insulin (IRI), glucagon (IRG), epinephrine (Epi), and norepinephrine (Norepi) basally and during euglycemic and hyperglycemic glucose clamp periods*

	No insulin study (N = 6)	Medium insulin study (200 μU/kg/min) (N = 6)	High insulin study (500 μU/kg/min) (N = 5)
Glucose (mg/dl)			
Basal	85 ± 3	83 ± 2	82 ± 2
Euglycemic clamp	85 ± 4	89 ± 5	89 ± 3
Hyperglycemic clamp	195 ± 5†	193 ± 5†	206 ± 2†
IRI (μU/ml)			
Basal	6 ± 2	6 ± 2	8 ± 2
Euglycemic clamp	1 ± 0.3†	18 ± 2†	47 ± 5†
Hyperglycemic clamp	1 ± 0.3†	18 ± 2†	45 ± 4†
IRG (pg/ml)			
Basal	56 ± 10	82 ± 17	89 ± 9
Euglycemic clamp	37 ± 9†	64 ± 17†	63 ± 10†
Hyperglycemic clamp	36 ± 9†	63 ± 15†	58 ± 10†
Epi (pg/ml)			
Basal	55 ± 12	43 ± 4	36 ± 10
Euglycemic clamp	48 ± 14	45 ± 7	31 ± 15
Hyperglycemic clamp	44 ± 10	40 ± 9	34 ± 9
Norepi (pg/ml)			
Basal	158 ± 33	160 ± 18	200 ± 36
Euglycemic clamp	150 ± 40	181 ± 27	225 ± 37
Hyperglycemic clamp	127 ± 29	185 ± 20	235 ± 20

* Clamp studies were performed with somatostatin + variable rate glucose infusion ± exogenous insulin infusion.
† Significantly different from basal level (all $P < 0.025$). All values are $\bar{x}$ ± SEM.

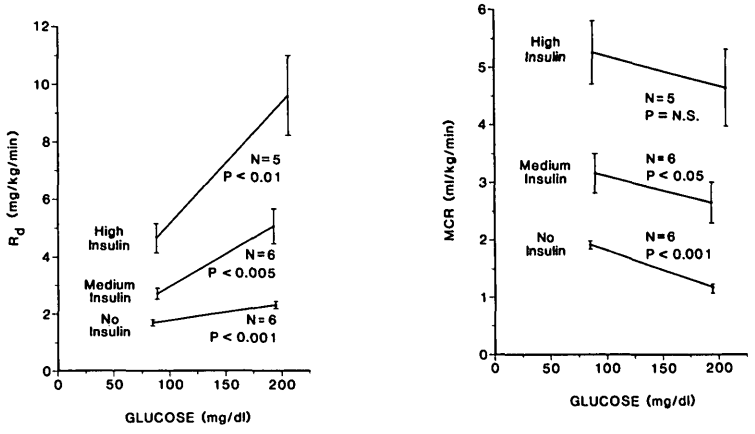

FIGURE 1. Glucose disposal rate (Rd, left panel) and metabolic clearance rate of glucose (MCR, right panel) during the euglycemic and hyperglycemic clamp periods. Values are shown as mean ± SEM during high insulin (500 μU/kg/min) and medium insulin (200 μU/kg/min) infusions, and when no insulin was infused.

insulin infusion rate ($P < 0.025$). An increase of plasma glucose concentration from 89 ± 3 to 206 ± 2 mg/dl led to an increase of Rd from 4.64 ± 0.55 to 9.63 ± 1.41 mg/kg/min ($P < 0.01$). MCR fell in four out of five subjects, but the difference was not significant (5.24 ± 0.57 vs. 4.64 ± 0.67 ml/kg/min). Thus, MCR did not remain constant when plasma glucose was increased, but fell by 11% at the higher insulin level, by 16% at the intermediate insulin level, and by 38% when insulin levels were very low.

If it is assumed that the total glucose disappearance rate is proportional to the glucose concentration (i.e., that the glucose clearance model is correct), the glucose disappearance rate during hyperglycemia should be predicted by:

$$MCR_2 = \frac{Rd_2}{G_2} = \frac{Rd_1}{G_1} = MCR_1 \text{ and } Rd_2 = \frac{G_2}{G_1} Rd_1$$

where Rd_1 = glucose disposal rate during the euglycemic clamp (glucose level G_1) and Rd_2 = glucose disposal rate during the hyperglycemic clamp (glucose level G_2).

As demonstrated in Table 2, this glucose clearance model was not a good predictor of Rd during hyperglycemia. A more accurate predictor of the actual values for glucose disposal was obtained with a model which assumes that there is a fixed uptake (not dependent on glucose level), plus proportional uptake. The formula for this model is:

$$Rd_2 = \frac{G_2}{G_1} (Rd_1 - \text{Rd fixed}) + \text{Rd fixed}$$

where Rd fixed = glucose disposal that is not dependent on the glucose level.

The value of Rd fixed for this group of subjects was derived as follows from the results shown in Figure 1. The lines connecting Rd during euglycemic and hyperglycemic clamps at the three different insulin levels can be extrapolated to meet the y intercept at approximately 1 mg/kg/min. This amount of glucose disposal is thus presumed to be independent of the glucose and insulin concentrations.

DISCUSSION

Glucose disposal rate is the sum of the rates of transfer of glucose from plasma into the cells of all the body tissues. Glucose is transferred from plasma into cells mainly by a facilitated transport mechanism, whose behavior can be described by Michaelis-Menten kinetics.[13] As a result, an increase in glucose concentration at a fixed insulin level will increase glucose transport into a particular tissue, provided that the glucose transport system for that tissue is not saturated. However, glucose uptake by some tissues such as brain may not increase very much during hyperglycemia because the glucose transport system across the blood-brain barrier probably becomes saturated at a glucose concentration near 100 mg/dl.[7] As shown in Figure 1, the glucose disposal rate at a given glucose level is also dependent on the insulin level. However, glucose transport to some tissues, particularly brain, seems to be influenced only modestly by increases in insulin.[14]

In this study hyperglycemia resulted in an increase in glucose disposal rate at all three insulin levels, but the increase was not proportional to the rise in glucose concentration. These findings are consistent with the concept that insulin-independent tissues such as brain have a relatively fixed glucose uptake while the insulin-sensitive tissues ex-

TABLE 2
Comparison of measured glucose disposal rate during the hyperglycemic clamp period with values predicted by the two models

	No insulin	Insulin (200 μU/kg/min)	Insulin (500 μU/kg/min)
Measured disposal rate (mg/kg/min)	2.30 ± 0.13	5.07 ± 0.65	9.63 ± 1.41
Glucose clearance model prediction (mg/kg/min)	3.73 ± 0.12**	6.00 ± 0.64*	10.81 ± 1.19
Fixed + proportional model prediction (mg/kg/min)	2.39 ± 0.17	4.80 ± 0.59	9.47 ± 1.19

* $P < 0.05$, ** $P < 0.001$: significantly different from measured disposal rate.

hibit a proportional (to glucose concentration) uptake of glucose. The model that included both types of glucose uptake accurately predicted Rd during hyperglycemia at fixed insulin levels (see Table 2) using a fixed uptake value of 1 mg/kg/min. This value is slightly less than the rate of glucose utilization by brain, estimated in man to be 95 mg/min or 1.3 mg/kg/min for a 75-kg man.[6] The blood-brain glucose transport system is not completely insensitive, however, to increases in glucose or insulin levels.[7,14]

Several physiologic conditions during this study could potentially affect the interpretation of the data. First, somatostatin was infused and was assumed to have no direct effect on glucose disposal or at least on the effect of hyperglycemia on glucose disposal. Studies in vivo and in vitro support the validity of this assumption[15,16] for experiments in animals. In man, the reduction of portal blood flow by somatostatin[17] could potentially affect glucose uptake by the gut and liver. However, it is unlikely that a reduction in blood flow to these tissues would explain the results of this study, as the somatostatin infusion rate was identical during all measurements of glucose disposal. Second, insulin was infused peripherally, altering the usual portal to peripheral insulin ratio. However, the hepatic contribution to glucose disposal during the intravenous infusion of insulin and glucose has been shown to be dependent more on glucose than on insulin concentration.[18] Finally, glucagon was not replaced during the somatostatin infusion because at the low insulin level it would have produced marked hyperglycemia, which would have prevented the measurement of glucose disposal over an adequate range of glucose concentration. There is some evidence that glucagon can inhibit glucose uptake, presumably by the liver,[19] but in animal studies the presence of glucagon did not prevent the increment in glucose uptake produced by hyperglycemia. In these studies, Cherrington et al. measured glucose disposal at several glucose levels by infusing dogs with somatostatin and intraportal replacement doses of insulin and glucagon.[20] When glucose concentration was increased from a mean level of 104 to 236 mg/dl, glucose disposal rate increased from 3.58 to 6.93 mg/kg/min. The value predicted by the fixed (1 mg/kg/min) plus proportional uptake model for glucose disposal rate at the higher glucose concentration is 6.87 mg/kg/min. Thus, the findings in dogs receiving the more physiologic intraportal replacement of both insulin and glucagon agree very closely with our model for glucose disposal in man.

In summary, these data provide evidence that glucose concentration is an important determinant of the rate of glucose disposal in man, even when insulin levels are below basal. However, the rate of glucose disposal in man is not proportional to the glucose concentration, probably because glucose uptake by some tissues, such as brain, does not increase very much during hyperglycemia. As a result, the MCR of glucose is partially dependent on the glucose concentration. Thus, MCR cannot be used to correct for the effect of hyperglycemia on glucose disposal in order to assess hormone effects on glucose uptake. The MCR model is particularly inaccurate at low insulin levels, when glucose uptake by non-insulin-dependent tissues accounts for a relatively large fraction of total glucose uptake.

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Note added in proof. Following submission of this manuscript, a paper describing the relationship between glucose concentration and glucose disposal at a fixed insulin level of 18 μU/ml has been published confirming our results for that insulin level (Verdonk, C. A., Rizza, R. A., and Gerich, J. E.: Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. Diabetes *30*: 535–37, 1981).

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