Rapid Publication

Effects of Plasma Glucose Concentration on Glucose Utilization and Glucose Clearance in Normal Man

CARLOS A. VERDONK, ROBERT A. RIZZA, AND JOHN E. GERICH

SUMMARY

Glucose clearance (glucose utilization ÷ plasma glucose) is commonly used to assess glucose utilization under conditions in which plasma glucose concentrations vary. The validity of this practice requires that glucose clearance itself be independent of plasma glucose concentration. The present studies were, therefore, undertaken to determine the relationship between glucose clearance and plasma glucose concentration in man. Using the glucose clamp technique, rates of glucose utilization (measured isotopically with 3-^{3}H-glucose) and glucose clearance were determined in 5 normal volunteers at steady-state plasma glucose concentrations of approximately 60, 95, 130, and 165 mg/dl, while plasma insulin concentrations were maintained constant (~18 μU/ml) by infusion of insulin and somatostatin. Despite virtually identical 0.4 mg · kg^{-1} · min^{-1} increments in glucose utilization for each 35-mg/dl increment in plasma glucose, glucose clearance decreased as a function of plasma glucose concentration ($r = -0.85$, $P < 0.001$). These results indicate that glucose clearance is not independent of changes in plasma glucose concentration and, thus, use of glucose clearance to evaluate glucose utilization at differing plasma glucose concentration is not valid. Whether this conclusion also applies to similar use of clearance for other substrates remains to be determined. DIABETES *30*:535–537, June 1981.

The clearance (rate of utilization ÷ plasma concentration[1]) of various substrates including glucose,[2–8] ketone bodies,[9,10] and amino acids[11] has frequently been used to characterize the overall efficiency of their utilization. Since glucose utilization in vivo is a function of both plasma insulin and plasma glucose concentrations,[12–14] it has become a common practice[2–8] to use the clearance of glucose to evaluate glucose utilization under conditions that alter plasma glucose concentration; absolute changes in glucose clearance are considered to reflect changes in tissue glucose utilization independent of the mass action effect of glucose concentration. The validity of this practice requires that glucose clearance itself be independent of changes in plasma glucose concentration.[13] However, such a relationship has not been established. Indeed, the fact that glucose clearance increases during development of hypoglycemia in insulinoma patients despite decreases in plasma insulin[15] suggests that glucose clearance may vary with changes in plasma glucose concentration. The present studies were, therefore, undertaken to determine the relationship between glucose clearance and plasma glucose concentration in man.

From the Endocrine Research Unit, Departments of Medicine and Physiology, Mayo Medical School and Mayo Clinic, Rochester, Minnesota 55901.
Address reprint requests to Dr. Gerich at the above address.
Dr. Verdonk's present address is the Department of Endocrinology, Yale University School of Medicine, New Haven, Connecticut.
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MATERIALS AND METHODS

Informed consent was obtained from 5 healthy adult volunteers (3 F, 2 M, aged 21–24 yr). All were within 10% of their ideal body weight (Metropolitan Life Insurance Table) and had no family history of diabetes mellitus. Subjects were studied on four occasions separated by at least 72 h.

All protocols were begun between 0700 and 0730 h. Subjects were postabsorptive and were infused with somatostatin (250 μg/h, courtesy of Dr. Jean Rivier and Dr. Roger Guillemin, Salk Institute, San Diego, California) and crystalline insulin (0.2 mU/kg/min, Iletin II pork insulin, Eli Lilly and Co., Indianapolis, Indiana) from 0 through 180 min to maintain plasma insulin and glucagon concentrations constant and equivalent under all experimental conditions.[7] Variable amounts of 50% glucose were infused to "clamp" plasma glucose levels at either 60, 95, 130, or 165 mg/dl as previously described.[7,14] The order of the experiments was randomized.

Arterialized-venous blood samples[16] were obtained at 15-min intervals for determination of plasma glucose (YSI, glucose analyzer, Yellow Springs Instrument Co., Yellow

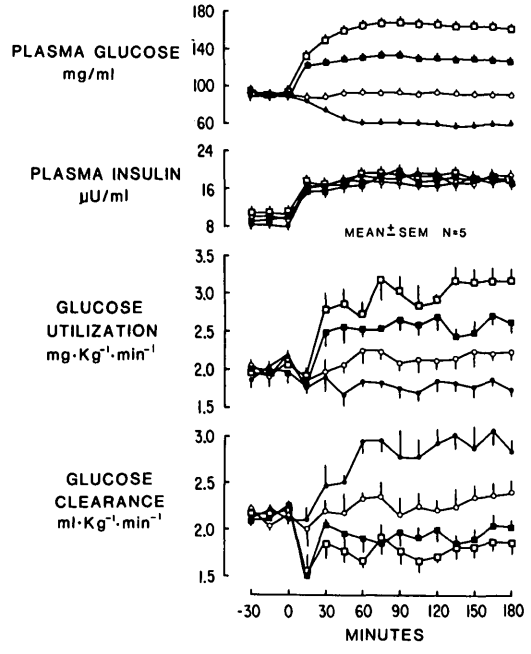
Springs, Ohio), glucose specific activity,[7] and insulin concentrations.[17] Glucose utilization was determined isotopically with 3-^{3}H-glucose[7,14] using equations of Steele et al.[18] as modified by DeBodo et al.[2] Glucose clearance was calculated by dividing the rate of glucose utilization by the prevailing plasma glucose concentration.[1] Data in text and figures are expressed as means ±SEM and were evaluated using a two-tailed paired *t* test. Since stable plasma glucose concentrations were not achieved before 90 min, clamps were not considered to be established before this time, and only data from 90–180 min were used for statistical analysis.

RESULTS

Plasma glucose and insulin concentrations and rates of glucose utilization and glucose clearance (Figures 1 and 2). Baseline (mean of −30, −15, and 0 min values) plasma glucose and plasma insulin concentrations were comparable in the four experiments. Plasma glucose concentrations were clamped at 62 ± 2 mg/dl (C.V. 3.9 ± 0.7%), 95 ± 0.6 mg/ml (C.V. 1.3 ± 0.2%), 131 ± 0.4 mg/ml (C.V. 1.6 ± 0.4%), and 165 ± 1.4 mg/ml (C.V. 1.4%) from min 90 through min 180. Plasma insulin concentrations over the same interval during each of the above studies were 17.8 ± 1.5, 17.8 ± 1.3, 18.5 ± 1.6, and 18.2 ± 1.1 μU/ml, respectively.

Baseline rates of glucose utilization and glucose clearance before each experiment were comparable. Over the range of plasma glucose concentrations studied, each 35-mg/dl increment resulted in a virtually identical (0.4 mg · kg^{-1} · min^{-1}) increment in glucose utilization. The rate of glucose utilization at 62 mg/dl (1.79 ± 0.08 mg · kg^{-1} · min^{-1}) was significantly less than that occurring at 95 mg/dl (2.17 ± 0.13 mg · kg^{-1} · min^{-1}, $P < 0.01$) which in turn was significantly less than that at 131 mg/dl (2.58 ± 0.09 mg · kg^{-1} · min^{-1}, $P < 0.01$), and the latter was less than that at 165 mg/dl (3.02 ± 0.16 mg · kg^{-1} · min^{-1}, $P < 0.05$). Despite these proportionate increases in glucose utilization, glucose clearance decreased as a function of plasma glucose concentration ($r = -0.85$, $P < 0.001$). Thus, glucose clearance at 62 mg/dl (2.89 ± 0.13 ml · kg^{-1} · min^{-1}) was significantly greater than that at 95 mg/dl (2.28 ± 0.13 ml · kg^{-1} · min^{-1}, $P < 0.01$) which in turn was significantly greater than that at 130 mg/dl (1.97 ± 0.08 ml · kg^{-1} · min^{-1}, $P < 0.01$). The rate at 165 mg/dl (1.83 ± 0.09 ml · kg^{-1} · min^{-1}), although still lower, was not significantly different from that at 130 mg/dl.

FIGURE 1. Plasma glucose and insulin concentrations and rates of glucose utilization and clearance.



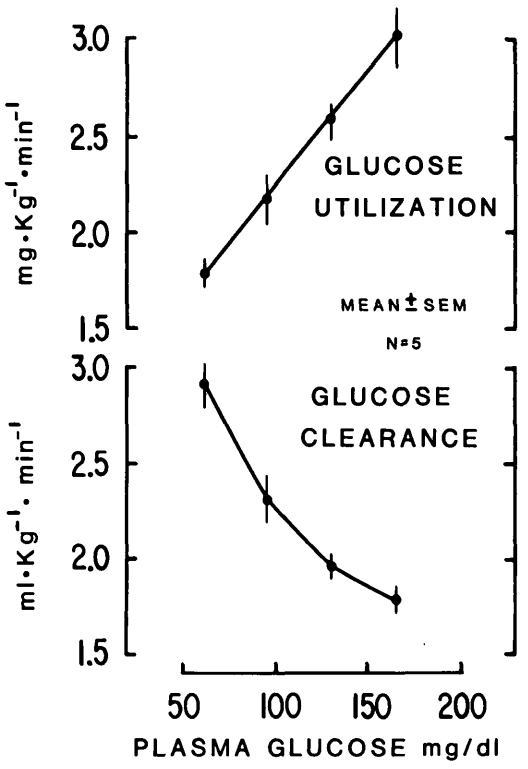


FIGURE 2. Effect of plasma glucose concentration on rates of glucose utilization and clearance.

DISCUSSION

Since glucose utilization is a function of plasma glucose concentration, glucose clearance has been used to assess glucose utilization under conditions in which plasma glucose concentrations vary.[2–8] The validity of this practice necessitates that glucose clearance itself be independent of changes in plasma glucose concentration. The present studies indicate that glucose clearance is not independent of changes in plasma glucose concentration, since under conditions in which plasma insulin was maintained constant, increases in plasma glucose concentration over the physiologic range (60–165 mg/dl) were associated with a progressive decrease in glucose clearance. This inverse relationship between glucose clearance and plasma glucose concentration occurred despite the fact that for each 35-mg/dl increase in plasma glucose concentration there was an identical increase in glucose utilization.

For glucose clearance to have remained constant over the range of plasma glucose concentrations studied, the

mathematical relationship between glucose utilization and plasma glucose concentration would have had to be a linear function of plasma glucose concentration passing through the origin. Linear regression analysis of our data indicates a y-intercept of 1.04 mg · kg^{-1} · min^{-1}. Our results are similar to those of a previous study in the dog[13] in which the relationship between glucose utilization and plasma glucose concentration was linear over the range 90–250 mg/dl, but yielded a y-intercept of 1.1 mg · kg^{-1} · min^{-1}. Although not calculated by the authors, there was, as in the present study, a significant negative correlation ($r = -0.52$, $P < 0.001$) between glucose clearance and plasma glucose concentration.

A positive y-intercept necessitates that a given change in glucose utilization for a given change in plasma glucose concentration results in unequal rates of changes in the numerator (glucose utilization) and denominator (plasma glucose concentration) of the equation used to derive glucose clearance. Consequently, glucose clearance must vary inversely as a function of plasma glucose concentration. Moreover, as shown in Figure 2, this relationship between glucose clearance and plasma glucose concentration is not constant. Since the contribution of the fixed component of glucose utilization (y-intercept) will become smaller as plasma glucose concentration increases, glucose clearance will decrease progressively less as a function of plasma glucose concentration until the capacity of tissues to take up glucose is saturated. Beyond this point, glucose clearance will then decrease precipitously. For these reasons, glucose clearance cannot be used to evaluate changes in glucose utilization under conditions in which plasma glucose concentrations differ. Our data suggest that a more appropriate approach is to calculate the *change* in glucose utilization per *change* in plasma glucose concentration. In the present study, this relationship was constant over the physiologic range of plasma glucose concentrations.

The positive y-intercept indicates that at plasma glucose concentrations between 0 and somewhere below 60 mg/dl, glucose utilization increases more rapidly as a function of plasma concentration than it does at higher plasma glucose concentrations. Since brain increases both its clearance and fractional extraction of glucose as plasma glucose concentration decreases,[19] and since the y-intercept (1.1 mg · kg^{-1} · min^{-1}) only slightly exceeds estimates of brain glucose uptake (0.92 mg · kg^{-1} · min^{-1}),[20] the y-intercept could be primarily accounted for by brain glucose uptake. This uptake of glucose is independent of insulin. Since utilization of glucose by the brain constitutes approximately 80% of glucose utilized in the postabsorptive state,[21] it is quite possible that the value for the y-intercept may approximate non-insulin-mediated glucose uptake in the postabsorptive state.

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Note added in proof. In experiments analogous to ours (constant insulinemia), Bedt, J., Taborsky, G., Halter, J., and Porte, D. (Clin. Res. *21*:536A, 1981) have also found that glucose clearance is not independent of plasma glucose concentration, whereas in experiments in which insulin secretion was allowed to vary, DeFronzo, R., and Ferrannini, E. (Clin. Res. *21*:404A, 1981) have found the opposite.

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