Effects of Oral Glucose on Systemic Glucose Metabolism During Hyperinsulinemic Hypoglycemia in Normal Man

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The widespread use of oral glucose in the treatment of hypoglycemia is mainly empirically based, and little is known about the time lag and subsequent magnitude of effects following its administration. To define the systemic impact and time course of effects following oral glucose during hypoglycemia, we investigated 7 healthy young men twice. On both occasions, a 6-hour hyperinsulinemic (1.5 mU/kg/min)-hypoglycemic clamp was performed to ensure similar plasma glucose profiles during a stepwise decrease toward a nadir less than 50 mg/100 mL after 3 hours. On the first occasion, subjects ingested 40 g glucose and 4 g 3-ortho-methylglucose ([3-OMG] to trace glucose absorption) dissolved in 400 mL tap water after 3.5 hours. The second examination was identical except for the omission of 40 g oral glucose, and glucose levels were clamped at hypoglycemic concentrations similar to those recorded on the first examination. Plasma glucose curves were superimposable, and all participants reached a nadir less than 50 mg/100 mL. Similar increases in growth hormone (GH) and glucagon were observed in both situations. The glucose infusion rates (GIRs) were lower after oral glucose, with the difference starting after 5 to 10 minutes, being statistically significant after 20 minutes, and reaching a maximum of 8.5 ± 1.6 mg/kg/min after 40 minutes. Circulating 3-OMG increased after 20 minutes. In both situations, infusion of insulin resulted in insulin levels of approximately 150 μU/mL and a suppression of C-peptide levels from 2.0 to 1.1 nmol/L ($P < .01$). After glucose ingestion, both serum C-peptide and glucagon-like peptide-1 (GLP-1) increased (C-peptide from 1.1 ± 0.05 to 1.4 ± 0.05 nmol/L and GLP-1 from 3.2 ± 0.8 to 18.1 ± 3.3 pmol/L), in contrast to the situation without oral glucose ($P < .05$). Isotopically determined glucose turnover was similar. In conclusion, our data suggest that oral glucose affects systemic glucose metabolism rapidly after 5 to 10 minutes. Quantitatively, the immediate impact is relatively small, with the gross impact observed after approximately 40 minutes. Future studies aiming to identify therapeutic oral agents with prompt effect seem warranted.

HYPOGLYCEMIA is the single most frequent complication of insulin treatment, causing considerable morbidity and mortality,[1] and intensive insulin therapy regimens invariably aggravate the problem. Concurrent with the ever-mounting evidence that strict metabolic control postpones the development of long-term complications, the occurrence of hypoglycemia, therefore, will likely increase.[2] The ensuring dilemma is further complicated by the fact that hypoglycemia per se predisposes to recurrent hypoglycemia through an attenuation of defense mechanisms, thereby initiating and maintaining a vicious cycle,[3-5] which has become known as ''hypoglycemia-associated autonomic failure.''[6]

Since the advent of insulin treatment, ingestion of carbohydrates has been the main therapeutic measure to counter hypoglycemia,[7] and relief has—on an empirical basis—been described to occur quickly. Considering the unequivocal clinical importance, data on the metabolic effects of oral glucose during hypoglycemia are nevertheless sparse.[8,9] Traditionally, glucose absorption has been assessed by means of the glycemic response to a glucose load during insulin-induced hypoglycemia, and a glycemic response has been reported to occur within 10 to 15 minutes.[9-11] In general, these studies have not been optimally controlled and have not attempted to quantify the importance of changes in the glucose turnover rate[12] and in glucose disposal following the ingestion of glucose. Furthermore, it is important to control the level of insulinemia, as differing concentrations of insulin have been shown to modify the counterregulatory response to equivalent hypoglycemia.[13]

Previously, we found that hypoglycemia had no independent effect on the absorption and appearance in plasma of the glucose analog 3-*O*-methyl-D-glucose (3-OMG) and that 3-OMG could be found in the circulation after a lag time of 20 minutes.[14] However, the study left open the questions of when, how, and at what magnitude oral glucose affects the changes in systemic glucose metabolism during hypoglycemia.

The present study was accordingly designed with the dual purpose of (1) establishing a method for quantitative assessment of the systemic impact of oral glucose during hypoglycemia and (2) defining the mechanisms of action and time course of effects after oral glucose ingestion during hypoglycemia. We used a modified hyperinsulinemic-hypoglycemic clamp during which systemic glucose levels were kept similar with and without a 40-g oral glucose load.

SUBJECTS AND METHODS

Design

Seven healthy young men (age, 28.6 ± 2.9 years; body mass index, 21.6 ± 0.6 kg/m^2) provided informed consent to participate in the study, which was approved by the local ethical committee. Participants were examined twice with an interval of at least 14 days. On both occasions, a 6-hour hyperinsulinemic-hypoglycemic clamp was performed (Fig 1A). Following an overnight fast, catheters were placed retrogradely in a deep cubital vein and contralaterally in a heated dorsal vein and a cubital vein for sampling and infusion, respectively. Infusion of insulin (Actrapid; NovoNordisk, Copenhagen, Denmark) 1.5 mU/kg/min (constant infusion rate throughout the clamp) was commenced at 8 AM. At the same time, infusion of 20% glucose (variable infusion rate) was started to achieve a controlled stepwise decrease in plasma glucose. The plasma glucose level was measured every 5 minutes to ensure comparable glucose levels on the two occasions. A nadir of approximately 50 mg/100 mL was scheduled after 3 hours. Note that since this

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Submitted January 14, 2000; accepted May 29, 2000.

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0026-0495/00/4912-0014$10.00/0
doi:10.1053/meta.2000.18558

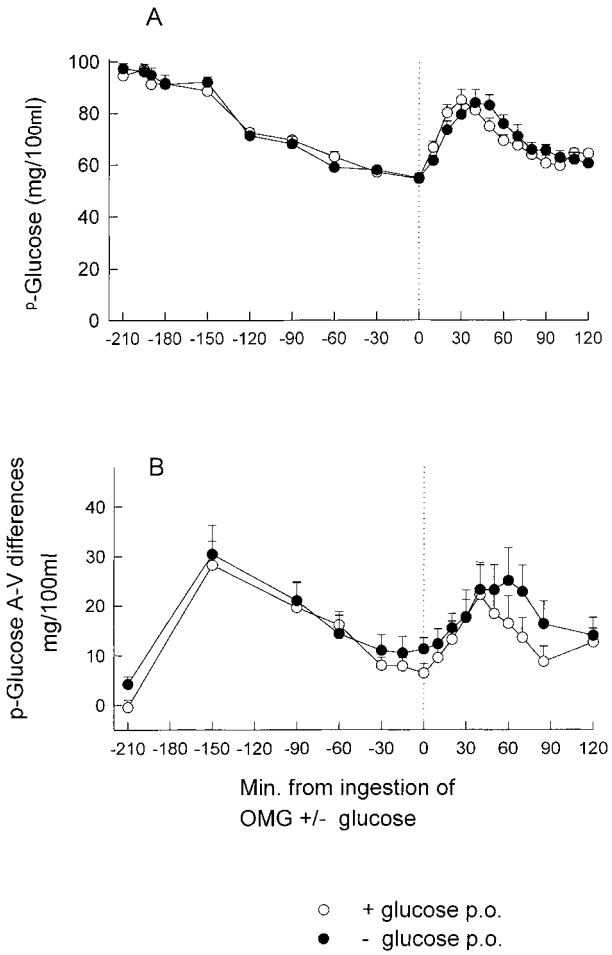

Fig 1. Arterialized (A) plasma glucose (p-glucose) and (B) arteriovenous (A-V) differences (mean ± SE) in the 2 situations with (+) and without (−) 40 g oral (p.o.) glucose. *T* = 0 represents the time for the oral glucose load on the first occasion (○).

nadir did not occur at exactly the same time point in all subjects, the mean glucose values are above 50 mg/100 mL. After an additional 30 minutes, subjects on the first occasion ingested 40 g glucose and 4 g 3-OMG dissolved in 400 mL tap water. After the glucose load, the glucose infusion rate (GIR) was tapered at a rate of approximately 10% every 5 minutes, while plasma glucose was allowed to increase gradually to ''absorb'' the effects of incoming oral glucose. GIRs were recorded for 2 hours after ingestion of glucose, whereafter insulin was discontinued. The second examination was identical to the first except for the omission of peroral glucose. It was essential to reproduce the gradual increase in plasma glucose after 3.5 hours as exactly as possible. Assuming identical systemic plasma glucose levels and turnover rates in the two situations, the difference in the GIR reflects the systemic appearance of the ingested glucose.

Analytical Methods

Plasma glucose was determined in duplicate on a glucose analyzer (Beckman Instruments, Palo Alto, CA). Twenty-four-hour urine was collected in containers with 0.5 mL sodium merthiolate (0.1 g/L), for determination of 3-OMG. Circulating concentrations of insulin, C-peptide, growth hormone (GH), glucagon, nonesterified fatty acids (NEFAs), glucagon-like peptide-1 (GLP-1), lactate, and alanine, and urine and plasma concentrations of 3-OMG were determined.[15-19] Indirect calorimetry was performed with a computerized open-circuit system measuring gas exchange across a 25-L canopy (Deltatrac; Datex Instrumentarium, Helsinki, Finland). Energy expenditure and the respiratory exchange ratio were assessed thrice for 30 minutes (commencing at $t = -90$, $t = 0$, and $t = 90$).[20]

During both clamps, [3-^{3}H]glucose was administered as an intravenous bolus of 30 μCi followed by a continuous infusion of 30 μCi/h. Non–steady-state glucose appearance and disposal rates (Ra and Rd) were calculated according to the equation of Steele as modified by deBodo et al.[21] We abstained from the use of tritiated glucose mixed with the cold glucose infusate (''hot GINF''), since this approach would have caused inappropriate tracer dilution after glucose ingestion. Catheters for measurement of arterial–deep venous substrate balance across the forearm were placed as previously described.[22] Preceding every deep-venous sample, total ipsilateral blood flow was determined by means of venous occlusion plethysmography[23] and substrate balances were calculated.[20,24]

Statistical Analysis

ANOVA for repeated measurements and Student's *t* test for paired comparisons were used when appropriate. A 2-tailed *P* value less than .05 was considered significant. All results are expressed as the mean ± SEM.

RESULTS

Plasma glucose curves were indistinguishable, and all participants reached a nadir less than 50 mg/100 mL (arterialized plasma values) after 180 to 210 minutes (Fig 1A). All subjects reported mild symptoms of hypoglycemia, including hunger and sweating. After the oral glucose load at 0 minutes plasma glucose increased to a maximal value of 82 ± 3 mg/100 mL after 30 minutes. During hypoglycemia, similar arteriovenous glucose differences (Fig 1B) were recorded. These differences mirrored the plasma glucose concentration, ie, a steep initial increase during hyperinsulinemia, a pronounced decrease during hypoglycemia, and a final increase as glucose increased at the time of oral glucose administration. Total forearm blood flow remained steady between 2 and 3 mL/100 mL/min in both protocols.

Prior to glucose ingestion, the GIR was approximately 4 mg/min/kg in both situations (Fig 2A). Following peroral glucose, a relative decrease in the GIR was visible after 5 to 10 minutes ($P > .05$), with the difference (ΔGIR, Fig 2B) becoming statistically significant at 20 minutes and reaching a maximum of 8.5 ± 0.6 mg/kg/min after 40 minutes. Figure 2C depicts the cumulated ΔGIR values, the total of which was 44.2 ± 4.8 g glucose after 2 hours. Figure 2D shows the time course of 3-OMG. Significant circulating levels of 3-OMG were measured 20 minutes after administration of oral glucose; in the control situation, 3-OMG concentrations peaked earlier and steeper, reflecting more rapid absorption (data not shown). Twenty-four-hour urinary excretion of 3-OMG was similar in the two situations (84% ± 4% peroral glucose and 87% ± 3% for no peroral glucose).

The isotopically determined Ra and Rd for glucose remained relatively stable and comparable ($P > .05$) between 6 and 8 mg/kg/min in both situations (Fig 3A and B).

Infusion of insulin resulted in comparable serum insulin levels of approximately 150 μU/mL, (Fig 4A), which in both situations suppressed C-peptide levels from 2.0 to 1.0 nmol/L ($P < .01$; Fig 4B). However, in contrast to the situation without

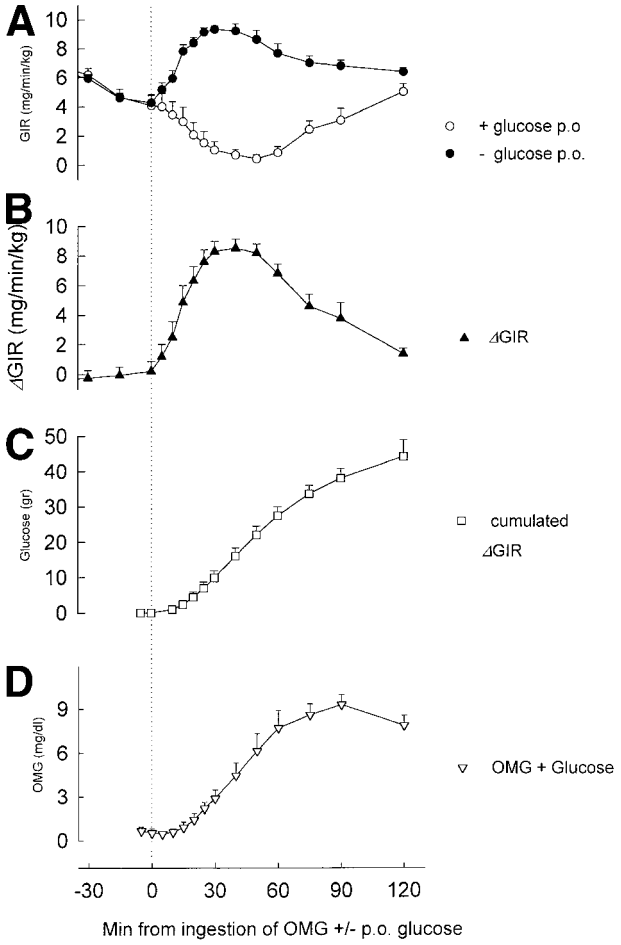

Fig 2. (A) GIR, (B) differences in GIR in the 2 situations (ΔGIR), (C) cumulated difference in GIR (cumulated ΔGIR), and (D) appearance of OMG (mean ± SE). *T* = 0 represents the time for the oral glucose load on the first occasion (○).

a peroral glucose load, an increase in serum C-peptide (from 1.1 ± 0.05 to 1.4 ± 0.05 nmol/L) and GLP-1 (from 3.2 ± 0.8 to 18.1 ± 3.3 pmol/L; Fig 5A) occurred after the peroral glucose load ($P < .05$).

Both plasma glucagon and serum GH showed similar and significant increases in the two situations (glucagon from 45 ± 2 to 147 ± 22 pg/mL and GH from 0.3 ± 0.1 to 19.8 ± 3.3 ng/mL, $P < .01$; Fig 5B and C).

Arterialized lactate and alanine showed similar and steady levels of approximately 1,000 and 200 μmol/L. NEFAs in both situations were significantly suppressed from 0.6 mmol/L ($t = -210$ minutes) to 0.02 mmol/L ($t = 10$ minutes, $P < .01$).

The indirect calorimetry data did not differ between the two examinations. Energy expenditure was 1,915 ± 58 kcal/24 h with peroral glucose and 1,940 ± 47 kcal/24 h without peroral glucose. In both situations, the respiratory exchange ratio was significantly lower during hypoglycemia (0.86 ± 0.02 with peroral glucose and 0.88 ± 0.01 without peroral glucose) compared with the initial readings (0.94 ± 0.01 with peroral glucose and 0.94 ± 0.02 without peroral glucose).

DISCUSSION

With the present protocol, we found that ingestion of glucose had systemic effects after 5 to 10 minutes and the bulk impact (ie, the highest systemic Ra) was found after 40 minutes. It is conceivable that our failure to detect any statistically significant difference until 20 minutes may relate to the limited number of patients studied. Moreover, we found that the overall impact terminated after roughly 2 hours, at which time an amount of glucose equal to the oral glucose load had appeared in the systemic circulation. The method used thus appears suitable for studies seeking to characterize precisely the effects of oral carbohydrates under conditions of high glucose turnover. The combined use of oral glucose and the glucose clamp has been validated recently in humans[25] and subsequently also in a porcine model.[26] Still, it should be underlined that the current approach quantifies the overall metabolic impact of glucose ingestion systemically but does not allow a precise determination of the relative contribution of changes in the Ra of exogenous glucose versus endogenous glucose. In addition, the clamp model implies that high levels of circulating insulin are inflicted, thereby making direct extrapolation to everyday clinical hypoglycemia (occurring at lower insulin levels) in diabetics difficult. Finally, it should be added that the current

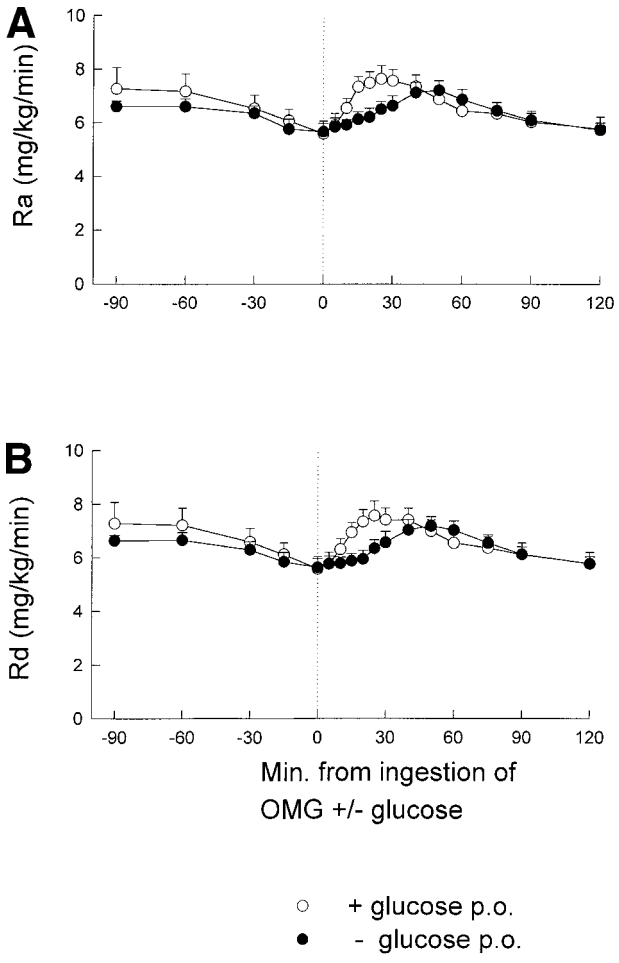

Fig 3. Glucose (A) and Ra and (B) Rd (mean ± SE). *T* = 0 represents the time for the oral glucose load on the first occasion (○).

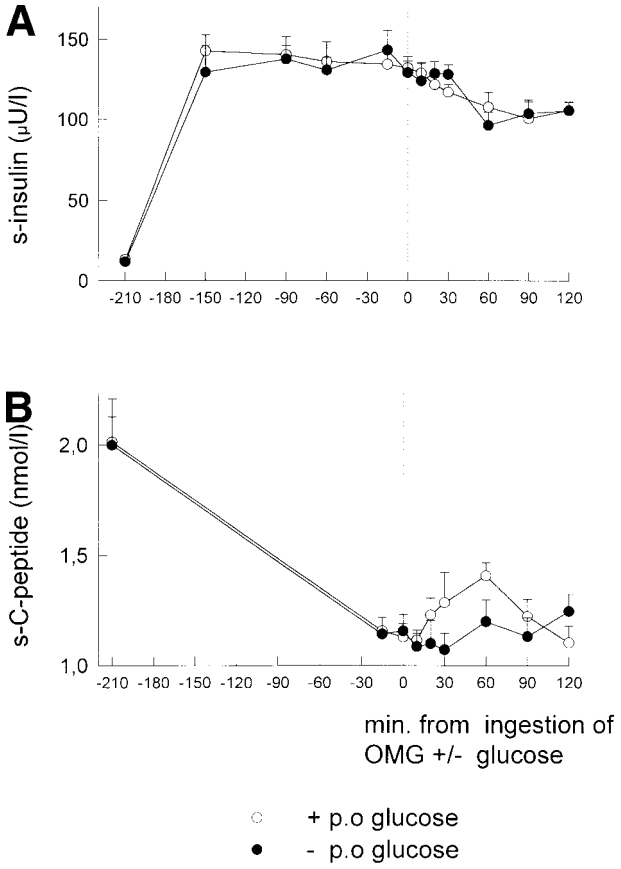

Fig 4. (A) Serum insulin (s-insulin) and (B) s-C-peptide (mean ± SE). *T* = 0 represents the time for the oral glucose load on the first occasion (○).

results do not necessarily extrapolate to diabetic subjects, in whom both defective counterregulation and altered gastrointestinal function may be present.

The defense against hypoglycemia depends critically on three homeostatic factors, namely restriction of glucose utilization, augmentation of endogenous glucose production, and supply of exogenous glucose. From a therapeutic point of view, ingestion of carbohydrates seems the most versatile and readily modifiable and the least well described.[27]

Presently, we used a modification of the hypoglycemic clamp technique with administration of oral glucose on one of two occasions. Apart from increases in GLP-1 and C-peptide levels following glucose ingestion, all metabolic and hormonal indices were comparable, unequivocally suggesting that the observed differences in GIRs are directly caused by glucose ingestion. As mentioned, it should be noted that the present study protocol differs from clinical reality in terms of the high insulin dose, which was selected to ensure appropriate hypoglycemia, and the composition of the carbohydrate solution, which was selected to ensure precise knowledge of the nature of the glucose ingested.

The total cumulated ΔGIR after glucose ingestion was −44.2 ± 4.8 g glucose—close to the ingested amount of glucose (40 g)—compatible with the notion that virtually all ingested glucose ultimately enters the systemic circulation and most of the glucose is absorbed within 2 hours. These observations are in line with the concept that during hypoglycemia, splanchnic storage of ingested glucose does not differ substantially as compared with intravenously administered glucose, ie, initial splanchnic glucose uptake is either negligible or rapidly followed by glucose release. It has been shown that the combined presence of hyperglycemia and hyperinsulinemia increases net hepatic glucose uptake in dogs[28] and humans.[29] Assuming a portal blood flow of about 1,000 mL/min,[29] the observed maximal alteration of the GIR induced by oral glucose of 8 mg/kg total body mass/min (corresponding to a total of 560 mg in a 70-kg subject) would increase portal glucose by 50 to 60 mg/100 mL, meaning that the liver is exposed to very modest hyperglycemia. This, of course, does not exclude the possibility that a proportion of the ingested glucose is transiently taken up by the liver and subsequently released as part of the counterregulatory response. However, it should be noted that DeFronzo et

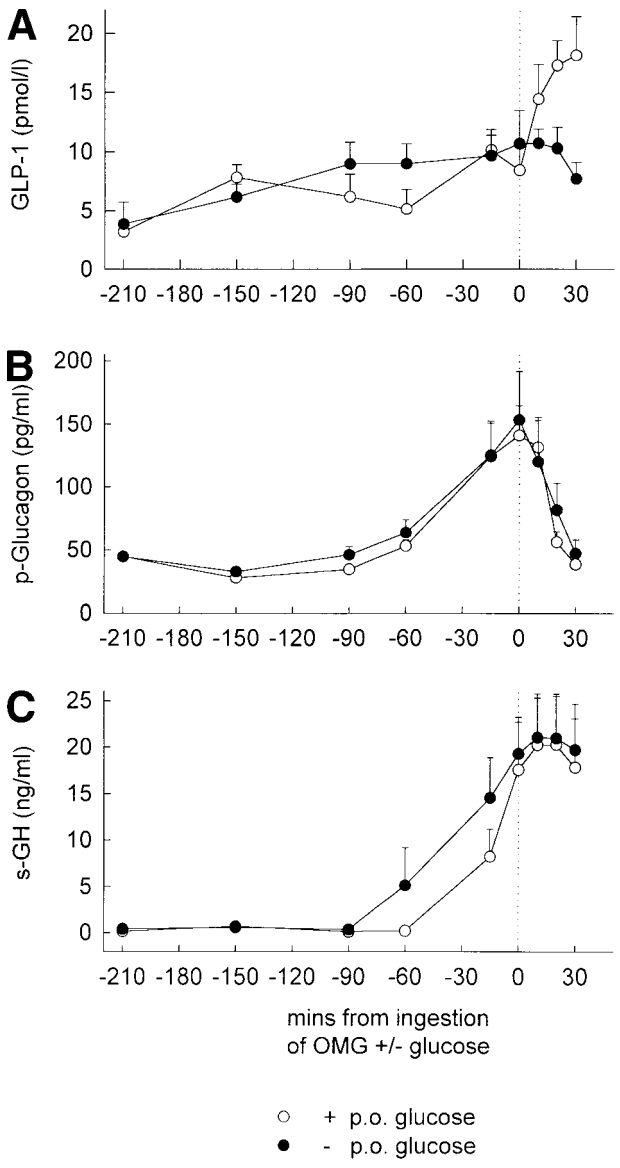

Fig 5. (A) GLP-1, (B) glucagon, and (C) GH (mean ± SE). *T* = 0 represents the time for the oral glucose load on the first occasion (○).

al,[29] using hepatic catheterization, found a maximal splanchnic glucose uptake of merely 1.3 mg/kg/min during systemic hyperglycemia, that isotopically measured initial splanchnic glucose uptake in general is less than 15% of the ingested glucose,[30] and that it is possible that stress hormone release during hypoglycemia may further inhibit hepatic glucose uptake. Interestingly, the present data obtained under hyperinsulinemic hypoglycemia are in agreement with data obtained by Radziuk et al[31] with administration of oral glucose in the basal state. Using a double tracer technique, they observed that more than 90% of the ingested glucose had entered the systemic circulation in unmetabolized form after 2 hours, indicating that glucose absorption at that time is almost complete and splanchnic extraction is small.[31]

At present, neither the dose nor the preparation of glucose that should be used for treatment of hypoglycemia have been identified.[32] At first glance, it would appear that a 10-mg/dL increment in circulating glucose would require administration of 1.5 g glucose in a 75-kg person with a glucose space of 20%. However, it has to be considered that increases in glucose concentrations per se will tend to increase glucose disposal because of increased mass action and reduced hormonal counterregulation. Dose-response curves for the effects of increasing glucose on glucose disposal and stress hormone responses during recovery from hypoglycemia are not available. The scenario is further complicated by the fact that glucose absorption may be delayed when plasma glucose concentrations increase into the hyperglycemic range.[33] In this study, we therefore tried to estimate the impact of oral glucose during clamped glucose concentrations using oral administration of 40 g 10% glucose solution, ie, a solution with a carbohydrate content close to that of juice and soft drinks. It has been shown previously that glucose is superior to other carbohydrates, and administration of up to 40 g carbohydrate is more effective than smaller amounts.[11] Little is known about the possible role of osmolality and the content of fat and salts.

It has been estimated that under conventional ''euglycemic'' conditions, more than 25% of a total oral glucose load of 70 g is taken up by muscle tissue.[34] Presently, we recorded an increase in glucose arteriovenous differences from less than 10 mg/100 mL to well above 20 mg/100 mL as plasma glucose values were allowed to increase after oral glucose. This would suggest that a decreased mass action of glucose plays a central role in the restriction of glucose utilization during hypoglycemia, and muscle becomes a major site for glucose disposal as circulating glucose concentrations increase following treatment of hypoglycemia with glucose. Assuming that the forearm blood flow is exclusively muscle-derived and that a 70-kg man has a muscle mass of 30 kg with a gravity of 1 kg/L, a blood flow of 3 mL/100 mL/min together with a net glucose uptake of 20 mg/100 mL extrapolates to a total glucose uptake of 180 mg, or 2.6 mg/kg/min in muscle. This still leaves approximately two thirds of the total Ra for glucose unaccounted for. From the present data, the issue of which tissues and biochemical pathways are responsible therefore cannot be addressed, but it is conceivable that augmented glucose cycling and lipogenesis explain some of the remaining glucose flux.

The extra stimulation of insulin secretion associated with ingestion rather than systemic infusion of glucose is well known. Our data showing increased levels of GLP-1 and C-peptide with peroral glucose suggest that GLP-1 secretion—which is detectable despite considerable hypoglycemia and hyperinsulinemia—is the reason for the preservation of the incretin effect. Since endogenous insulin constitutes a minute fraction of the measured insulin, evidence of insulin secretion could only be detected by C-peptide measurements. We did not observe differences in glucagon secretion as a consequence of the different ways of administering glucose.

It is surprising that we were unable to detect 3-OMG in the circulation before 20 minutes elapsed. Both glucose and 3-OMG are transported over the intestinal mucosa by the same carrier, but glucose has a higher affinity (K_m glucose = 10 mmol/L *v* K_m 3-OMG = 123 mmol/L).[18,35] Thus, substrate competition at the level of the intestinal carrier and reduced assay sensitivity in the very low range could explain this paradox.

In conclusion, the data obtained in this study suggest that ingestion of glucose during hypoglycemia affects systemic glucose metabolism rapidly after 5 to 10 minutes. However, the magnitude of the immediate response is relatively small and the peak impact is observed after approximately 40 minutes. It should be added that the time lag before glucose ingestion has an impact on systemic glucose concentrations and becomes available for the brain, with all likelihood, is further increased in diabetic patients with clinical or subclinical diabetic gastropathy.

ACKNOWLEDGMENT

A. Mengel and K. Mathiesen are acknowledged for excellent technical assistance.

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