Lack of Effects of Hypoglycemia on Glucose Absorption in Healthy Men

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OBJECTIVE — To assess the effects of hypoglycemia on glucose absorption by examining the systemic appearance of 3-OMG (a glucose analogue that is transported by the same mechanism as glucose) after oral administration.

RESEARCH DESIGN AND METHODS — Six healthy males 22–31 yr of age were studied during a hypoglycemic (50 mg [2.7 mM]/100 ml) and a euglycemic (90 mg [5.0 mM]/100 ml) glucose clamp. At 50 min after exposure to insulin, an oral glucose load containing 20 g of glucose and 4.5 g of 3-OMG dissolved in 300 ml of tap water was administered. Insulin administration was interrupted 30 min after oral glucose administration.

RESULTS — Plasma glucose was clamped at 88 ± 1.3 mg (4.9 ± 0.1 mM)/100 ml during euglycemia and at 50 ± 1.9 mg (2.7 ± 0.1 mM)/100 ml during hypoglycemia. Concentrations of glucagon, growth hormone, cortisol, and epinephrine were significantly elevated during hypoglycemia. After 60 min, circulating 3-OMG concentrations increased to zeniths of 11.4 ± 0.2 mg (585 ± 10.0 mM)/100 ml (hypoglycemia) and 11.6 ± 1.1 mg (585 ± 56.0 μM)/100 ml (euglycemia; $P = 0.95$). Absorption of 3-OMG was evident between 15 and 20 min after administrations in both situations. Serum insulin was significantly lower during hypoglycemia compared with the control situation (345 ± 50 μM [hypoglycemia], 445 ± 50 μM [euglycemia], $P = 0.03$).

CONCLUSIONS — We conclude that hypoglycemia does not seem to affect intestinal absorption of glucose as judged by systemic appearance of 3-OMG.

Hypoglycemia is a frequent and inevitable complication of insulin treatment. Through the years, administration of oral glucose or other carbohydrates has been the mainstay in the therapy of this disorder, and relief has been described to occur within a few minutes after glucose administration (1). Precise documentation of the acute glycemic effect of orally administered carbohydrates is, however, not available (2). A glycemic response to a glucose load during insulin-induced hypoglycemia has been reported to occur within 10–15 min after ingestion in diabetic patients (3). Augmentation of endogenous glucose production during hypoglycemia (4) may, however, contribute to the increase in circulating glucose concentrations observed after oral glucose during hypoglycemia. Release of counter-regulatory hormones during hypoglycemia may theoretically delay intestinal glucose absorption because, for example, glucagon and epinephrine are known to inhibit gut motor activity (5), thus postponing the acute effect of oral glucose. Because most previous studies have estimated glucose absorption indirectly through changes in plasma glucose, we examined the absorption rate of the glucose analogue 3-OMG during hypoglycemia and during euglycemia in normal men. 3-OMG is absorbed through the same mechanisms as glucose (6), but is not further metabolized and therefore is excreted unaltered in the urine (7).

RESEARCH DESIGN AND METHODS

— After approval by the local ethics committee, 6 healthy normal-weight adult males 22–31 yr of age agreed to participate in the study. After an overnight fast of 10 h, all were studied twice in the basal state. At 0730, catheters were placed in a cubital and a heated dorsal hand vein for infusion and blood sampling, respectively. At 0800, insulin (Actrapid, Novo/Nordisk) infusion of 1 $mU \cdot kg^{-1} \cdot min^{-1}$ was commenced. Hypoglycemia occurred after 45–55 min. With infusion of 20% glucose, plasma glucose was clamped at 50 mg (2.7 mM)/100 ml for 10 min based on frequent plasma glucose measurements (Beckman Instruments, Palo Alto, CA) at least every 5 min. After 10 min of hypoglycemia, an oral glucose load containing 20 g of glucose and 4.5 g of 3-OMG

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3-OMG, 3-*O*-METHYL-D-GLUCOSE; NEFA, NONESTERIFIED FATTY ACIDS; GH, GROWTH HORMONE; IVGTT, I.V. GLUCOSE-TOLERANCE TEST; OGTT, ORAL GLUCOSE-TOLERANCE TEST.

dissolved in 300 ml of tap water was administered. The molarity of the test solution was 450 mmol/L. Insulin infusion continued for 30 min, and the subjects were observed for an additional 150 min. Blood samples were taken as indicated in the figures. The 24-h urine samples were collected in containers containing 0.5 ml of sodium merthiolate (0.1 g/L [0.25 mM]) for determination of 3-OMG. On the second occasion, experimental conditions were identical, except for the higher target level of glycemia.

Circulating concentrations of insulin, C-peptide, growth hormone, glucagon, NEFA, epinephrine, and norepinephrine, and urine and plasma concentrations of 3-OMG were determined as described (8–11). Serum concentrations of cortisol were measured by routine methods.

Analysis of variance for repeated measurements was used when appropriate (12). Otherwise, Student's *t* test for paired comparisons was used. A *P* value < 0.05 (2-tailed) was considered significant. All results are expressed as means ± SE.

RESULTS— Plasma glucose was clamped at 88 ± 1.3 mg (4.9 ± 0.1 μM)/100 ml during euglycemia and at 50 ± 1.9 mg (2.7 ± 0.1 μM)/100 ml during hypoglycemia (Fig. 1). During euglycemia, 7.40 ± 0.05 (4.1 ± 0.3 μM) mg · kg^{-1} · min^{-1} glucose was administered i.v., and during hypoglycemia, 0.86 ± 0.51 (4.8 ± 2.8 μM) mg · kg^{-1} · min^{-1} ($P < 0.01$). After oral glucose administration, plasma glucose increased after 5 min in the hypoglycemic situation (Fig. 1) and after 20 min in the euglycemic situation. Plasma levels of 3-OMG were superimposable (Fig. 2). Detectable plasma values of 3-OMG were seen 20 min after glucose ingestion in both situations. After hypoglycemia, 3-OMG increased to peak levels of 11.4 ± 0.2 mg (585 ± 10.0 μM)/100 ml, and after euglycemia, to 11.6 ± 1.1 mg (595 ± 56.0)/100 ml ($P = 0.95$). Twenty-four-hour urinary excretion of

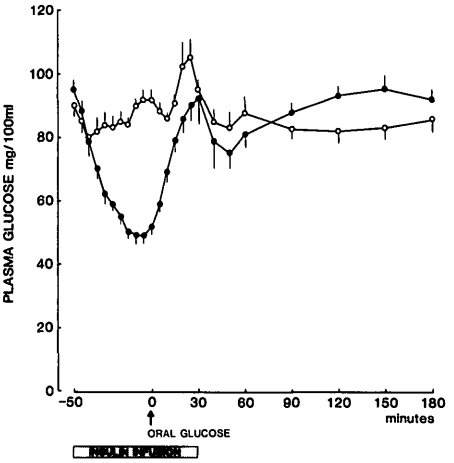

Figure 1—*Plasma glucose (mean ± SE) during euglycemia (○) and during hypoglycemia (●).*

3-OMG remained unaffected (86 ± 3% [hypoglycemia] vs. 92 ± 3% [euglycemia]; $P = 0.31$). Serum insulin was significantly lower during hypoglycemia (345 ± 50 μM [hypoglycemia], 445 ± 50 μM [euglycemia]; $P = 0.03$). This difference was also reflected in significantly increased serum C-peptide levels during euglycemia (576 ± 26 vs. 391 ± 17 pM; $P < 0.01$; data not shown). Insulin infusion caused a decrease in serum NEFA in both situations. During euglycemia, serum NEFA remained at stable levels, whereas hypoglycemia caused a later increase in serum NEFA (304 ± 12 vs. 414 ± 24 μM; $P < 0.01$; data not shown). Hypoglycemia increased circulating concentrations of serum GH (12.7 ± 2.1 vs. 0.2 ± 0.1 ng/ml; $P < 0.01$), plasma glucagon (38.9 ± 9.4 vs. 13.0 ± 3.7 pM; $P < 0.01$), plasma epinephrine (2641 ± 912 vs. 519 ± 109 pM; $P < 0.01$), plasma norepinephrine (3.17 ± 0.97 vs. 0.88 ± 0.28 pM; $P = 0.09$), and serum cortisol (459 ± 41 vs. 367 ± 27 nM; $P = 0.02$). All subjects reported hypoglycemia-related discomfort on relevant occasions.

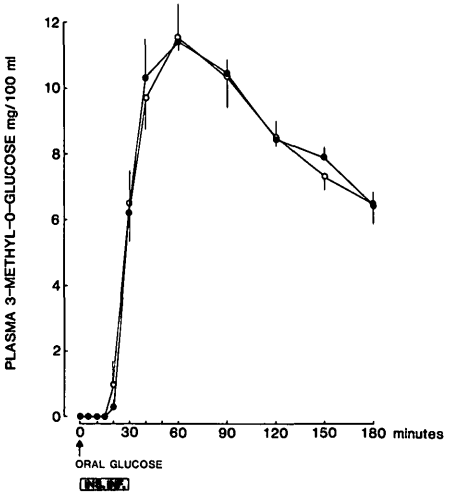

Figure 2—*Plasma 3-O-methyl-D-glucose (mean ± SE) during hypoglycemia (●) and euglycemia (○; P = 0.95).*

CONCLUSIONS— The purpose of this study was to assess intestinal glucose absorption through application of the glucose analogue 3-OMG during hypoglycemia and during euglycemia in healthy adult males. As judged by identical plasma concentration patterns of 3-OMG, glucose absorption was not affected by hypoglycemia. A surprisingly long period of 20 min passed before 3-OMG could be detected in plasma. Counterregulatory hormones such as glucagon and epinephrine inhibit gastric motility (7) and may also decrease splanchnic blood flow. Therefore, intestinal absorption of the glucose analogue 3-OMG might be anticipated to occur later in the hypoglycemic state than in the euglycemic state. A previous study of 3 subjects failed to demonstrate any effects of hypoglycemia on glucose absorption (13). In our study, plasma epinephrine, plasma glucagon, serum cortisol, and serum growth hormone increased significantly, leaving no doubt as to the appropriate magnitude of the hypoglycemic stimulus. Still, no difference in the absorption rate of 3-OMG was observed, thus supporting the above report. It is still possible that with more prolonged

and severe hypoglycemia, a delay in absorption of glucose may supervene.

Note that more than 15 min elapsed in both situations before a rise in plasma 3-OMG could be detected; this is longer than would be expected (3). The slow absorption of 3-OMG could be caused by hypertonicity in the test solution; however, the test solutions used in other studies reporting quicker glucose absorption were also hypertonic (3), and the recommended treatment of hypoglycemia is hypertonic glucose (1). Glucose and 3-OMG are transported over the intestinal mucosa by the same carrier, but glucose has a higher affinity for this carrier. The K_m for glucose is 10 mM and for 3-OMG, 123 mM (14). These K_m mean that glucose is absorbed at an increased rate and that concomitant administration of glucose and 3-OMG slows down the absorption rate of 3-OMG. Nevertheless, the difference in K_m should not delay the onset of absorption. Alternatively, the observed late intestinal glucose absorption could be caused by hyperinsulinemia. In a study by McGregor et al. (15), an IVGTT was shown to inhibit intestinal absorption of glucose. Others have shown that an OGTT impairs gastric emptying (16) and that hyperglycemia inhibits gastric motility (17). This hyperglycemia-associated impairment of glucose absorption could in theory be mediated by hyperinsulinemia.

In as much as 3-OMG data may be extrapolated to genuine glucose, our data indicate that intestinal glucose absorption is not affected by hypoglycemia. Future studies could focus on a possible role of insulin in regulating intestinal glucose absorption and seek to quantify the contribution of augmented endogenous glucose release during hypoglycemia.

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