Physiological changes in blood glucose do not affect gastric compliance and perception in normal subjects

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Verhagen, M. A. M. T., C. K. Rayner, J. M. Andrews, G. S. Hebbard, S. M. Doran, M. Samsom, and M. Horowitz. Physiological changes in blood glucose do not affect gastric compliance and perception in normal subjects. Am. J. Physiol. 276 (Gastrointest. Liver Physiol. 39): G761–G766, 1999.—Marked hyperglycemia (blood glucose ~14 mmol/l) slows gastric emptying and affects the perception of sensations arising from the gut. Elevation of blood glucose within the physiological range also slows gastric emptying. This study aimed to determine whether physiological changes in blood glucose affect proximal gastric compliance and/or the perception of gastric distension in the fasting state. Paired studies were conducted in 10 fasting healthy volunteers. On a single day, isovolumetric and isobaric distensions of the proximal stomach were performed using an electronic barostat while the blood glucose concentration was maintained at 4 and 9 mmol/l in random order. Sensations were quantified using visual analog scales. The blood glucose concentration had no effect on the pressure-volume relationship during either isovolumetric or isobaric distensions or the perception of gastric distension. At both blood glucose concentrations, the perceptions of fullness, nausea, bloating, and abdominal discomfort, but not hunger or desire to eat, were related to intrabag volume (P < 0.002) and pressure (P < 0.01). We conclude that, in the fasted state, elevations of blood glucose within the physiological range do not affect proximal gastric compliance or the perception of gastric distension.

barostat

The effects of hyperglycemia on gastrointestinal motility are also dependent on the magnitude of the elevation in blood glucose (9, 39). It has recently been established that changes in the blood glucose concentration within the physiological postprandial range also affect gastrointestinal motor (5, 8, 10, 20, 30, 40) and sensory (1, 30) function. For example, at a blood glucose concentration of 8–10 mmol/l compared with 4–6 mmol/l, gastric emptying is slowed (43) and antral pressure waves are suppressed (5, 20). The effects of physiological hyperglycemia may be site specific. For example, anorectal function appears not to be affected by physiological hyperglycemia (39), in contrast to the esophagus (8), antrum (5), and gallbladder (18).

The rate of gastric emptying is dependent on the integration of motility in the pylorus, antrum, pylorus, and proximal small intestine (23). A reduction in proximal antral tone may contribute to slowing of gastric emptying (10) and also may modify the perception of gastric distension (21, 22).

The purpose of this study was to determine the effects of physiological changes in the blood glucose concentration on proximal gastric compliance and the perception of gastric distension.

METHODS

Subjects. Ten healthy volunteers were studied (1 female, 9 males; median age 27 yr, range 19–39; body mass index 23 kg/m2, range 21–27). No subject had a history or symptoms of systemic or gastrointestinal disease nor was taking medication. The female subject was in the follicular phase of the menstrual cycle. Smoking was prohibited on the study day. Written, informed consent was obtained, and the protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Protocol. In each subject, measurements of fasting gastric compliance and sensations induced by distension of the proximal stomach were obtained when the blood glucose concentration was maintained at 4 and 9 mmol/l. The two parts of the study were performed on 1 day, using a single blind, randomized, crossover design. As perception of gastric distension is related to both pressure and volume (21, 34), both pressure- and volume-driven distensions were performed.

After an overnight fast, at around 10:00 AM, a catheter incorporating a distal polyethylene bag was inserted through an anesthetized nostril and positioned in the proximal stomach. With the use of an electronic barostat, 500 ml of air were introduced to unfold the bag in a controlled manner. The bag was then completely deflated to a pressure of 0 mmHg with respect to the atmosphere. Subjects were seated in a semi-
kneeling position, in a specially designed chair, with their upper body upright (21). Their arms were allowed to rest on a table that was adjusted to the height of the elbows. Intravenous cannulas were inserted in an antecubital vein in each arm, one for the intravenous infusion of dextrose or saline and the other for obtaining blood samples. Before the distensions commenced, the pressure required to overcome the intra-abdominal pressure (the minimal distension pressure) was determined, by increasing the intragastric bag pressure with steps of 1 mmHg and identifying the lowest pressure at which continuous respiratory fluctuations in the intrabag volume, to >30 ml, were detected (21).

The blood glucose concentration was stabilized at either 4 or 9 mmol/l using a glucose-clamp technique (22), in random order. After the blood glucose had been maintained at the desired concentration for 30 min, a series of distensions at steps of fixed volume (isovolumetric) and a series of distensions at steps of fixed pressure (isobaric) were performed, also in random order. The duration of each volume or pressure step was 3 min. Isovolumetric distensions were performed using steps of 100 ml. During isobaric distensions, intrabag pressure was increased by 1 mmHg at every step, starting 1 mmHg below the previously defined minimal distension pressure. The measured intrabag volumes were corrected on-line for air compression by applying an experimentally determined correction factor (1.848 ml/mmHg; see Refs. 41, 47). Distensions were stopped at an intragastric bag pressure of 20 mmHg, an intragastric bag volume of 800 ml, or if the subject reported marked discomfort.

Between the isovolumetric and isobaric distensions, the intragastric bag was deflated completely, and there was a “rest” period of at least 10 min. When both series of distensions had been performed, the blood glucose concentration was stabilized at the alternative level for 30 min, and the isovolumetric and isobaric distensions were repeated in identical fashion.

Stabilization of blood glucose concentrations. Physiological hyperglycemia (blood glucose 9 mmol/l) was achieved by intravenous infusion of 25% dextrose, starting with a bolus of 40–100 ml, followed by an infusion that was adjusted according to the blood glucose concentration. In the study performed during euglycemia (blood glucose 4 mmol/l), saline was infused at a rate of 100 ml/h. Blood glucose was measured every 5–10 min, using a Reflolux II M glucometer (Boehringer Mannheim, Castle Hill, NSW, Australia).

Performance of gastric distensions. An electronic barostat (Distender Series II; G & J Electronics, Ontario, Canada) was used to perform the gastric distensions. The barostat was connected via a polyvinyl chloride catheter assembly (750 mm long, internal diameter of 2.5 mm) to a sealed polyethylene bag. Changes in intrabag volume occurred at a rate of 33 ml/s. The intrabag pressure, measured by a pressure sensor in the electronic barostat, was monitored via a separate channel above the barostat bag, which was connected to a low-compliance, water-perfused, manometric system. The pressure recordings were used to position the intragastric bag so that the point of respiratory reversal at the diaphragm was located between the two manometric side holes.

Data from the barostat (sampled at 1 Hz) were recorded on a Powermac 7100 computer (Apple Computer, Cupertino, CA), using custom-written data-acquisition software (Labview; National Instruments, Austin, TX). This software was also used to program the barostat to perform distensions in stepwise volume or pressure increments.

Data were imported into a display and analysis program (Acqknowledge, Biopac Systems, Goleta, CA). The mean volume and pressure during the last 2 min of each distension step, allowing 1 min for equilibration, were determined.

For comparison of isobaric distensions, pressures are given relative to the minimal distension pressure observed at the start of each distension series (41). For the comparison of isovolumetric distensions, pressures are given relative to pressure in the bag during the first volume step for each distension series (100 ml), which is taken as a convenient basal pressure (21).

Evaluation of sensation. Perceptions of fullness, abdominal discomfort, nausea, bloating, hunger, and desire to eat were scored by each subject two times in the 5 min before each series of distensions and in the last minute of each distension step, using 100-mm visual analog scales (21, 26).

Statistical analysis. Data relating to pressure, volume, and sensation were evaluated, using analysis of variance with repeated measures (SPSS for Windows 7.0), after logarithmic transformation of the data. Both the order of distensions (isobaric or isovolumetric) and blood glucose concentration (4 or 9 mmol/l) were included in the analysis as between-subject factors. The Wilcoxon signed rank test was used for individual comparisons. Significance was accepted at a P value <0.05. Data are presented as median values with interquartile ranges, except for the sensation scores, which are represented as mean values ± SE, as the latter were distributed normally.

RESULTS

All 10 subjects completed the study. The blood glucose concentration was maintained in the desired range; the mean blood glucose (calculated from 10 minutely measurements during the distensions) was 4.4 mmol/l (range 3.2–5.9 mmol/l) during euglycemia and 9.3 mmol/l (range 7.1–10.7 mmol/l) during hyperglycemia. The volume of fluid infused intravenously was 230 ml (range 146–495 ml) during euglycemia and 229 ml (range 131–795 ml) during hyperglycemia. The duration of the rest period between isobaric and isovolumetric distensions was 20 min (range 10–22 min) during euglycemia and 19 min (range 10–30 min) during hyperglycemia.

During isovolumetric distensions, the maximal volume of 800 ml was reached in eight subjects in the study performed during euglycemia and in nine subjects during hyperglycemia. In two subjects, the isovolumetric distension was stopped at 700 ml due to the occurrence of marked discomfort. Isobaric distensions were not completed in four subjects during euglycemia and in three subjects during hyperglycemia because discomfort was reported. In the other isobaric distensions, the maximum bag volume (800 ml) was reached. In nine subjects, the intrabag pressure was increased to 7 mmHg above the minimal distension pressure in both arms of the study.

In the analysis of pressure-volume relationships and sensations, no effects of the order of distensions, nor for the sequence of hyper- and euglycemia, were evident.
Pressure-volume relationships. The pressure-volume relationships during the isovolumetric and isobaric distensions are shown in Fig. 1. Intrabag pressure rose as volume was increased (P < 0.001); similarly, an increase in volume was observed when intrabag pressure was increased (P < 0.001). During the isovolumetric distension, there was no difference in intragastric pressure after inflation of 100 ml of air between the study performed during hyperglycemia [6.5 mmHg (5.2–7.1)] and euglycemia [6.3 mmHg (5.0–6.9)]. There was no difference in the pressure/volume relationship during either isovolumetric or isobaric distensions between the two experimental conditions (Fig. 1).

Perception of gastric distension. Sensation scores are shown in Fig. 2. Sensations of fullness, nausea, abdominal discomfort, and bloating all increased with increasing volume (P < 0.002) and pressure (P < 0.01) during both euglycemia and hyperglycemia. In contrast, there was no effect of either volume or pressure on sensations of hunger or desire to eat. There were no differences in any sensation between euglycemia and hyperglycemia (P > 0.23 in all comparisons).

DISCUSSION

The results of this study indicate that, in the fasted state, 1) physiological hyperglycemia does not affect either proximal gastric compliance or sensory response to proximal gastric distension, and 2) proximal gastric distension triggers sensations of fullness, nausea, and abdominal discomfort but does not affect sensations of hunger or desire to eat.

Most studies of the effects of hyperglycemia on gastrointestinal motor and sensory function have examined the impact of marked hyperglycemia (blood glucose 14–16 mmol/l; see Refs. 5, 6, 11, 17, 20–22, 32, 33, 35, 38–40, 45), which occurs in patients with diabetes mellitus but not in healthy subjects. Elevation of the blood glucose to this level has been shown to affect the motor and sensory function of the stomach (5, 6, 17, 20–22, 33, 40), and every other segment of the gastrointestinal tract that has been examined, including the esophagus (11), gallbladder (32, 35), intestine (38), and anorectum (9, 39). The mechanisms by which marked hyperglycemia influences motility and the perception of sensation are uncertain but may involve changes in vagal activity (12) and/or the release of gastrointestinal hormones (5, 6, 14). Of the latter, the role of insulin is controversial (7, 9, 13, 20, 45). However, any role for insulin is likely to be minor given that hyperglycemia also affects gastrointestinal motor and sensory function in patients with type I diabetes who are insulin deficient (17, 28, 40).

There is much less information about the effects of physiological changes in the blood glucose concentration on gastrointestinal function (5, 8, 18, 20, 30, 43). It has recently been reported that gastric emptying is slower at a blood glucose concentration of 8 mmol/l when compared with 4 mmol/l (43). There is also evidence that this slowing of gastric emptying may be associated with a delay in oral drug absorption (19). Both fasting and postprandial antral pressure waves are suppressed at a blood glucose level of 8 mmol/l compared with 4 mmol/l (5, 20). In contrast, the stimulation of pyloric motility by duodenal distension is increased during physiological hyperglycemia (30). Physiological hyperglycemia also inhibits gallbladder emptying (18). In the antrum and gallbladder, the effects of hyperglycemia are, therefore, dose related (5, 18). In the esophagus, however, physiological hyperglycemia increases esophageal peristaltic velocity (8), whereas the latter is diminished at a blood glucose concentration of 15 mmol/l (11). Anorectal motor and sensory function is not altered at a blood glucose concentration of 8 mmol/l when compared with 4 mmol/l, whereas elevation of the blood glucose concentration to 12 mmol/l has marked effects (39).

Previous studies by our group have demonstrated in normal subjects that marked hyperglycemia (blood glucose of ~15 mmol/l) increases the compliance of the proximal stomach during gastric distension both in the fasted state (22) and during intraduodenal lipid in-
Fig. 2. Sensation scores. Sensation recorded during isovolumetric (A) and during isobaric (B) distensions at blood glucose concentrations of 4 and 9 mmol/L. Sensations of fullness, nausea, abdominal discomfort, and bloating increased with increasing intrabag volume ($P \leq 0.002$ for all sensations) and with increasing intrabag pressure ($P \leq 0.006$). Hunger and desire to eat were not affected by increasing volume or pressure. There were no differences between hyperglycemia and euglycemia.
Changes in gastric motility induced by hyperglycemia in subjects with uncomplicated type I diabetes mellitus are comparable to those in healthy subjects. In patients with diabetes, hyperglycemia also delays gastric emptying (17, 43) and inhibits antral motor activity (40). It is possible, therefore, that our observations also apply to patients with uncomplicated type I diabetes mellitus.

Our findings also highlight the complex relationship between fullness and hunger, showing that one is not simply the reciprocal of the other. During the fasted state, gastric distension increased the sensation of fullness, but hunger and desire to eat were not correspondingly diminished. These findings are in agreement with previous observations that distension of the proximal stomach requires concurrent stimulation of small intestinal nutrient receptors to induce satiation (4, 14, 15, 29). There is evidence that postprandial fullness is closely related to antral distension, but hunger is not (27). Patients with type I diabetes, and those with functional dyspepsia, report more abdominal discomfort (pain, bloating, and fullness) after a meal than normal subjects and also have a wider antrum (46).

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