Effects of duodenal distension on antropyloroduodenal pressures and perception are modified by hyperglycemia

T. LINGENFELSER, W.-M. SUN, G. S. HEBBARD, J. DENT, AND M. HOROWITZ
Department of Gastrointestinal Medicine, Royal Adelaide Hospital, and Department of Medicine, University of Adelaide, Adelaide, South Australia 5000, Australia

Lingenfeler, T., W.-M. Sun, G. S. Hebbard, J. Dent, and M. Horowitz. Effects of duodenal distension on antropyloroduodenal pressures and perception are modified by hyperglycemia. Am. J. Physiol. 276 (Gastrointest. Liver Physiol. 39): G711–G718, 1999.—Marked hyperglycemia (blood glucose ∼15 mmol/l) affects gastrointestinal motor function and modulates the perception of gastrointestinal sensations. The aims of this study were to evaluate the effects of mild hyperglycemia on the perception of, and motor responses to, duodenal distension. Paired studies were done in nine healthy volunteers, during euglycemia (∼4 mmol/l) and mild hyperglycemia (10 mmol/l), in randomized order, using a crossover design. Antropyloroduodenal pressures were recorded with a manometric, sleeve-side hole assembly, and proximal duodenal distensions were performed with a flaccid bag. Intrabag volumes were increased at 4-ml increments from 12 to 48 ml, each distension lasting for 2.5 min and separated by 10 min. Perception of the distensions and sensations of fullness, nausea, and hunger were evaluated. Perceptions of distension (P < 0.001) and fullness (P < 0.05) were greater and hunger less (P < 0.001) during hyperglycemia compared with euglycemia. Proximal duodenal distension stimulated pyloric tone (P < 0.01), isolated pyloric pressure waves (P < 0.01), and duodenal pressure waves (P < 0.01). Compared with euglycemia, hyperglycemia was associated with increases in pyloric tone (P < 0.001), the frequency (P < 0.05) and amplitude (P < 0.01) of isolated pyloric pressure waves, and the frequency of duodenal pressure waves (P < 0.001) in response to duodenal distension. Duodenal compliance was less (P < 0.05) during hyperglycemia compared with euglycemia, but this did not account for the effects of hyperglycemia on perception. We conclude that both the perception of, and stimulation of pyloric and duodenal pressures by, duodenal distension are increased by mild hyperglycemia. These observations are consistent with the concept that the blood glucose concentration plays a role in the regulation of gastrointestinal motility and sensation.

duodenum; pylorus; gastrointestinal sensation

DISORDERED GASTROINTESTINAL motility (13, 23–25, 28, 34, 38, 39) and gastrointestinal symptoms (42) both occur frequently in patients with diabetes mellitus, but their etiology is poorly defined. It has been assumed for many years that both abnormal gut motility and gastrointestinal symptoms reflect irreversible vagal damage, occurring as part of a generalized autonomic neuropathy (25). However, it is now clear that acute changes in the blood glucose concentration have a substantial, and reversible, effect on motor function in a number of regions of the gastrointestinal tract (4, 6–8, 12, 14, 15, 17–20, 27, 32, 35–38, 40, 41, 44). In normal subjects, marked hyperglycemia (blood glucose ∼15 mmol/l) affects motility in the esophagus (7), stomach (4, 12, 14, 17–20, 32, 35), gallbladder (6, 8), small intestine (36), colon (44), and anorectum (37). The slowing of gastric emptying by acute hyperglycemia is evident in patients with diabetes (14, 38) and normal subjects (32, 35) and is associated with inhibition of fundic motility (19, 20), antral pressure waves (4, 17, 38), and stimulation of phasic and tonic pressure waves localized to the pylorus (12). There is evidence that changes in the blood glucose concentration within the physiological range also affect gastrointestinal motor function (2, 5, 6, 15, 17, 40); for example, in both normal subjects and patients with uncomplicated insulin-dependent diabetes, gastric emptying is slower at a blood glucose of 8 mmol/l compared with 4 mmol/l (40).

Recent studies suggest that the blood glucose concentration may also modulate sensory feedback from the gastrointestinal tract and thereby contribute to upper gastrointestinal symptoms. In normal subjects, sensations arising from nutrient stimulation of the small intestine (18) and proximal gastric distension (19, 20) are greater during marked hyperglycemia. In patients with insulin-dependent diabetes, gastrointestinal symptoms occur more frequently in those patients with poor glycemic control (42), and the perception of postprandial fullness is related to the blood glucose concentration (27). There is also evidence that mild (physiological) elevation of the blood glucose concentration may affect gastrointestinal sensation (2, 5).

In normal subjects, feedback from mechanical and chemical small intestinal receptors plays a major role in the regulation of gastric emptying and the etiology of gastrointestinal sensations (3, 9, 11, 43). We have reported in normal subjects that duodenal balloon distension stimulates phasic and tonic pyloric pressure waves and suppresses antral pressure waves (9); this motor pattern is known to be associated with slowing of gastric emptying (21, 22). Duodenal distension also results in sensations of fullness and nausea in proportion to the distending volume (9). The interaction of the blood glucose concentration with stimuli arising from the small intestine and stomach may be important in the etiology of upper gastrointestinal symptoms and disordered gastric motility in patients with diabetes mellitus (18, 19) and the regulation of gastric motility and postprandial sensations in normal subjects (2). During marked hyperglycemia (∼15 mmol/l), the effects of small intestinal triglyceride infusion on proximal gastric motility and fullness are increased in normal subjects (19). In normal subjects, the effects of
small intestinal lipid infusion on antropyloric pressures and the perception of appetite are modified by physiological changes in the blood glucose concentration (2). The possibility that the blood glucose concentration may modify the perception of, and motor responses to, mechanical stimulation of the small intestine has not been evaluated.

We have now evaluated the hypothesis that the perception of, and antropyloroduodenal motor responses to, duodenal distension are modified by changes in the blood glucose concentration within the mildly hyperglycemic range.

MATERIALS AND METHODS

Subjects. Nine healthy volunteers (6 male, 3 female; age 21–29 yr; body weight, 53–70 kg) participated in the study after written, informed consent had been obtained. None had a history of gastrointestinal disease or took medication. Smoking was prohibited for at least 24 h before and throughout each experiment. The study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Protocol. Each subject participated in two studies separated by 3–7 days, using a randomized, single-blind, crossover (hyperglycemia/euglycemia or euglycemia/hyperglycemia) design (Fig. 1). At ~0800, after a 12-h overnight fast, the manometric assembly was introduced via an anesthetized nostril, and for the remainder of the study the subject was kept supine with the head of the bed raised to 25°. The manometric assembly incorporated a sleeve sensor to measure pyloric pressures, antral and duodenal pressure recording side holes, an inflatable balloon (maximum volume 60 ml) at its tip to aid passage along the duodenum, and a second balloon for duodenal distension (see Measurement of antropyloroduodenal pressures). Correct positioning of the sleeve sensor across the pylorus was verified by measurement of the antroduodenal transmucosal potential difference (TMPD) gradient (21, 22). An in-dwelling cannula was inserted in an antecubital vein for infusion of 25% glucose or normal saline (Imed 927 Volumetric Infusion Pump, Abingdon, UK). “Arterialized” blood was drawn for blood glucose levels from a cannulated vein of the contralateral hand, which was kept in a heated chamber.

Before studies were started, the duodenal distension balloon inflation/deflation procedure was explained to the subject. Ten minutes after the first episode of duodenal phase III activity of the interdigestive migrating motor complex had been recorded, either hyperglycemia was initiated by intravenous infusion of 25% glucose or euglycemia was maintained by infusion of normal saline (Fig. 1). After 10 min, 2.5-min intraduodenal bag inflations were tested serially at 4-ml steps, starting at 12 ml and ending at 48 ml. The bag was deflated within 5 s between distensions, and subsequent distensions were initiated after an interval of 7.5 min, i.e., one distension was performed every 10 min. Subjects were not aware of the order of distensions. After the maximal distension volume of 48 ml was reached, four distensions of 44 ml were performed so that a total of 14 distensions were tested, which took ~140 min to perform (Fig. 1). The distensions were performed by one of the investigators who was unaware of the blood glucose concentration, and the duration of distensions was timed, using a clock, to ensure an inflation rate of 1 ml/min. During each distension, antropyloroduodenal pressures and perception were measured. After a “washout period” of 20 min, the alternative glycemic plateau was established within 20 min, and the sequence of duodenal distensions was repeated in identical fashion. Each study therefore took ~5 h to complete.

Stabilization of blood glucose concentrations and measurement of plasma insulin. Blood glucose concentrations were maintained at either euglycemic (4 mmol/l) or mildly hyperglycemic (10 mmol/l) levels using a glucose-clamp technique (2, 14, 40). To induce hyperglycemia, the blood glucose concentration was increased to ~10 mmol/l by infusing a bolus of 25% glucose intravenously and subsequently was maintained at this level by a variable infusion of glucose adjusted on the basis of blood glucose measurements. In the euglycemic phase of the study, saline was infused after a saline bolus of similar volume to the glucose bolus. Blood samples were analyzed every 5 min by a portable blood glucose meter (Refolux IIM; Boehringer Mannheim, Castle Hill, Australia). Both plasma glucose (hexokinase technique) and insulin (radioimmunoassay) were measured subsequently, on blood samples obtained at 15-min intervals.

Measurement of perception. Recognition and intensity of perception of duodenal distension were evaluated with the following rating scale, adapted from that of Azpiroz and Malagelada (3): 0, no perception; 1, vague perception of mild sensation; 2, definite perception of mild sensation; 3, vague perception of moderate sensation; 4, definite perception of moderate sensation; 5, discomfort; and 6, pain. A visual analog scale was used to assess feelings of fullness, nausea, and hunger where 0 = not present at all and 100 mm = present very strongly (43). The perception threshold was defined as the first perception, i.e., when the subject first indicated a change in the perception score from zero. Questionnaires were completed before the first distension (baseline) and at the end of each distension.

Measurement of antropyloroduodenal pressures. The purpose-built manometric assembly was made from a silicone rubber extrusion of 4.4 mm outer diameter with 11 channels. It included a 4.5-cm sleeve sensor, in parallel with four side holes 1.5 cm apart along the sleeve, to measure pyloric pressures (Dentsleeve, Parkside, South Australia). Side holes...
RESULTS

The studies were well tolerated by all subjects. The manometric catheter was positioned correctly for 94% of the time. There were no significant differences in the volume of glucose and saline infused intravenously either within or between each of the two studies [262 ± 21 and 274 ± 23 ml (25% glucose) and 260 ± 10 and 261 ± 13 ml (saline)].

Plasma glucose and insulin concentrations. Plasma glucose concentrations were maintained in the desired range (Fig. 2). During euglycemic phases, plasma glucose was 4.1 ± 0.5 and 4.0 ± 0.07 mmol/l, and during hyperglycemia plasma glucose levels were 10.4 ± 0.1 and 10.1 ± 0.2 mmol/l. Hyperglycemia was associated with an increase in plasma insulin, with there being no difference between the two studies (i.e., euglycemia/hyperglycemia vs. hyperglycemia/euglycemia) in the magnitude of this increase [39 ± 2 to 243 ± 15 pmol/l (P < 0.01) and 59 ± 34 to 269 ± 14 pmol/l (P < 0.01), respectively]. The baseline plasma insulin concentration during euglycemia was slightly higher (P < 0.05) if it was preceded by hyperglycemia (Fig. 2).

Sensory responses. During euglycemia, the threshold for perception of distension was 26.0 ± 1.5 ml. The intensity of perception of distension increased, approximately in a linear fashion, with volumes up to 32 ml (Fig. 3). No subject experienced discomfort or pain. The perception of fullness also increased (P < 0.05) with greater duodenal distension volumes. The mean score of nausea was low throughout, with little change until a distension volume of 32 ml was reached (P < 0.05; Fig. 3 and Table 1). Subjects were more hungry (P < 0.05) when the euglycemic phase was done second. The score of hunger did not change significantly when the euglycemic phase was done first.

During hyperglycemia, the threshold for perception of distension was 18.8 ± 1.0 ml, and there was an increase in the intensity of perception from a volume of 24 ml. Six subjects experienced discomfort at a volume of 48 ml. The sensation of both fullness (P < 0.001) and

Plasma glucose and insulin concentrations during hyperglycemia and euglycemia. Plasma insulin concentrations are greater (P < 0.001) during hyperglycemia. *P < 0.05, euglycemia first vs. euglycemia second. Data are means ± SE.
nausea ($P < 0.05$) increased as the distension volumes became larger, whereas the score of hunger ($P < 0.001$) decreased (Fig. 3).

The perception of distension was greater ($P < 0.01$) during hyperglycemia compared with euglycemia at distension volumes $\geq 28$ ml. Similarly, feelings of fullness ($P < 0.05$) and nausea ($P < 0.05$) were greater, whereas hunger was less ($P < 0.001$), during hyperglycemia (Fig. 3). To evaluate the possibility that the increased perception during hyperglycemia reflected a difference in duodenal compliance, scores of all sensations were also plotted against pressure; in this situation, there was no difference between hyperglycemia and euglycemia (Fig. 4).

Motor responses. During euglycemia, there were virtually no antral pressure waves and no IPPWs immediately before duodenal distension. The number of duodenal pressure waves increased ($P < 0.01$) during duodenal distension, with a plateau at a volume of $\sim 20$ ml (Fig. 5), and phase III-like motor activity was stimulated in two subjects. With increasing distension volumes, intraballooon pressure increased (Fig. 6). Duodenal distension was associated with volume-related increases in both the number ($P < 0.01$) and amplitude ($P < 0.01$) of IPPWs, with a plateau at $\sim 20$ ml (Fig. 7). There was also a similar, volume-related increase ($P < 0.01$) in pyloric tone with a plateau at $\sim 16$ ml (Fig. 8). The phasic and tonic pyloric responses returned to baseline values within 5 min of deflation of the bag. There were no antral pressure waves during duodenal distension.

During hyperglycemia, there were very few antral pressure waves immediately before duodenal balloon distension. There was an increase ($P < 0.01$) in the number of duodenal pressure waves during duodenal distension, with a maximum response at 36 ml (Fig. 5), and phase III-like motor activity was induced in eight subjects, in each case at volumes $\geq 40$ ml. IPPWs were recorded in two subjects during the 10-min basal recording period. The number of IPPWs increased ($P < 0.01$) during duodenal distension in a volume-related fashion (Fig. 7). At the maximal distension volume of 48 ml, the rate of IPPWs was three per minute in eight of the nine subjects. Duodenal distension also stimulated volume-related increases ($P < 0.01$) in pyloric tone (Fig. 8).

The total number of duodenal pressure waves was greater ($P < 0.01$) during hyperglycemia compared with euglycemia (Fig. 5), due in part to an increased prevalence of phase III-like activity (2/9 subjects vs. 6/9 subjects). The intraduodenal pressure-volume relationship was steeper during hyperglycemia, indicating a reduction ($P < 0.05$) in duodenal compliance (Fig. 6). During duodenal distension, the number of IPPWs was greater ($P < 0.05$) during hyperglycemia compared with euglycemia (Fig. 5).
with euglycemia at distension volumes ≥24 ml. A similar effect (P < 0.01) was observed for the amplitude of IPPWs (Fig. 7). Pyloric tone was greater (P < 0.01) during hyperglycemia than euglycemia at all distension volumes (Fig. 8).

**DISCUSSION**

This study demonstrates in healthy individuals that both sensations and motor responses related to duodenal distension are modified by elevation in the blood glucose concentration to the upper limit of the normal postprandial range. A randomized/crossover study design was employed to control for potential order effects due to adaptation of motor and sensory responses with repetitive mechanical stimuli. By incorporating a thin-walled, flaccid bag in the manometric assembly, measurements of antropyloroduodenal pressures could be performed concurrently with duodenal distensions. Sensations of distension and fullness and stimulation of pyloric and duodenal pressure waves were substantially greater during mild hyperglycemia compared with euglycemia. These observations are compatible with the concept that modest elevation of the blood glucose concentration influences gastrointestinal motor function and symptoms in both patients with diabetes mellitus and normal subjects (2, 6,18, 19, 27, 38, 40).

It has recently been reported that the threshold for perception of esophageal distension is lower at a blood glucose concentration of 8 mmol/l compared with 4 mmol/l in normal subjects (5). The confirmation in our study that mild hyperglycemia increases the perception of mechanical distension of the gut is of considerable interest, indicating that the blood glucose concentration may act as a physiological modulator of gastrointestinal sensitivity and that there is a synergistic relationship between the blood glucose concentration and stimuli arising from small intestinal mechanical stimulation. In a recent study, we demonstrated in normal subjects that, during small intestinal nutrient infusion, distal gastric motor function and the perceptions of appetite and nausea are affected by variations in the blood glucose level within the physiological range. This effect is indicative of synergy between the blood glucose concentration and stimulation of small intestinal chemoreceptors (2). For example, during intraduodenal lipid infusion, appetite is less at a blood glucose concentration of 8 mmol/l compared with 5 mmol/l (2). In patients with insulin-dependent diabetes mellitus, there is a high prevalence of upper gastrointestinal symptoms, such as fullness, nausea, and abdominal discomfort (42), but only a weak relationship between such symptoms and gastrointestinal motility disturbances (23, 24, 28). Also, in patients with insulin-dependent diabetes mellitus, gastrointestinal symptoms occur more frequently in those with poor glycemic control (42), and the symptom of postprandial fullness is related to the blood glucose concentration (27). There is, therefore, circumstantial support for the concept that acute changes in the blood glucose concentration are also important in the etiology of gastrointestinal symptoms in patients with diabetes (27, 42). This

<table>
<thead>
<tr>
<th>Distension Volume, ml</th>
<th>Euglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>3.2 ± 2.2</td>
<td>3.3 ± 1.9</td>
</tr>
<tr>
<td>32</td>
<td>4.3 ± 1.8</td>
<td>5.7 ± 2.4</td>
</tr>
<tr>
<td>48</td>
<td>6.3 ± 2.5*</td>
<td>11.0 ± 5.9*†</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE, in cm. In study 1, hyperglycemia preceded euglycemia, whereas in study 2 euglycemia preceded hyperglycemia. *P < 0.05 cf. 16 ml; †P < 0.05, hyperglycemia vs. euglycemia.

Fig. 4. Relationship between the score for perception of distension and intraballoon pressure during euglycemia and hyperglycemia. Data are means ± SE.

Fig. 5. Effects of duodenal distension on the number of duodenal pressure waves. Duodenal distension stimulated duodenal pressure waves (P < 0.01), the response being volume related (P < 0.05) and greater (P < 0.001) during hyperglycemia than euglycemia (by ANOVA). Data are means ± SE.
hypothesis now warrants more formal evaluation, ideally by longitudinal, rather than cross-sectional, studies (27, 42).

The present study shows that mild hyperglycemia affects antropyloroduodenal motility both before and in response to duodenal distension. The observed effects of hyperglycemia on pyloric and duodenal motility are likely to be associated with retardation of gastric emptying, as the combination of inhibition of antral, and stimulation of pyloroduodenal, pressure waves would be expected to increase gastric outflow resistance (21, 22). Edelbroek et al. (9) reported in normal subjects that duodenal balloon distension stimulates pyloric and duodenal pressure waves, with a pattern that is influenced by the site of distension. We have now established that this presumably mechanoreceptor-mediated motor reflex is enhanced by mild hyperglycemia. In contrast to the stimulatory effect of mild hyperglycemia on pyloric and duodenal pressure waves, marked hyperglycemia inhibits gastrocolonic responses, colonic peristaltic reflexes (44), and proximal gastric tone (19, 20). During hyperglycemia, duodenal compliance (as indicated by the pressure-volume relationship) was reduced compared with euglycemia; this response contrasts with the proximal stomach where the reduced threshold for perception of distension during marked hyperglycemia is associated with an increase in proximal stomach compliance (19, 20). These and other studies (12, 36) therefore establish that the effects of hyperglycemia on motility may vary throughout the gastrointestinal tract. Our observations relating to the effects of hyperglycemia on the antropyloroduodenal motor responses to duodenal distension in normal subjects should not be extrapolated to patients with diabetes mellitus. In particular, it is uncertain whether the response to hyperglycemia is influenced by previous blood glucose control. However, although it is possible that the threshold (or overall) gastrointestinal motor response to hyperglycemia may differ in patients with diabetes from normal subjects, previous studies suggest that this is not the case (14, 38).

The mechanisms by which hyperglycemia modifies gastrointestinal motor reflexes and visceral sensation are poorly defined. Both the sympathetic nervous system and the vagus nerve play an important role in mediating duodenogastric reflexes (3, 16). Sensory input can be modulated at a number of levels: peripherally at the afferent nerve, at the level of prevertebral ganglia, or at the spinal cord, brain stem, or cortex (33). Although changes in duodenal compliance may potentially lead to changes in perception, this is unlikely to account for the increased sensitivity to duodenal distension during hyperglycemia, as no differences were evident when sensation scores were plotted against intraballloon pressure, as opposed to balloon volume. A direct effect of hyperglycemia on smooth muscle seems unlikely in the face of both stimulatory and inhibitory effects of acute hyperglycemia on motility in different regions of the gastrointestinal tract (12, 17, 19, 36). There is evidence that insulin may affect gastrointestinal motor function (10), and hyperinsulinemia has been shown to increase sympathetic activity (1), possibly by a central nervous system action (31). Furthermore, activation of the sympathetic nervous system may increase visceral sensation (26).
gastrointestinal motor function is, however, likely to be minor as changes in the blood glucose concentration affect gut motility in patients with insulin-dependent diabetes who have no endogenous insulin secretion (8, 14, 38, 40). In considering other potential mechanisms, there is recent evidence (reported in abstract form) that hyperglycemia may have a direct effect on the myenteric plexus; in the rat small intestine, removal of extracellular glucose hyperpolarizes intestinal enteric neurons (29).

We thank K. Willson for assistance with the statistical analyses and S. Suter for typing this manuscript.

This study was supported by a grant from the National Health and Medical Research Council of Australia. T. Lingenfelser was the recipient of a research fellowship from the J ung Stiftung fur Forschung und Wissenschaft (J ung Foundation for Research and Science). Address for reprint requests and other correspondence: M. Horowitz, Dept. of Medicine, Royal Adelaide Hospital, North Terrace, South Australia 5000, Australia.

Received 20 July 1998; accepted in final form 13 November 1998.

REFERENCES


