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Hyperglycemia Affects Gastric Electrical Rhythm and Nausea During Intraduodenal Triglyceride Infusion

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Hyperglycemia slows gastric emptying and increases the intensity of perception of gastric distension during fasting and small intestinal nutrient stimulation. In order to examine the possibility that abnormalities of gastric electrical rhythm may be associated with the effects of hyperglycemia, the gastric electrical rhythm (cutaneous electrogastrogram) and the perception rating scores for upper gastrointestinal sensations (visual analog scale) were examined. Studies were performed during intraduodenal triglyceride infusion in 10 healthy volunteers under euglycemic and hyperglycemic (≈15 mmol/liter) conditions. During fasting, hyperglycemia had no effect on either gastric electrical rhythm or sensation. Intraduodenal triglyceride infusion was associated with an increase in bradygastria (<2.4 cpm) during both euglycemia (33 ± 9%) and hyperglycemia (36 ± 10%, $P < 0.05$ vs baseline for each). During intraduodenal triglyceride infusion, tachygastria (>3.6 cpm) was more prevalent during hyperglycemia when compared to euglycemia (25 ± 10% vs 1 ± 1%, $P < 0.05$) and the perception rating scores for nausea and abdominal discomfort were greater during hyperglycemia ($P < 0.05$ for both). The intensity of nausea correlated with the proportion of time spent in tachygastria ($r = 0.64$, $P < 0.01$). These data are consistent with the concept that postprandial upper gastrointestinal symptoms in patients with diabetes mellitus may be modulated by the blood glucose concentration.

KEY WORDS: gastric emptying; electrogastrography; hyperglycemia; gastrointestinal sensation.

Recent studies indicate that blood glucose concentration has a major impact on gastrointestinal motor function (1). Hyperglycemia slows gastric emptying in normal subjects and patients with both insulin dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) (2–4), affecting motility of the antrum, pylorus, and proximal stomach (5–7). The mechanisms mediating the effects of hyperglycemia on gastric motor function are poorly understood. The timing of gastric contractions is controlled by a pacemaker situated in the proximal stomach (8), and it is possible that hyperglycemia may influence gastric motor function by affecting the gastric electrical rhythm. A high prevalence of abnormalities of gastric electrical rhythm has been demonstrated in studies of diabetic patients with upper gastrointestinal symptoms and/or autonomic neuropathy (9, 10), but blood glucose concentrations were not monitored in these studies. The concept that the observed abnormalities

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of gastric electrical activity may have been a consequence of hyperglycemia rather than diabetes *per se* is supported by studies indicating that induced hyperglycemia is associated with an increase in tachygastria in both patients with IDDM and normal individuals (11, 12). Furthermore, during euglycemia, the prevalence of disordered gastric electrical activity is not increased in patients with IDDM who have autonomic neuropathy (13). In the fed state, interpretation of studies of the gastric electrical response to hyperglycemia is complicated by differences in gastric motor function and gastric emptying during hyperglycemia when compared to euglycemia (2–7). For example, it would not be surprising if effects on gastric pacemaker function were dependent on the rate of nutrient delivery to the small intestine. In order to investigate more definitively the effects of hyperglycemia on the gastric electrical rhythm, we have controlled nutrient feedback to the stomach by the infusion of triglyceride directly into the duodenum.

Upper gastrointestinal symptoms are common in patients with diabetes mellitus and correlate poorly with abnormalities of gastric emptying (14), suggesting that other factors, such as disordered sensory function, are likely to be important in the genesis of symptoms. We have previously shown that hyperglycemia increases the sensitivity of the proximal stomach to distension in normal subjects (7, 15). The interaction of nutrients with postulated receptors in the small intestine plays a major role in the etiology of upper gastrointestinal symptoms (16, 17) and the regulation of appetite (18). We have now further investigated the effects of hyperglycemia on the perception of sensations associated with nutrient stimulation of the small intestine.

MATERIALS AND METHODS

Subjects. Ten healthy volunteers (5 women, 5 men, age range 20–32 years) participated in the study. Subjects had no gastrointestinal symptoms, were not taking medication, and had not had any previous abdominal surgery. The study protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Methods. Gastric electrical rhythm and perception rating scores for gastrointestinal sensations prior to and during intraduodenal triglyceride infusion were examined during euglycemia and hyperglycemia in paired studies on separate days. Volunteers were not aware as to which arm of the study they were undergoing on any particular day.

The experimental protocol is summarized in Figure 1a. Subjects attended the laboratory on two separate days at 9:00 AM following an overnight fast. A tube was passed transnasally into the stomach and then into the duodenum during phase III of the gastric migrating motor complex.

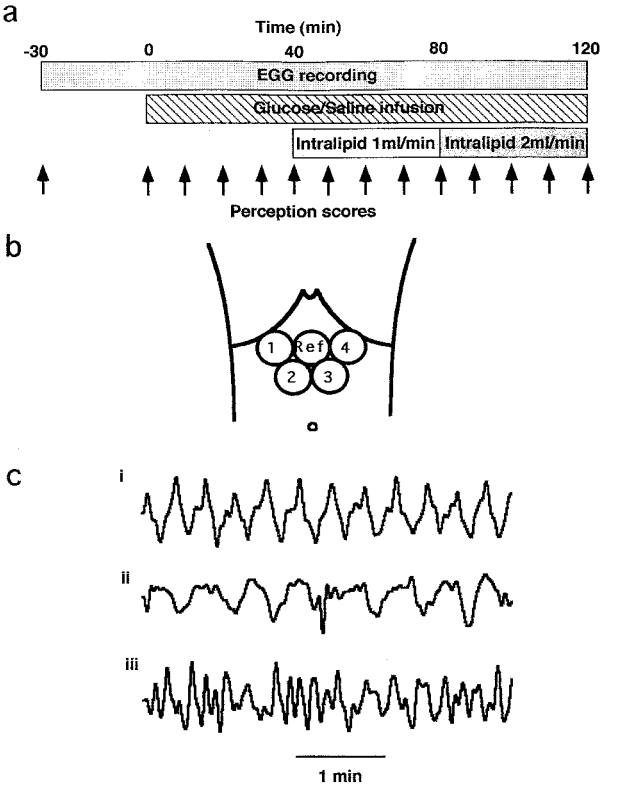

Fig 1. (a) Experimental protocol; (b) arrangement of EGG electrodes on abdomen; and (c) examples of gastric electrical rhythms: (i) normal rhythm, (ii) bradygastria, and (iii) tachygastria with a short period of normal rhythm.

The tube was 3 mm in outer diameter and contained three lumina. Two lumina, opening at sideholes 10 cm apart, were perfused with saline (0.1 ml/min) and used to confirm the position of the tube in the proximal duodenum by measurement of transmucosal potential difference, according to established criteria (19). The third lumen (1.5 mm diameter, sidehole positioned 5–10 cm beyond the pylorus) was used for intraduodenal infusion of triglyceride. Subjects were then randomized to either the euglycemia or hyperglycemia arm of the study by a computer program. Cannulae were placed intravenously in both cubital fossae, one for infusion of saline or glucose and the other for obtaining blood samples for determination of the blood glucose concentration. Following cleansing of the skin with 70% isopropyl alcohol and light abrasion, five electrodes (Red Dot, 3M Medical Devices, St Paul, Minnesota) were placed on the abdomen. The reference electrode was placed two thirds of the way between the umbilicus and the xiphisternum. Four recording electrodes were placed around the central reference electrode, as described by Jebbink et al (11) (Figure 1b). The cutaneous electrogastrogram (EGG) was recorded continuously throughout the study (see below). Following an initial 30-min recording period (basal period), either glucose or normal saline was infused intravenously. Hyperglycemia was established by intravenous infusion of 100–150 ml of 25% glucose at 50 ml/min until the blood glucose concentration was $\geq$14 mmol/liter. Hy-

perglycemia was maintained by infusion of glucose thereafter, initially at 150 ml/hr, with this rate then being varied to maintain the blood glucose concentration at about 15 mmol/liter. In studies conducted under euglycemic conditions, 150 ml of normal saline was initially infused over three minutes followed by a constant infusion at a rate of 150 ml/hr. Blood glucose concentrations were measured every 10 min throughout both studies using a portable blood glucose meter (Reflolux IIM, Boehringer Mannheim Pty Ltd, Castle Hill, NSW, Australia). Forty minutes after the commencement of the intravenous infusions, an intraduodenal triglyceride (10% Intralipid, 1.1 kcal/ml, 300 mosm, Baxter Healthcare, Toongabbie, Australia) infusion was commenced, initially at 1 ml/min for 40 min, followed by a rate of 2 ml/min for a further 40 min.

Perception rating scores for the sensations of epigastric fullness, nausea, abdominal discomfort, and hunger were recorded prior to and every 10 min during the study period using a validated 100 mm visual analog scale (18).

Electrogastrography. EGG signals were amplified and filtered using custom-built analog circuitry. A LabNB card (National Instruments Corporation, Austin, Texas) digitized the analog signal at 10 Hz and the digitized data were then recorded on a Macintosh SE computer using Labview-based software (National Instruments). EGG recordings were analyzed in 4-min blocks (240 sec) with a 3-min overlap. Custom-written software based on Labview (National Instruments) filtered the data [4th order Chebyshev filter, upper limit 0.2 Hz (12 cpm), lower limit 0.02 Hz (1.2 cpm)] and calculated power spectra for each period. In addition, running spectra for each channel covering the entire period of the study were displayed as grey-scale images (NIH Image, National Institutes of Health, Bethesda, Maryland). Raw and filtered data were displayed simultaneously with power spectra and grey-scale images on the computer screen to facilitate identification of artefacts due to noise.

EGG data were analyzed by investigators blinded to the experimental conditions. The dominant rhythm for each 4-min period was determined by simultaneous inspection of raw and filtered data and power spectra for each channel for that period. Power spectra were used as the primary basis for the classification of gastric electrical rhythm for each period (Figure 1c) according to the following criteria, based on those used by Jebbink et al (11):

(1) normal rhythm—a dominant rhythm with a frequency of 0.04–0.06 Hz (2.4–3.6 cpm) in at least one channel;
(2) tachygastria—a dominant rhythm in the range of 0.06–0.15 Hz (3.6–9 cpm) in the absence of any other identifiable rhythm;
(3) probable tachygastria—a dominant rhythm with a frequency of 0.06–0.15 Hz in the presence of a rhythm of lower power with a frequency in the normal or bradygastria range;
(4) bradygastria—a dominant rhythm in the range 0.02–0.04 Hz (1.2–2.4 cpm) in the absence of any other identifiable rhythm; and
(5) indeterminate rhythm—the absence of a discernible rhythm in any channel.

Statistical Analysis

Differences in dominant gastric rhythm were determined by comparing the proportion of time each rhythm could be identified in each subject for each period of the study (ie, prior to intraduodenal triglyceride infusion, intraduodenal triglyceride infusion at 1 ml/min, 2 ml/min). Changes in perception rating scores were calculated by subtracting the basal perception rating score for each sensation from all subsequent scores for that subject. A mean change in perception rating score was then calculated for each subject for each period and these were compared.

Differences between euglycemia and hyperglycemia and over time for individual data series were analyzed using repeated measures analysis of variance (SuperAnova, Abacus Concepts Inc, Berkeley, California). If an overall difference between euglycemia and hyperglycemia was detected individual data points were compared. Differences over time were computed by comparing data points with the initial value in each series if a significant interaction with time was detected. $P < 0.05$ was considered significant in all analyses. Data values are given as mean ± SEM.

RESULTS

Most of the subjects tolerated the study well. One subject vomited 17 min after the commencement of triglyceride infusion at 1 ml/min during hyperglycemia and accordingly that arm of the study was not completed. Two subjects needed to urinate during the study period, both during hyperglycemia. The mean blood glucose concentration was 14.9 ± 0.2 mmol/liter in the studies done during hyperglycemia, and 4.0 ± 0.1 mmol/liter during the studies conducted under euglycemic conditions. The volumes of 25% glucose solution (497 ± 30 ml) infused intravenously during the hyperglycemia arm of the study and saline (434 ± 17 ml) infused intravenously during the euglycemia arm of the study were similar.

EGG Rhythm. A total of 119 data analysis periods could not be classified because of artifacts associated with movement (33), micturition (22), and the subject who vomited (64), leaving a total of 1482 periods of studies conducted during euglycemia and 1434 periods of studies conducted during hyperglycemia that were analyzed.

Prior to the intraduodenal triglyceride infusion, all subjects had a dominant pacemaker rhythm in the normal range. There was no difference in the proportion of time spent in normal rhythm between euglycemia (99 ± 0.2%) and hyperglycemia (94 ± 4.5%, Figure 2).

In the studies conducted during euglycemia, intraduodenal infusion of triglyceride was associated with a reduction in the proportion of time spent in normal rhythm to 75 ± 7.4% while triglyceride was

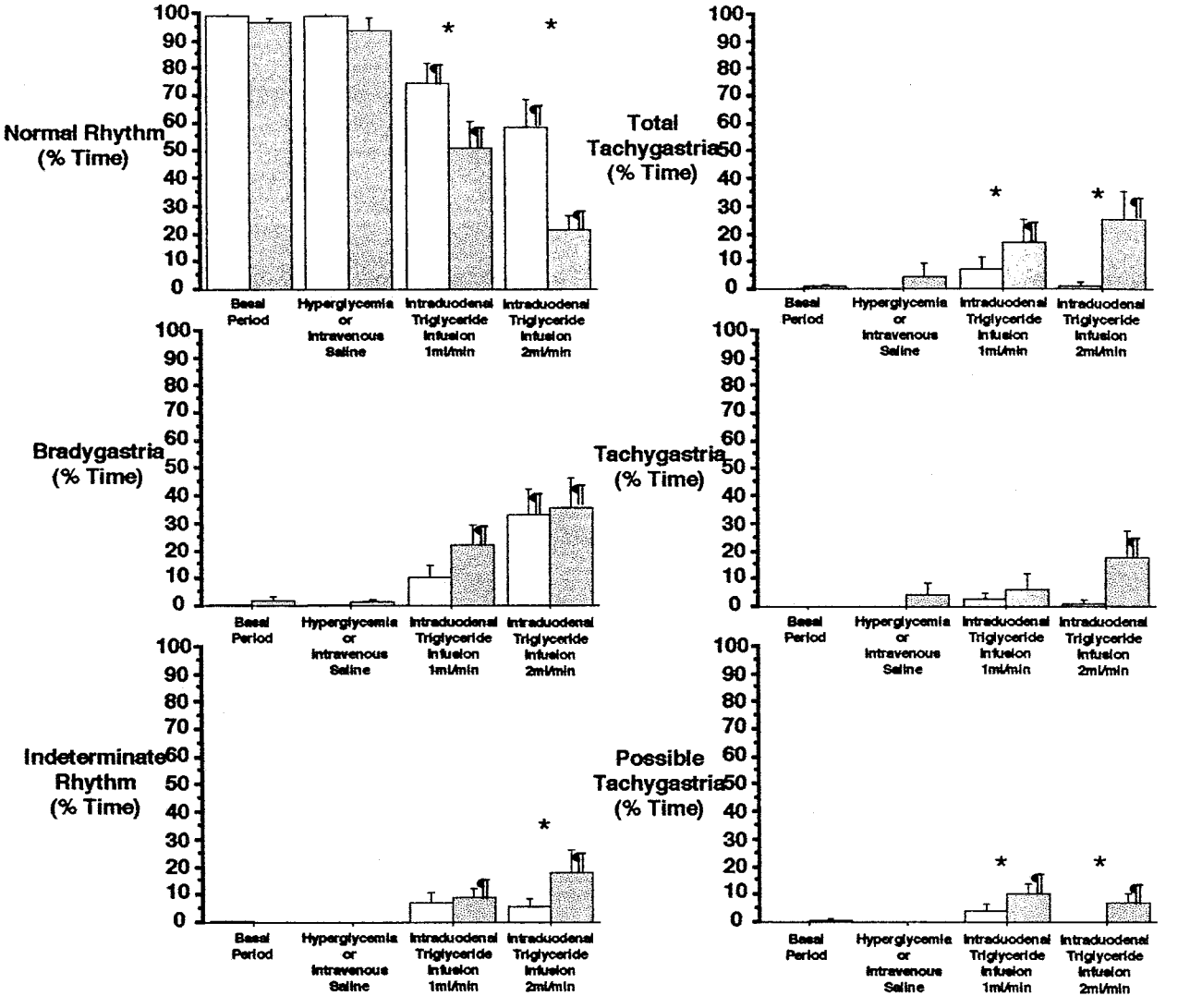

Fig 2. Proportion of time spent in each gastric electrical rhythm in the basal (fasting) period and with triglyceride infusion, during euglycemia (open bars) or hyperglycemia (filled bars). *Difference ($P < 0.05$) between euglycemia and hyperglycemia; ¶difference from basal value. $N = 10$ except at intraduodenal triglyceride infusion 2 ml/min where $N = 9$.

infused into the duodenum at 1 ml/min, and a further decrease to 59 ± 10.2% during intraduodenal triglyceride infusion at 2 ml/min ($P < 0.05$ for both, Figure 2). During hyperglycemia the same effect was seen, but the magnitude of the fall was greater, with a reduction to 51 ± 9.4% while triglyceride was infused into the duodenum at 1 ml/min ($P < 0.05$ vs euglycemia) and 21 ± 5.0% during triglyceride infusion at 2 ml/minute ($P < 0.05$ vs euglycemia). The reduction in the proportion of time spent in a normal rhythm during intraduodenal triglyceride infusion and euglycemia was largely accounted for by an increase in bradygastria (33 ± 9%, $P < 0.05$ vs prior to intraduodenal triglyceride infusion, Figure 2). Neither tachygastria (1 ± 1%) nor indeterminate rhythms (6 ± 3%) increased with intraduodenal triglyceride infusion under euglycemic conditions. During hyperglycemia and intraduodenal triglyceride infusion, an increase in bradygastria similar to that during euglycemia was seen (36 ± 11%, $P < 0.05$ vs prior to intraduodenal triglyceride infusion, $P > 0.05$ vs euglycemia), but in contrast to euglycemia, there was also an increase in tachygastria (25 ± 10%, $P < 0.05$ vs prior to intraduodenal triglyceride infusion, Figure 2) and indeterminate rhythms (19 ± 8%, $P < 0.05$ vs prior to intraduodenal triglyceride infusion, Figure 2). The differences in gastric electrical rhythm between euglycemia and hyperglycemia were therefore largely

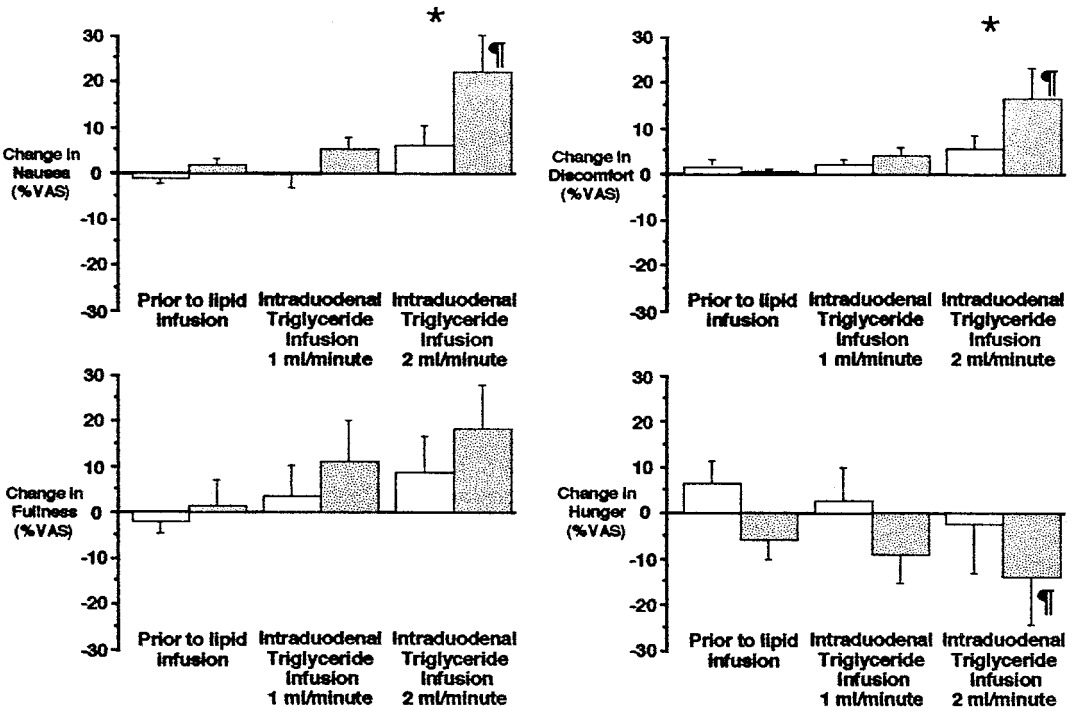

Fig 3. Effect of intraduodenal triglyceride infusion on perception rating scores for gastrointestinal sensations during euglycemia (open bars) or hyperglycemia (filled bars). Values represent mean change in perception rating score (millimeters on visual analog scale) from baseline score. *Difference ($P < 0.05$) between euglycemia and hyperglycemia; ¶difference from baseline score. $N = 10$ except at intraduodenal triglyceride infusion 2 ml/min where $N = 9$.

accounted for by the increases in tachygastria and indeterminate rhythms during hyperglycemia ($P < 0.05$ hyperglycemia compared to euglycemia for each).

Perception of Gastrointestinal Sensations. Prior to intraduodenal triglyceride infusion, perception rating scores for the sensations of fullness, nausea, abdominal discomfort, and hunger did not differ between euglycemia and hyperglycemia (Figure 3, $P > 0.05$). By the end of the 2 ml/min period of intraduodenal triglyceride infusion, perception rating scores for both nausea and abdominal discomfort increased during hyperglycemia ($P < 0.05$ vs prior to intraduodenal triglyceride infusion), but not euglycemia. Perception rating scores for nausea (22 ± 9% vs 6 ± 4%, $P < 0.05$ hyperglycemia vs euglycemia) and abdominal discomfort (16 ± 7% vs 5 ± 3%, $P < 0.05$ hyperglycemia vs euglycemia) were therefore greater during hyperglycemia than during euglycemia.

Infusion of triglyceride into the duodenum did not alter the perception rating scores for fullness during either euglycemia or hyperglycemia (Figure 3) and, although mean values tended to be higher during hyperglycemia, there was no significant difference between hyperglycemia and euglycemia (18 ± 9% vs 8 ± 8%, $P = 0.08$). Perception rating scores for hunger fell ($P < 0.05$ vs prior to intraduodenal triglyceride infusion) during hyperglycemia and intraduodenal triglyceride infusion. Although this did not reach statistical significance ($P = 0.09$ vs prior to intraduodenal triglyceride infusion), a similar effect was seen during euglycemia. Changes in hunger over time did not differ between euglycemia and hyperglycemia. No subject experienced abdominal pain during either arm of the study (data not shown).

Relationship Between Perception Rating Scores for Gastrointestinal Sensations and Gastric Electrical Rhythm. During euglycemia, there was no relationship between the perception rating scores for any sensation and the proportion of time spent in any gastric electrical rhythm. During hyperglycemia, the mean score for nausea correlated ($r = 0.64$, $P < 0.01$) with the proportion of time spent in tachygastria (Figure 4). A weaker inverse relationship also existed between nausea and the proportion of time spent in a normal rhythm during hyperglycemia ($r = -0.51$, $P < 0.01$). There was no significant correlation between nausea and the proportion of time spent in brady-

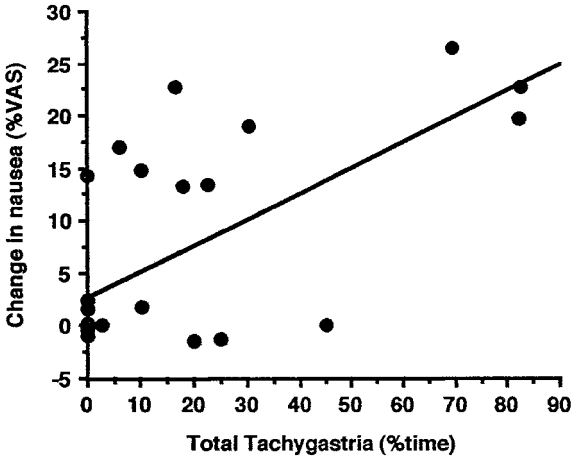

Fig 4. Relationship between perception rating score for nausea and proportion of time spent in tachygastria during hyperglycemia for each subject and phase of intraduodenal triglyceride infusion ($r = 0.64$, $P < 0.05$).

gastria or indeterminate rhythms or between perception rating scores for any of the other sensations and gastric electrical rhythm during hyperglycemia.

DISCUSSION

We have demonstrated, during intraduodenal triglyceride infusion, that hyperglycemia affects gastric electrical rhythm and modulates the perception rating scores for gastrointestinal sensations in normal subjects. Moreover, the increased perception rating score for nausea during hyperglycemia correlated with changes in gastric electrical rhythm, in particular, tachygastria.

The EGG reflects the gastric electrical control activity (20, 21), which determines the fundamental frequency of antropyloric contractions (22). Our observation that intraduodenal triglyceride infusion increases bradygastria is novel. A transient reduction in frequency of the gastric electrical rhythm after a meal has been reported previously (11); however, the changes that we observed were both greater and sustained. Bradygastria was usually evident within a few minutes of the commencement of the triglyceride infusion and persisted for the duration of the infusion.

The increased incidence of tachygastria during hyperglycemia is consistent with previous studies that have demonstrated that hyperglycemia induces tachygastria in both patients with IDDM and normal individuals after a meal (11, 12). It can now be concluded that these effects are independent of changes in the rate of gastric emptying induced by hyperglycemia, as in our study nutrient was delivered directly into the duodenum.

We did not observe any change in gastric electrical rhythm during hyperglycemia in the fasting state, suggesting that the presence of nutrients in the intestine may modulate the effects of hyperglycemia on the electrical and mechanical activity of the stomach. Although hyperglycemia is associated with changes in gastric motor function in the fasted state (5–7), our results are consistent with those of MacGregor et al, who reported that hyperglycemia delayed gastric emptying of nutrient liquids, but not a non-nutrient-containing liquid in normal subjects (2).

The retardation of gastric emptying by hyperglycemia is associated with reduced antral and fundic contractile activity and increased numbers of pyloric pressure waves (3, 5–7). It is possible that changes in gastric electrical activity could play a role in mediating these effects. In support of a direct role, both spontaneous and induced gastric dysrhythmias have been noted to be associated with delayed gastric emptying and a reduction in antral motor activity (20, 23, 24).

The mechanisms mediating the effects of hyperglycemia on gastric motor and electrical function are poorly understood. Prostaglandin infusion induces tachygastria in the isolated, perfused canine stomach (25), and indomethacin, a cyclooxygenase inhibitor prevents the induction of tachygastria by hyperglycemia in normal subjects (12), indicating a potential role for prostaglandins in the genesis of tachygastria. Indomethacin also modulates the pyloric electrical response to high fat meals in dogs (26), indicating that the presence of triglyceride in the proximal small intestine may be associated with changes in endogenous prostaglandin concentrations. These effects on prostaglandin-dependent pathways may provide a potential mechanism whereby intraduodenal triglyceride and hyperglycemia could interact to modulate gastric electrical activity.

It is important to consider whether our observations in relation to gastric electrical activity could be explained in part by technical factors. Both hyperglycemia (5–7) and small intestinal triglyceride infusion (27, 28) induce gastric relaxation, which could have altered the position of the stomach during the EGG recording. We recorded simultaneously from four pairs of electrodes in an attempt to minimize any such effect, but it is theoretically possible, albeit unlikely, that some or all of the periods during which a rhythm could not be detected were due to changes in gastric

position relative to the cutaneous electrodes. The observed differences between hyperglycemia and euglycemia during periods in which a signal was identified, however, cannot be explained on such a basis.

Small intestinal nutrient stimulation and gastric distension interact in the genesis of upper gastrointestinal sensations. For example, during small intestinal saline infusion gastric distension is perceived initially as a pressure sensation and, with progressive distension, as painful (16, 29). In contrast, during intestinal nutrient stimulation, gastric distension is perceived as a more meal-like sensation until, with increasing distension, nausea occurs (16, 29). Hyperglycemia has previously been reported to affect somatic sensation (30); however, there is only limited information concerning the effects of hyperglycemia on visceral sensation. We have previously demonstrated that hyperglycemia increases the perception rating scores for nausea during gastric distension both in the fasting state and during intraduodenal triglyceride infusion (7, 15), and the current study extends these observations to the sensations induced by triglyceride infusion in the absence of gastric distension.

We found that the increased perception rating score for nausea during hyperglycemia and intraduodenal triglyceride infusion correlated with the proportion of time spent in tachygastria. An association between tachygastria and nausea has been noted previously (31), but the mechanism of the effect is uncertain. Our study did not have sufficient resolution to detect a difference in the time of onset of nausea and tachygastria, but in studies of motion sickness, the onset of tachygastria has been closely related to nausea (31). In our study, we observed that several subjects had tachygastria without nausea and the one subject who vomited had no tachygastria, indicating that the link between the two phenomena is not invariable.

The levels of blood glucose achieved in our studies are commonly seen in patients with diabetes mellitus, particularly during the postprandial period, and the observed changes in the perception rating scores for some gastrointestinal sensations during hyperglycemia may therefore have significant implications for the pathogenesis of postprandial symptoms in these patients. It remains to be determined whether such symptoms may be exacerbated by hyperglycemia, but there is some evidence that this may be the case (32, 33).

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