Physiological changes in blood glucose affect appetite and pyloric motility during intraduodenal lipid infusion


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Abstract

It has recently been shown that acute changes in blood glucose concentration affect gastrointestinal motility in both normal subjects and in patients with diabetes. In particular, elevation of blood glucose to pathological levels (12–16 mmol/l) has been shown to decrease peristaltic velocity in the esophagus (9), slow gastric emptying (17), inhibit antral motility (3, 16, 18, 36), stimulate pyloric motility (16), increase proximal gastric compliance (19), attenuate gallbladder contraction (10), prolong small intestinal transit time (34), alter colonic motility (30, 41), and blunt the rectoanal inhibitory reflex (6). Moreover, less marked, i.e., “physiological,” changes in blood glucose within the normal postprandial range (8–11 mmol/l) have also been shown to affect gastrointestinal motor function, specifically to accelerate peristaltic velocity in the esophagus (5), slow gastric emptying (29, 39), alter fasting gastric interdigestive motor patterns (3), and reduce gallbladder contraction (8). Conversely, hypoglycemia has been shown to accelerate gastric emptying in both healthy volunteers and patients with insulin-dependent diabetes (37, 40).

The rate of gastric emptying is closely regulated and is dependent on the coordinated motor activity of the fundus, antrum, pylorus, and small intestine. By virtue of its position at the gastric outlet, the pylorus plays a crucial role in determining the rate of gastric emptying. In the fasting state, marked hyperglycemia is known to increase phasic pyloric motility (16) and this is likely to play a role in the slowing of gastric emptying. The effect of more modest physiological elevation of blood glucose on pyloric motility is unknown. It is likely that small intestinal nutrients will modulate the pyloric motor response to physiological hyperglycemia, because gastric emptying of saline, compared with nutrients, is unaffected by hyperglycemia (29).

The perception of distension and nutrient-induced sensations arising from the gut is also known to be modulated by acute elevation of blood glucose to pathological levels (6, 21, 25, 35). Although changes in esophageal sensation have been reported with modest elevation of blood glucose within the physiological range (5), it is not known whether these modest increases in blood glucose affect gastric sensation. Controversy also exists as to whether physiological changes in blood glucose levels affect appetite. Although hyperglycemia is a positive stimulus to appetite and some groups have hypothesized that physiological elevation of blood glucose acts as a satiety factor (31), we have recently shown (28) that physiological changes in peripheral blood glucose do not affect appetite, in the absence of nutrients in the small intestine.

The presence of nutrients within the small intestine modifies a number of gut functions so that gastrointestinal motility and the perception of both appetite (7, 28) and stimuli, such as distension (13) are different in the fasted compared with the fed state. Thus, ideally, both the fasting and fed states should be examined when assessing gastric motor and sensory function.

The major aims of this study were to determine whether the effects of small intestinal nutrient infusion on antpyloric pressures and perception of appetite are modified by physiological changes in blood glucose concentration (5 and 8 mmol/l).

METHODS

Subjects

Ten healthy males, aged 19–40 yr (mean 24 yr) and with a body mass index of 22.5–29.6 kg/m² (mean 26.8 kg/m²), were

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recruited by advertisement. None had any history of gastrointestinal disease or was taking any medication. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and all subjects gave written, informed consent.

Protocol

Subjects arrived at 9 AM at the laboratory on two separate days after an overnight fast. On one day, the blood glucose was maintained at 5 mmol/l and on the other at 8 mmol/l. The two studies were performed in random order in single-blind fashion. The protocol is summarized in Fig. 1. On arrival, subjects were intubated, through an anesthetized nostril, with a 3.5-mm silicone rubber manometric assembly (Dentsleeve, Bowden, South Australia, Australia), which included six antral channels at 1.5-cm intervals, a 4.5-cm sleeve sensor that straddled the pylorus, two equally spaced channels (P1 and P2) situated on the back of the sleeve, and one duodenal channel at the distal end of the sleeve sensor. An eleventh channel, situated 10 cm distal to the sleeve, was used for infusion of lipids into the small intestine. The tip of the assembly was allowed to pass into the duodenum by peristalsis, and the position of the sleeve across the pylorus was monitored continuously using measurement of transmucosal potential difference (TMPD) (22). We recorded intraluminal pressures at 10 Hz, using custom-written software (MAD, Dr. C. H. Malbert, Rennes, France) in Labview (National Instruments, Houston, TX) on a Power Macintosh 7100/80 (Apple Computer, Cupertino, CA).

Once the manometric assembly was positioned correctly, an intravenous cannula was inserted in each of the subjects’ arms; in the right forearm for administration of 25% glucose and in the left cubital fossa for normal saline (Baxter Healthcare, Old Toongabbie, New South Wales, Australia) and in the left cubital fossa for sampling of venous blood. At t = -15 min each subject was familiarized with the visual analog scales (VAS) that were used to assess appetite and had baseline venous blood samples taken for blood glucose estimation. At t = 0, an intravenous infusion of either 25% glucose or normal saline (Baxter Healthcare, Old Toongabbie, New South Wales, Australia) and in the left cubital fossa for sampling of venous blood. At t = -15 min each subject was familiarized with the visual analog scales (VAS) that were used to assess appetite and had baseline venous blood samples taken for blood glucose estimation. At t = 0, an intravenous infusion of either 25% glucose or normal saline was commenced, in a single-blind fashion, and continued at a rate to maintain the blood glucose at either 5 or 8 mmol/l. Venous blood glucose was measured every 5–15 min with a portable glucometer (MediSense 2, Balwyn, Victoria, Australia), and the infusion rate of glucose was adjusted accordingly. At t = 90, an intraduodenal infusion of a triglyceride emulsion (10% lipid, Intralipid, Kabi Pharmacia) was commenced at 1.5 kcal/min (82 ml/h) and continued for 90 min.

Statistical Analysis

Each subject acted as his own control. Data analysis was performed by a biostatistician. Differences over time between a blood glucose level of 5 and 8 mmol/l and between the fasting and fed states were examined by tests for fixed effects, using mixed model, repeated measures ANOVA (SAS Institute, Carey, NC). The total numbers of antral waves and IPPWs at each blood glucose concentration in the fasted state and between the fasted and fed states were compared using a two-tailed paired Student’s t-test. Data are shown as means ± SE. In all analyses, P < 0.05 was regarded as significant.

RESULTS

Of the 10 subjects recruited, two subjects declined to return for the second study day and their data are not included in the analysis. The other eight subjects completed the protocol, with both study days being completed within a mean of 12 (range 7–19) days. No subject had significant nausea or vomited on the day on which the blood glucose concentration was 5 mmol/l. In contrast, three subjects had troublesome nausea on the 8 mmol/l blood glucose concentration day, with two withdrawing 61 min into the lipid infusion, and an-
other vomiting after 90 min at extubation. In all three subjects, the onset of nausea was sudden; data from time points at which significant nausea was present are not included (apart from in the rating of nausea).

Blood glucose concentrations closely approximated the desired levels (Fig. 2).

Appetite

During the 90-min fasting period (Fig. 3), there were no significant changes in hunger, desire to eat, or projected consumption compared with baseline, nor were there any differences between a blood glucose concentration of 5 and 8 mmol/l (hunger, \(P = 0.15\); desire to eat, \(P = 0.96\); projected consumption, \(P = 0.92\)). In contrast, fullness was greater at a blood glucose level of 8 mmol/l compared with 5 mmol/l (\(P = 0.01\)), although fullness was not different from baseline at either blood glucose level. No nausea was reported during fasting.

During the 90-min intraduodenal lipid infusion (Fig. 4), positive symptoms of appetite decreased from baseline at a blood glucose concentration of 8 mmol/l (hunger, \(P = 0.034\); desire to eat, \(P = 0.0001\); projected consumption, \(P = 0.0002\)); whereas, at a blood glucose level of 5 mmol/l they were no different from baseline. Consequently, during intraduodenal lipid infusion, positive symptoms of appetite were diminished at a blood glucose level of 8 mmol/l compared with 5 mmol/l (hunger, \(P = 0.02\); desire to eat, \(P = 0.04\); projected consumption, \(P < 0.001\)). Fullness, however, increased at a blood glucose level of 5 mmol/l compared with baseline (\(P = 0.0003\)), while remaining unchanged at a blood glucose level of 8 mmol/l; so that fullness during intraduodenal lipid was greater at a blood glucose level of 5 vs. 8 mmol/l (\(P < 0.001\)). This latter result is partly accounted for by the fact that fullness did not change between fasting and the period of intraduodenal lipid infusion at a blood glucose level of 8 mmol/l (\(P = 0.16\)), while it increased between fasting and intraduodenal lipid (\(P < 0.001\)) at a blood glucose level of 5 mmol/l. In post hoc analysis, the absolute score for fullness was not significantly higher in the last 45 min of intraduodenal lipid at a blood glucose level of 5 vs. 8 mmol/l (20.31 ± 6.2 vs. 10.06 ± 3.8 mm, respectively; \(P = 0.12\)). There was more nausea reported at a blood glucose level of 8 vs. 5 mmol/l during intraduodenal lipid (\(P = 0.002\)), attributable to an increase in nausea between fasting and intraduodenal lipid at a blood glucose level of 8 mmol/l (\(P = 0.003\)), since there was no change in nausea between fasting and intraduodenal lipid at a blood glucose level of 5 mmol/l (\(P = 0.77\)).

Antropyloric Pressures

During the 90-min fasting period, there were fewer antral pressure waves at a blood glucose level of 8 vs. 5...
mmol/l (38.4 ± 12.8 vs. 87.6 ± 14.3, respectively; P = 0.018). For the total number of IPPWs, there was, however, no difference between a blood glucose level of 5 or 8 mmol/l (20.38 ± 7.25 vs. 24.8 ± 4.77; P = 0.41). Pyloric tone did not change from baseline, nor did it vary between the two blood glucose levels during fasting (data not shown).

During intraduodenal lipid infusion, antral waves were suppressed compared with the fasting state at both blood glucose concentrations (5 mmol/l: 87.6 ± 14.3 vs. 14.4 ± 8.7, P = 0.006; 8 mmol/l: 38.4 ± 12.8 vs. 3.1 ± 2.1, P = 0.03), with no difference in the number of antral waves noted between the two blood glucose levels during intraduodenal lipid (P = 0.26). Compared with the fasting state, intraduodenal infusion of lipid stimulated IPPWs at both blood glucose levels (5 mmol/l: 20.38 ± 7.25 vs. 88.38 ± 15.55, P = 0.01; 8 mmol/l: 24.8 ± 4.77 vs. 65.38 ± 11.17, P = 0.019). The total number of IPPWs during lipid infusion was not significantly different between the two blood glucose levels (88.38 ± 15.55 vs. 65.38 ± 11.17, P = 0.09). However, the temporal patterning of IPPWs differed between blood glucose levels of 5 and 8 mmol/l. Initially, the rate of IPPWs was higher at a blood glucose concentration of 8 mmol/l (P = 0.035); however, during the last 20 min of lipid infusion, the frequency of IPPWs was greater at a blood glucose concentration of 5 mmol/l than at 8 mmol/l (P < 0.04) (Fig. 5A). The amplitude of IPPWs was greater at a blood glucose level of 5 mmol/l than 8 mmol/l (P < 0.001 for whole curves) (Fig. 5B).

Pyloric tone rose in response to intraduodenal lipid at both blood glucose levels; however, there was attenuation in this response after 55 min, giving an overall nonsignificant change from baseline by ANOVA (5 mmol/l, P = 0.35; 8 mmol/l, P = 0.068 for whole curves). Although the initial rise in pyloric tone was greater at a blood glucose concentration of 8 mmol/l than at 5 mmol/l, this was not significant (Fig. 6).

**DISCUSSION**

It is well established that marked hyperglycemia has major effects on gastrointestinal motor (8–11, 16–21, 29, 30, 34, 36, 41) and sensory function (6, 19–21, 25, 30, 35). In contrast, there is only limited information about the potential impact on gut function of variation of the blood glucose concentration within the physiologi-
cal range (3, 5, 18, 32a, 39). We have now shown that both distal gastric motor function and perception of appetite and nausea are affected by modest changes in blood glucose levels within the physiological range. Moreover, these effects are modified by the presence of nutrient (lipid) within the small intestine, suggesting synergy between the blood glucose concentration and small intestinal nutrient receptor stimulation in the modulation of gastric motor and sensory function.

Specifically, we have demonstrated for the first time that at a blood glucose concentration of 8 mmol/l compared with 5 mmol/l, the following occurs: 1) during fasting, fullness is increased, and 2) during intraduodenal lipid, appetite is reduced, nausea is increased, and both the temporal patterning and amplitude of IPPWs are altered. The suppression of antral pressure waves by physiological hyperglycemia has been previously reported (18).

Appetite

Short-term regulation of appetite is multifactorial, involving oral sensory stimulation (33), gastric distension (4), and the interaction of nutrients with the small intestine (2, 7, 28). In our model we have simplified this, bypassing the oral and gastric regions and delivering nutrients directly to the small intestine. Similar models have been used previously (2, 7, 28) with consistent observations. The rate of caloric delivery (1.5 kcal/min) used in our study is slightly less than that in these previous studies (2–2.9 kcal/min) and was selected to reduce the incidence of nausea noted at higher rates. It remains, however, within the normal caloric range for gastric emptying (32) and is sufficient to convert motility from the fasting to the fed pattern, although its effect on appetite alone, without concurrent manipulation of blood glucose, has not been evaluated. This latter issue, however, was not the main focus of the study, but rather the perception of appetite (and antropyloric motility) during physiological hyperglycemia and whether the presence of nutrients in the small intestine modified these responses. For practical reasons, the order of the fasting period and intraduodenal lipid infusion was not randomized, hence the possibility of an order effect arises. To minimize this, a new baseline was calculated immediately before the intraduodenal lipid infusion, so that any changes occurring during the infusion would be clearly related to differences between blood glucose levels during the infusion and not simply carryover effects from the fasting period.

Little difference in appetite ratings was apparent between a blood glucose concentration of 5 and 8 mmol/l in the fasting period, consistent with a previous study suggesting that modest elevations of blood glucose concentration alone do not affect appetite (28); however, during intraduodenal lipid infusion, all positive symptoms of appetite, i.e., hunger, desire to eat, and projected consumption, were diminished at a blood glucose level of 8 mmol/l compared with 5 mmol/l, indicative of synergy between blood glucose concentration and stimulation of small intestinal nutrient receptors in modulat...
ing appetite. The finding of increased fullness in the fasting state at a blood glucose level of 8 vs. 5 mmol/l is consistent with previous data in diabetic subjects (25). However, during intraduodenal lipid, there was a greater change in fullness at a blood glucose level of 5 mmol/l rather than at 8 mmol/l. This suggests that both the glycemic state and the presence of nutrients in the small intestine are capable of signaling fullness.

Nausea was profoundly affected by the combination of elevated blood glucose and the presence of lipid in the small intestine. In previous studies, we have noted a high incidence of nausea when nutrients are delivered to the small intestine at caloric rates >2 kcal/min and also when the blood glucose concentration is elevated to pathological levels (~12–15 mmol/l; unpublished observations). This study confirms that blood glucose and small intestinal nutrients have a synergistic effect in this regard, leading to nausea at a physiologically normal blood glucose level, and at a lower rate of caloric delivery than we have previously noted. Although this has not been previously reported, other examples of synergy between the presence of small intestinal nutrients and other stimuli include distension (13, 21) and vection (12). Abnormalities of gastric electrical control activity are known to be increased by both marked hyperglycemia (~14 mmol/l) and intraduodenal lipid (20) and may be important in the etiology of nausea.

In light of these apparent interactions between glycemic state and the presence of small intestinal nutrients in healthy volunteers, it would be of interest to evaluate patients with functional gastrointestinal symptoms, in whom symptoms are commonly augmented by food. These patients are known to have heightened sensitivity to other gut stimuli, such as distension and electrical stimulation (1, 43).

Antropyloric Pressures

Both marked and physiological hyperglycemia suppress antral pressure waves (3, 18, 36) and slow gastric emptying (17, 39). Pathological hyperglycemia stimulates phasic and tonic pyloric pressures (16). These motor mechanisms are known to be associated with slowing of gastric emptying (22, 23). Our findings of fewer antral waves in the fasting state at the higher blood glucose level are consistent with previous observations (3, 18). We did not, however, find more fasting IPPWs at the higher blood glucose level as previously noted (16), although in this earlier study blood glucose was elevated to >12 mmol/l.

It is well documented that small intestinal nutrient infusion stimulates IPPWs, elevates pyloric tone, and suppresses antral waves (15, 16, 22–24). Although not statistically significant, the fact that fewer IPPWs were stimulated by intraduodenal lipid at the higher blood glucose level was somewhat unexpected. It should be recognized, however, that the effect of hyperglycemia on gut function is not always predictable with both regional variations at the same blood glucose level reported; [at a blood glucose level of 8 mmol/l there is slowing of gastric emptying (39) but no effect on anorectal motility (35)] and variation within regions depending on the degree of hyperglycemia induced, with both accelerated (5) and slowed (9) esophageal peristaltic velocity being reported at a blood glucose level of 8 and 15 mmol/l, respectively. On closer inspection of our data, it is also apparent that the stimulation of IPPWs is a time-dependent phenomenon, with more IPPWs early at a blood glucose level of 8 mmol/l and more IPPWs later with a blood glucose level of 5 mmol/l. Variability in the temporal patterning of IPPWs has been previously reported (15). Pyloric tone was no different between a blood glucose concentration of 5 and 8 mmol/l during fasting or intraduodenal lipid. However, it did appear to rise from baseline during the lipid infusion, as previously reported (7, 15). The fact that the elevation of tone in response to lipid was not more clear cut in this study is likely to represent a type 2 error.

Although we did not evaluate gastric emptying, it has been demonstrated to be faster at a blood glucose concentration of 4 mmol/l than 8 mmol/l (39). Because the IPPWs and pyloric tone were similar at both blood glucose levels, it is difficult to attribute the slowing of gastric emptying to changes in pyloric motility, despite the number of IPPWs (presumably as a measure of pyloric resistance) being negatively correlated with the rate of gastric emptying (42). It is possible that the demonstrated antral hypomotility at a blood glucose level of 8 mmol/l is primarily responsible for retarding gastric emptying. Changes in proximal gastric motility may also be potentially important, although variation of blood glucose level within the physiological range does not affect proximal gastric motor function in the fasting state (32a).

The mechanisms mediating the synergy between blood glucose concentrations and the presence of nutrients in the small intestine in modulating gastric motor and sensory functions were not addressed in the current study. Hyperglycemia (~15 mmol/l) is known to reduce vagal efferent tone (26, 27), during euaglycemia, cholinergic transmission is known to be necessary for the production of IPPWs (15), and during hypoglycemia, atropine prevents the acceleration of gastric emptying (38). All emphasize the importance of cholinergic transmission in acutely regulating gastric motor function, regardless of the blood glucose level. Less is known, however, about how signals from nutrient receptors in the small intestine may respond to variations in the blood glucose level and whether they alter cholinergic outflow to the antropyloric region. It is, however, known that the stimulation of CCK release by intraduodenal lipid is not affected by hyperglycemia (11). It is also possible that blood glucose levels sensed centrally may modulate perception of appetite, but on the basis of our results [and those of Lavin et al. (28)] this only seems to occur if an additional stimulus, such as an intraintestinal nutrient, is present.

Gastric motor and sensory function is known to be influenced by a number of common stimuli, including small intestinal nutrients (2, 7, 13, 15, 20–24, 28, 34), cold stress (14), pathological hyperglycemia (16–21), and motion (12). We have now demonstrated for the
first time synergy between physiological variation of blood glucose level and the presence of small intestinal nutrients. The importance of this observation lies in the fact that these two stimuli not only occur commonly but also commonly occur simultaneously; this therefore represents a further insight into the physiological mechanisms involved in gastric motor and sensory function. The hierarchy, relative magnitude, and specificity of this interaction should be addressed in future studies.

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