Stimulation of small intestinal burst activity in the postprandial state differentially affects lipid and glucose absorption in healthy adult humans

L. K. Bryant, R. J. Fraser, R. Vozzo, B. Zacharakis, G. M. Matthews, and R. Butler

Investigation and Procedures Unit, Repatriation General Hospital, Daw Park 5041; Department of Medicine, Royal Adelaide Hospital, Adelaide 5000; and Centre for Paediatric and Adolescent Gastroenterology, Women’s and Children’s Hospital, Adelaide, South Australia 5006

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Bryant, L. K., R. J. Fraser, R. Vozzo, B. Zacharakis, G. M. Matthews, and R. Butler. Stimulation of small intestinal burst activity in the postprandial state differentially affects lipid and glucose absorption in healthy adult humans. Am J Physiol Gastrointest Liver Physiol 287: G1028–G1034, 2004. First published June 10, 2004; doi:10.1152/ajpgi.00091.2004.—Small intestinal motor activity is important for the optimal digestion and absorption of nutrients. These motor responses to feeding are frequently abnormal during critical illness, with the persistence of migrating bursts of contractions during enteral feeding, which was approved by the Research and Ethics Committee of the Repatriation General Hospital in November 2002.

Small intestinal motility is frequently disturbed during critical illness. Migrating bursts of activity resembling phase III of the interdigestive MMC persist during enteral feeding, indicating a failure of conversion to the postprandial motor pattern (6, 38). The potential impact of this abnormality on nutrient transit and absorption has not previously been assessed.

Quantitative data on the interrelationships among motility, flow, and absorption in humans is limited. Loperamide increases the rate of 3-O-methylglucuronic acid (3-OMG) absorption in healthy subjects (27), suggesting that transit may be important for absorption even for nutrients requiring minimal processing. Animal studies on the effect of fasting motility on glucose absorption have produced conflicting results, demonstrating both increases (7) and decreases (29) in absorption during phase III activity. A recent study (34) in humans showed a positive association between glucose absorption and small intestinal pressure wave number. Absorption however, was unaffected by treatment with cisapride, which increased the amplitude but not the frequency of pressure waves and did not stimulate phase III activity (34). It is unknown whether a stronger prokinetic such as erythromycin, which stimulates phase III-like activity, would influence absorption.

The aim of the present study was to investigate in healthy adult humans the effect of small intestinal burst activity stimulated by intravenous erythromycin on lipid and glucose absorption. Studies were performed in healthy subjects to eliminate the confounding factors of altered mucosal function that exist in critically ill patients (14).

METHODS

Subjects. Studies were performed in 10 healthy adult subjects (6 males, 4 females, aged 19–47 yr, body mass index range 19–27 kg/m²). No subject had a history of gastrointestinal disease, previous abdominal surgery, or was taking any medication known to affect gastrointestinal motility. One subject was a light smoker (<5 cigarettes/day) who refrained from smoking 24 h before each study. Subjects gave written informed consent before entering the study, which was approved by the Research and Ethics Committee of the Repatriation General Hospital in November 2002.

Manometry. Small intestinal motility was assessed using a manometric perfusion technique, described in detail elsewhere (25). In
brief, intraluminal pressures were measured using a 200-cm multilumen assembly (outer diameter 4 mm; Dentsleeve, Adelaide, South Australia) incorporating 16 pressure-recording channels (diameter 0.4 mm) and a duodenal feeding channel. The two most proximal side-holes (A1 and A2) spaced 5 cm apart were positioned in the gastric antrum, and the following 14 (D1-D14) were positioned at 12.5-cm intervals in the duodenum and proximal jejunum. Channels distal to D2 were considered to be jejunal based on catheter length. The infusion port, which was located 142 cm from the catheter tip, enabled delivery of the test meal into the mid-duodenum. All manometric lumina were perfused with degassed distilled water at a rate of 0.16 ml/min. Pressures were measured by external transducers (Abbott Critical Care, Chicago, IL) and recorded on a power Macintosh G3 computer using purpose written software (HAD, G Hebland, Melbourne, Australia) and Labview as a base program. Correct positioning of the assembly was facilitated by small weights and a balloon located at the catheter tip and was identified by the analysis of pressure-wave frequencies (25). Manometric data were converted into Acqknowledge 3.2.7 (Biopac System, Santa Barbara, CA) for storage and analysis.

Test meal. Small intestinal lipid and glucose absorption was assessed using the [13C]triolein breath test (39) and plasma analysis of 3-OMG (8), respectively. The test meal consisted of 60 ml of a mixed nutrient solution (containing: 13% protein, 13% carbohydrate, 21% fat, and 1 kcal/ml energy content; Abbott Laboratories, Columbus, OH), mixed with 200 µl [1,1,1-13C3]Triolein (99%, 200 mg; Cambridge Isotope Laboratories, Andover, MA) and 2 g of 3-OMG (98%, C12H20O6 Sigma-Aldrich, Steinheim, Germany). The 3-OMG was dissolved in water (5 ml) before being added to the preparation. The meal was agitated for 1 min before intraduodenal infusion to ensure homogeneity.

Experimental protocol. Subjects were studied for 6 h on two separate occasions, approximately 1 wk apart. Subjects received an intravenous infusion of either erythromycin (1 mg/kg), to stimulate small intestinal burst activity (2), or saline placebo (0.9%) in randomized double-blind fashion. Motor patterns and nutrient absorption were analyzed before randomization disclosure.

Intubation. Subjects arrived at the Gastrointestinal Procedures Unit, Repatriation General Hospital, at 8 AM following an overnight fast. Subjects were instructed to avoid foods naturally enriched with 13C (e.g., corn, pineapple, and cane sugar) for 24 h before each study (32). The manometric assembly was introduced into the stomach via an anesthetized nostril, after which the subject was positioned in the right lateral position until the tip of the assembly had passed beyond the pylorus. Subsequent progression of the assembly along the small intestine was assisted by inflation of the catheter balloon with 7 ml of air. When only the two most proximal side-holes remained in the gastric antrum, the balloon was deflated and two intravenous cannulas (20 gauge) were inserted into each of the subject’s antecubital veins for intravenous infusion and blood sampling, respectively.

Infusions. Both the intravenous and intraduodenal infusion commenced at T = 0 min. Erythromycin (or saline) was administered at a rate of 5 ml/min over 20 min. The test meal was infused intraduodenally at 2 ml/min for 30 min.

Data collection. At baseline $T = -15$ min, the commencement of the intravenous and intraduodenal infusions ($T = 0$), and every 30 min thereafter, subjects were asked to exhale through a straw into a 10-ml glass tube (Exetainers, Southern Cross Science, Melrose Park, South Australia) for end-expiratory breath sample collection. Blood samples (8 ml) were collected at baseline and at $T = 0$, 5, 10, 15, 20, 30, 45, 60, 90, and 120 min. Small intestinal motility was recorded continuously for 6 h, commencing on the start of the intravenous and intraduodenal infusion.

Breath sample analysis. Breath samples were analyzed for 13CO2 concentration using an isotope ratio mass spectrometer (Europa Scientific, ABCA model 20/20, Crewe, UK). Samples were considered to be end-expiratory if the CO2 concentration was >1%. The 13CO2 concentration of each sample was expressed relative to the international standard (PDB Limestone), which has the highest natural enrichment of 13C (33). The values obtained were converted to percent dose recovery (PDR) per hour from the baseline and used to determine the cumulative percent dose recovery (cPDR) per hour during the 6 h following label administration. Subjects rested supine during the study, because exercise has been shown to affect the recovery pattern of CO2 (16).

3-OMG analysis. 3-OMG is an analog of glucose, which uses the same intestinal active transport mechanism. Unlike glucose, 3-OMG is not metabolized by the liver and is renally cleared. Plasma concentrations of 3-OMG have therefore been used as an index of glucose absorption (8). Plasma 3-OMG concentrations were measured using high-performance exchange chromatography ( Dionex BioLC) with pulsed amperometric detection. Plasma 3-OMG concentration was assessed for 2 h after starting the test meal infusion. Peak 3-OMG concentration and the time to peak concentration were also determined.

Manometric analysis. Motility recordings were analyzed manually to determine the frequency, timing, and characteristics of small intestinal burst activity over the 6-h study period. A burst was defined as the presence of ≥10 pressure waves per minute for at least 2 min that migrated sequentially over four or more side-holes. Involvement of the antrum in burst activity was defined as the presence of two to three pressure waves per minute for at least 2 min that preceded (within 2 min) or occurred simultaneously with the onset of burst activity in the consecutive duodenal channels. Periods of intestinal pressure wave activity of ≥10 waves per minute that failed to meet burst criteria were considered to be burstlike (25).

Burst frequency was calculated for the first hour following commencement of the intraduodenal infusion and for the total 6-h period. The timing of burst activity, in particular the time to the first burst episode after commencement of the intraduodenal infusion, was determined.

Burst characteristics assessed were the site of origin, length, and duration of burst migration (from the first contraction to the corresponding most distal site of activity). The percent contribution of motor quiescence during the 6-h period, defined as less than three pressure waves per 10 min (25), was also quantified.

Statistical analysis. Differences among treatments in burst frequency, timing, origin, length and duration of burst migration, and contribution (%) of motor quiescence during the study period were assessed using the Student’s paired t-test (Statview Version 4.5, Abacus Concepts, Berkeley, CA). The t-test was also used to assess the 3-OMG area under the curve (AUC) at 2 h, the peak plasma 3-OMG concentration, and the time to peak concentration. Analysis of 13CO2 recovery was performed by a statistician using SAS software version 8.2 (SAS Institute, Cary, NC). Differences in the cPDR were determined using a mixed model analysis of variance, with a quadratic polynomial fitted to the mean recovery curves. All 13CO2 data were square-root transformed before analysis to correct for data non-normality. Cumulative data from both treatments were combined to assess whether a relationship existed between the time to onset of burst activity and the recovery of 13CO2, using a linear regression analysis with robust standard errors. Data are expressed as means ± SE. A P value of <0.05 was considered statistically significant.

RESULTS

The study protocol was well tolerated by all subjects, and the erythromycin infusion caused no adverse effects.

Small intestinal manometric data. The intraduodenal nutrient infusion resulted in the replacement of fasting small intestinal motility with a postprandial motor pattern on all study days.

The infusion of erythromycin was followed by a more rapid onset of small intestinal burst activity (fig. 1), with the time to
onset of burst activity following commencement of the intraduodenal infusion reduced to one-half that of saline (30 ± 6.1 vs. 58 ± 10.7 min; P < 0.05, respectively; fig. 2). The frequency of bursts during the first hour after initiation of the intraduodenal infusion was greater with erythromycin compared with saline (1.2 ± 0.13 vs. 0.3 ± 0.15 bursts/h; P < 0.005, respectively; fig. 3).

There was no difference between treatments in the percent contribution of motor quiescence or burst frequency at the end of the 6-h period. The site of burst origin, length, and duration of burst migration were also similar (table 1).

Triolein absorption. The infusion of erythromycin was associated with a slower recovery rate of $^{13}$CO$_2$ during the 6 h after the start of the intraduodenal infusion compared with saline [slope 0.006 (95% confidence interval); 0.004–0.009 vs. 0.009 (0.006–0.011); P < 0.01, respectively; fig. 4]. There was also a trend for a lower cPDR at 6 h with erythromycin (10.6 ± 2.7 vs. 18.2 ± 5.1%, respectively; P = 0.1).

There was a positive correlation between the time to onset of burst activity following initiation of the intraduodenal infusion and the recovery of $^{13}$CO$_2$ during the 6-h period (P < 0.001).
OMG absorption. Infusion of erythromycin had no effect on the 3-OMG AUC at 2 h after commencement of the intraduodenal infusion (AUC 120min, 29.2 ± 0.7 vs. 28.7 ± 1.7, P > 0.05), the peak plasma 3-OMG concentration (0.38 ± 0.07 vs. 0.38 ± 0.02 mmol; P > 0.05, respectively), or the time-to-peak 3-OMG concentration (43.5 ± 8.5 vs. 52.5 ± 5.1 min; P > 0.05) compared with saline.

**DISCUSSION**

The major finding in this study is that stimulation of small intestinal burst activity, by intravenous erythromycin, differentially affects lipid and glucose absorption in healthy adult humans. These results show that an interruption in postprandial small intestinal motility, with migrating bursts of contractions similar to interdigestive phase III activity, reduces the rate of lipid absorption, although glucose absorption is unaffected. Previous studies on the effect of phase III activity on nutrient absorption (7, 24, 26, 29) have been limited to the assessment of glucose absorption in animal models and have yielded conflicting results. In the present study, the concurrent absorption of lipid and glucose was assessed in healthy human subjects, where mucosal dysfunction is not an issue. The results suggest that disordered small intestinal motility may contribute to reduced nutrient absorption in patient groups such as the critically ill, in which similar motor patterns occur.

The conversion from fasting to postprandial small intestinal motility after a meal is believed to optimize the digestion and absorption of ingested nutrients. This is supported by animal studies, in which fasting motor activity reduces the rate of glucose absorption compared with the postprandial state (26, 29). Furthermore, a study in humans showed a positive association between glucose absorption and the frequency of small intestinal pressure waves (34), suggesting that enhanced motor activity facilitates nutrient exposure to the mucosa.

Knowledge of the effect of fasting small intestinal motility on nutrient absorption in humans is limited. Studies in animal models have produced conflicting results, reporting both increases (7, 24) and decreases (26, 29) in the absorption of glucose during interdigestive phase III activity. This discrepancy may reflect methodological differences, such as in the animal species studied (24, 29), the way in which absorption was assessed (7, 29), or whether the study was performed under fasting or fed conditions (24, 29). A recent study in humans (34) showed a positive association between the rate of glucose absorption and duodenojejunal pressure wave frequency; however, absorption was unaffected by treatment with cisapride. Our study concurs with this finding, because the administration of erythromycin, which stimulated small intestinal burst activity, had no effect on glucose absorption.

Fig. 3. The frequency and timing of burst activity during the 2-h period following the start of the intraduodenal infusion with intravenous saline (A) and erythromycin (B; periods of nutrient and intravenous infusion shown by text boxes). Dark blocks indicate the onset of small intestinal burst activity. A higher frequency of burst episodes was recorded during the first hour after the start of the nutrient infusion with erythromycin, compared with saline (P < 0.005).
The finding that small intestinal burst activity differentially affects lipid and glucose absorption may reflect differences in the digestion and absorption of nutrients within the gut. Lipid is absorbed by a multistep process that involves mixing with pancreatic enzymes, chemical digestion, and sufficient exposure to absorptive sites along the mucosa (1). Furthermore, gut mechanisms such as the ileal brake are required to facilitate absorption (30, 37). Given such complexity, it is not surprising that alterations in the patterning of postprandial motility may interrupt the needs for mixing and mucosal contact of lipid, reducing its absorption. This is supported by the present study with the finding that burst activity during and shortly after duodenal nutrient delivery reduces the rate of triolein absorption in healthy human subjects.

Glucose requires minimal digestive processing and is rapidly absorbed by the gut using a highly specific transport mechanism (1). This is likely to explain our finding that erythromycin had no effect on 3-OMG absorption. The quantity of 3-OMG delivered into the small intestine in the present study was well below the maximum absorptive capacity. Although it is possible that at higher doses of 3-OMG, motor disruptions could lead to changes in absorption, this is likely to be nonphysiological.

The influence of erythromycin on small intestinal motility was only evident in the first hour of the study. Interestingly, our results show that triolein absorption was impaired for up to 6 h after test meal administration and potentially beyond, because the recovery curves from erythromycin-treated and control studies appear to be diverging. The mechanism responsible for this effect is unclear. It is possible that changes in small intestinal motility influence the relationship between nutrient transit and pancreaticobiliary secretion. Evidence in humans suggests that the pancreatic response to a meal is regulated by the rate of nutrient delivery (17). In addition, Holtmann et al. (12) showed an inverse relationship between small intestinal transit and pancreatic lipase activity. An accelerated transit of the nutrient meal, through the stimulation of small intestinal burst activity, may have blunted the pancreatic response and could explain the diminution of lipid uptake.

Fatty acid chain length influences triglyceride absorption in the small intestine (22). Medium-chain triglycerides are readily absorbed in the absence of pancreatic lipase, unlike long-chain triglycerides such as triolein (3). It is therefore possible that shorter triglycerides may be less affected by changes in small intestinal motility. This could have implications for the optimal formulation of enteral diets in the critically ill; however, this clearly requires further study.

A depression in gut absorptive capacity has been reported in patients following severe trauma or sepsis (9, 36). Inadequate nutrition contributes to impaired immune function and serious infections in the critically ill (10, 20). The cause of this disturbance is unclear, but it is likely to be multifactorial. A disruption in mucosal function has been reported, which is likely to reduce intestinal absorption (14). The results from the current study support the hypothesis that an abnormal patterning of small intestinal motor activity may also contribute to impaired nutrient absorption in the critically ill. Similar motor patterns are seen during critical illness (6, 38), at which time postprandial motility is disrupted by bursts of activity that resemble phase III of the MMC. Further direct studies examining the potential impact of changes in motor activity on nutrient absorption in critically ill patients are thus required.

Small intestinal transit was not measured in this study. However, the motor patterns recorded would be expected to result in a more rapid flow of small intestinal content based on previous studies (19, 29). Kerlin (19) showed a rapid increase in small intestinal transit during interdigestive phase III activity. Other studies (1a, 5, 40) have shown that intestinal transit

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<th>Table 1. Characteristics of small intestinal burst activity</th>
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<td>Burst duration, min</td>
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Values are expressed as means ± SE for n = 10. The duration, length and origin of burst activity during the 6 hours after the start of the duodenal nutrient infusion with intravenous erythromycin (1 mg/kg) and saline (0.9%). Total burst frequency and the contribution of motor quiescence (%) are also shown. *Negative value denotes distance proximal to the infusion port.

The absorption curve for 13C-labeled triolein during normal postprandial motility (○) and after stimulation of small intestinal burst activity by erythromycin (■). During burst activity, the rate of triolein absorption is reduced (mean ± SE; *P < 0.01 erythromycin vs. saline).
is increased after intravenous administration of erythromycin at a dose comparable with the present study. Furthermore, fat absorption is increased when luminal flow is slowed in minipigs (13). Conversely, it is possible that rapid small intestinal transit may reduce nutrient absorption (11). These studies and others (11) suggest that the stimulation of small intestinal burst activity by erythromycin would accelerate postprandial nutrient transit, which may impair nutrient absorption. Similar motor patterns in critically ill patients would therefore have substantial effects on the effectiveness of enteral nutrition.

The limitations of the present study need to be recognized. The triolein breath test is a simple test to perform, but background levels of $^{13}$C can interfere with marker recognition. This was minimized by a dietary restriction of foods naturally enriched with $^{13}$C, such as corn, pineapple, and cane sugar, for 24–48 h before each study (32). In addition, exercise has been shown to produce disturbances in the CO$_2$ recovery pattern (16), requiring all subjects to remain relatively immobile for the duration of the study. The dose of 3-OMG selected for the present study was based on a previous study by Jones et al. (15) examining gastric emptying. On the basis of their data, we calculated that this dose would provide a sufficient quantity of 3-OMG, while avoiding carrier saturation. Under normal conditions, the amount of glucose exposed to the mucosa is less than the maximum absorptive capacity. A lower concentration of 3-OMG was therefore selected to mimic normal glucose delivery into the small intestine. Other studies (23, 24) that have shown an effect of small intestinal motility on glucose absorption have used greater quantities of 3-OMG. Pancreatic secretion was not measured in this study. An alteration in the coordination of pancreatic secretions may have contributed to the reduction in lipid absorption in the present study. Further studies are necessary to examine this.

In summary, stimulation of small intestinal burst activity in the postprandial state is associated with a reduction in lipid but not glucose absorption in healthy human adults. These findings could have implications for critically ill patients, in which inappropriate burst activity during enteral feeding may contribute to impaired nutrient absorption. To optimize absorption in these patients, the delivery of nutrition may need to be altered depending on motor activity. Studies assessing the effect of normalization of motor function on nutrient absorption in critically ill patients are also warranted.

GRANTS
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REFERENCES


