Role of 5-hydroxytryptamine mechanisms in mediating the effects of small intestinal glucose on blood pressure and antropyloroduodenal motility in older subjects

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ABSTRACT

Postprandial hypotension is an important clinical problem, particularly in the elderly. 5-hydroxytryptamine 3 (5-HT3) mechanisms may be important in the regulation of splanchnic blood flow, blood pressure and in mediating the effects of small intestinal nutrients on gastrointestinal motility. The aims of this study were to evaluate the effects of the 5-HT3 antagonist, granisetron, on the blood pressure (BP), heart rate (HR) and antropyloroduodenal (APD) motility responses to intraduodenal glucose in the healthy elderly. Ten subjects (5M, 5F, aged 65-76 years) received an intraduodenal glucose infusion (3 kcal/min) for 60 minutes (t = 0-60 min), followed by intraduodenal saline for a further 60 minutes (t = 60-120 min) on two days. Granisetron (10µg/kg) or control (saline) was given intravenously at t = -25 min. BP (systolic and diastolic), HR and APD pressures were measured. Pressure waves in the duodenal channel closest (‘local’) to the infusion site were quantified separately. During intraduodenal glucose, there were falls in systolic and diastolic BP and a rise in HR (P < 0.0001 for all); granisetron had no effect on these responses. Granisetron suppressed the number and amplitude (P < 0.05 for both) of ‘local’ duodenal pressures during intraduodenal glucose. Otherwise, the effects of intraduodenal glucose on APD motility did not differ between study days. We conclude that in healthy older subjects 5-HT3 mechanisms modulate the ‘local’ duodenal motor effects of, but not the cardiovascular responses to, small intestinal glucose.

Keywords: heart rate, 5-hydroxytryptamine 3, granisetron, intraduodenal glucose, antropyloroduodenal motility.
**INTRODUCTION**

Postprandial hypotension, defined as a fall in systolic blood pressure of ≥ 20 mmHg within 2 hours of a meal that is sustained for at least 30 minutes, is now recognized as a major cause of morbidity and mortality [1,2] by predisposing to a number of disorders including syncope, transient ischemic attacks, stroke and angina [2]. Postprandial hypotension occurs more frequently than orthostatic hypotension [2] and those at greatest risk include the elderly and patients with autonomic dysfunction; the latter usually secondary to diabetes [2]. Current treatment options are suboptimal.

Several factors, including impaired regulation of splanchnic blood flow, the release of gastrointestinal hormones and duodenal sympathetic nerve activity, have been identified as possible pathophysiological mechanisms in postprandial hypotension [2]. The magnitude of the fall in blood pressure is dependent on meal composition; ingestion of carbohydrate, particularly glucose, has been reported to have the greatest suppressive effect on blood pressure [3]. The onset of the fall in blood pressure after a meal is almost immediate, with a maximum response at 30 - 60 minutes [2], suggesting a direct relationship between the magnitude of the hypotensive response and the rate of delivery of carbohydrate to the small intestine. This is the case in both healthy older subjects [4,5] and patients with type 2 diabetes [6,7] and has been established by a series of studies by our group. For example, in healthy older subjects when glucose is administered intraduodenally at a rate of 1 kcal/min or 3 kcal/min, the fall in blood pressure and increase in heart rate are substantially greater during the 3 kcal/min infusion [8]. The hypotensive response to small intestinal glucose appears to be load-, rather than concentration-, dependent [9]. Following a meal, there is a substantial increase in splanchnic blood volume (~ 20% of total blood volume), with an approximate doubling of superior mesenteric arterial flow that is associated with reductions in systemic
vascular resistance and skeletal muscle blood flow [2]. The magnitude of the postprandial increase in mesenteric blood flow is comparable in healthy young and old individuals, despite the greater fall in blood pressure in the latter group, indicating that there is inadequate cardiovascular adjustment for the shift of blood volume into the splanchnic system [10].

The presence of glucose in the small intestine also inhibits antral and proximal duodenal pressures and stimulates both pyloric tone and phasic pyloric activity [11,12] and slows gastric emptying [13] (as a result of inhibitory feedback arising from receptors located throughout the small intestine [14,15]). In healthy subjects, gastric emptying of glucose is known to be regulated at 2 - 3 kcal/min, after an initial emptying phase that may be somewhat faster [16].

5-hydroxytryptamine (5-HT) is an important neurotransmitter in the gastrointestinal tract, formed predominantly in enterochromaffin cells of the intestinal mucosa [17]. Recent studies suggest that enterochromaffin cells [18,19], act as ‘glucose sensors’ in the small intestine, activating signal transduction pathways, in the presence of D-glucose, galactose and α-D-glucopyranoside (aMG) [18,19] via the release of 5-HT. There is evidence that 5-HT mechanisms play a role in the regulation of splanchnic blood flow [5,20]. For example, in the dog both low (4µg/kg/min) and higher (10µg/kg/min) dose 5-HT infusions increase gastrointestinal blood flow [20]. The role of 5-HT mechanisms in the regulation of postprandial blood pressure and heart rate has not yet been evaluated in healthy older subjects, nor in any other group susceptible to postprandial hypotension.

In rodents, the release of 5-HT by D-glucose is also known to inhibit gastric emptying by activation of nervous pathways containing 5-hydroxytryptamine 3 (5-HT3) receptors [18,21-
The role of 5-HT3 mechanisms in mediating the antropyloroduodenal (APD) motility responses to intraduodenal glucose and fat has been assessed in two studies in humans [25,26]. While the 5-HT3 antagonist, ondansetron (8 mg po), does not appear to affect the proximal gastric motor responses to intraduodenal infusion of lipid (20%) [25], the 5-HT3 antagonist, granisetron (10µg/kg intravenously), has been shown to attenuate the suppression of antral waves induced by intraduodenal lipid, but not intraduodenal glucose, in healthy young subjects [26]. A limitation of the latter study was that the amount of glucose infused was small (5ml of 25% dextrose) and given over a short time interval (60 seconds) [26]. Furthermore, the study design did not allow evaluation of the impact of 5-HT3 mechanisms on ‘local’ duodenal motility ie near to the site of infusion, to be evaluated.

The aims of our study were to evaluate the role of 5-HT3 mechanisms in mediating the effects of intraduodenal glucose on blood pressure and APD motility in healthy older subjects.
MATERIALS AND METHODS

SUBJECTS

Ten healthy older subjects (five female and five male), with a median age of 70 years (range: 65 - 76 years) and body mass index of 24.5 kg/m² (range: 21.1 - 29.1 kg/m²), recruited by advertisement, were studied. All subjects were non-smokers. None had a history of gastrointestinal disease or surgery, diabetes mellitus, significant respiratory, renal, hepatic or cardiac disease, chronic alcohol abuse or epilepsy, or was taking medication known to influence blood pressure or gastrointestinal function.

The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and each subject provided written, informed consent prior to their inclusion. All experiments were carried out in accordance with the Declaration of Helsinki.

PROTOCOL

Each subject was studied on two occasions, separated by at least seven days, in double-blind, randomized order. On each day, the subject attended the University of Adelaide, Discipline of Medicine, Royal Adelaide Hospital, at 08.30h following an overnight fast (10.5h for solids; 8.5h for liquids) [27]. At that time, a 17-channel manometric catheter (Dentsleeve International Ltd, Mui Scientific, Ontario, Canada) was introduced into the stomach via an anaesthetized nostril [28]. The catheter was allowed to pass through the stomach and into the duodenum by peristalsis [28] (which took between 20 and 165 minutes) and included 16 side holes (spaced 1.5cm apart) and an infusion channel with a port located ~ 10cm distal to the pylorus (ie in the duodenum, 1.5cm distal to channel 16). Six side-holes (channels 1 - 6) were positioned in the antrum, a 4.5cm sleeve sensor (channel 7), with 2 channels (channels 8 and 9) on the back of the sleeve, was positioned across the pylorus, and 7 channels (channels 10 -
were positioned in the duodenum [28] (Figure 1). The correct positioning of the catheter, with the sleeve sensor straddling the pylorus, was maintained by measurement of the antroduodenal transmucosal potential difference (TMPD), using a saline-filled, reference electrode (20 gauge intravenous cannula) inserted subcutaneously into the subject’s forearm as a reference [8]. The manometric channels were perfused with degassed, distilled water, except the TMPD channels, which were perfused with degassed saline (0.9%), at 0.15 ml/min [13]. An intravenous cannula was positioned in a right antecubital vein for blood sampling, and an automated blood pressure cuff placed around the left arm [8]. Once intubated, subjects were studied in the recumbent position. Approximately 25 minutes after the tube was in position (t = -25 min), intravenous granisetron (Kytril, F. Hoffmann-La Roche, Basel, Switzerland) (10 µg/kg) (ie 0.58 - 0.87ml) in a volume of 25ml or placebo (25ml normal saline) was given as a bolus over 5 minutes. Twenty minutes later (ie at t = 0 min), an intraduodenal infusion of 50g glucose dissolved in saline (0.9%) in a total volume of 300ml was commenced and maintained at a rate of 5 ml/min (ie 3 kcal/min) for 60 minutes [8]. Between t = 60 - 120 min, saline (0.9%) was infused intraduodenally at the same rate. At t = 120 min the catheter and intravenous cannula were removed and the subject was given a light meal. On one day cardiovascular autonomic nerve function was evaluated immediately following the study [29].

MEASUREMENTS

Blood pressure and heart rate

Systolic and diastolic blood pressure and heart rate were measured using an automated oscillometric blood pressure monitor (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI, USA) immediately prior to intravenous administration of granisetron (ie t = -25 min), at the commencement of intraduodenal infusion (ie ‘baseline’ at t = 0 min), and then
every 3 minutes until \( t = 120 \) min \[8\]. Postprandial hypotension was defined as a fall in systolic blood pressure \( \geq 20 \) mmHg after commencement of intraduodenal glucose that was sustained for at least 30 minutes \[2\]. Blood pressure and heart rate before the administration of granisetron were calculated as the mean of measurements taken at \( t = -34, -31 \) and \(-28\) minutes.

**Antropyloroduodenal (APD) pressures**

Manometric pressures were digitized and recorded on a computer-based system running commercially available software (Flexisoft®, Version 3, Associate Professor GS Hebbard, Royal Melbourne Hospital, Melbourne, Australia, written in Labview 3.1.1 (National Instruments)), and stored for subsequent analysis. APD pressures pertaining to channels 1 - 16 were analyzed for: (i) number and amplitude of antral pressure waves (PWs), (ii) basal pyloric pressure (tone), (iii) number and amplitude of isolated pyloric pressure waves (IPPWs), (iv) number and amplitude of duodenal PWs, and (v) number and length of pressure wave sequences involving the antrum, pylorus and duodenum, using custom-written software (Gastrointestinal Motility Unit, University Hospital Utrecht, Utrecht, The Netherlands \[28\]).

In addition, pressures recorded from the channel closest to the duodenal infusion port (ie channel 16) were analyzed separately for the number and amplitude of duodenal PWs to evaluate potential ‘local’ effects of intraduodenal glucose. Basal pyloric pressure was determined by subtracting the mean basal pressure recorded at the most distal antral side-hole from the mean basal pressure recorded at the sleeve, using custom-written software (MAD, Professor Charles Malbert, Institut National de la Recherche Agronomique (INRA), Rennes, France) \[28\]. Phasic PWs in the antrum and pylorus were defined by pressure increases which lasted 1 - 20 seconds and that had an amplitude of \( > 10 \) mmHg, with a minimum interval of 15 seconds between peaks. Phasic PWs in the duodenum were defined as those having an amplitude of \( > 10 \) mmHg, with a minimal interval of 3 seconds between peaks. APD pressure
wave sequences (APD PWSs) were defined as two or more temporally related PWs with onsets within ± 5 seconds (in the antrum) or ± 3 seconds (in the duodenum) of each other [28].

**Blood glucose concentrations**

Venous blood samples (~ 5ml) were obtained both before the intravenous dose of granisetron (t = -27 min) and commencement of the intraduodenal infusion (ie t = -2 min), and then at 15 minute intervals between t = 0 - 120 min. Blood glucose concentrations were determined immediately using a portable blood glucose meter (Medisense Precision Q-I-D™ System, Abbott Laboratories, Medisense Products Inc., Bedford, MA, USA) [6].

**Autonomic function**

On one of the study days, after completion of the intraduodenal infusions, autonomic nerve function was evaluated using standardized cardiovascular reflex tests [29]. Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the response to standing ("30:15" ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test results was scored according to age-adjusted predefined criteria as 0 = normal, 1 = borderline and 2 = abnormal for a total maximum score of 6. A score ≥ 3 was considered to indicate autonomic dysfunction [29].

**Statistical analysis**

Data were evaluated using repeated measures 2 way Analysis of Variance (ANOVA) with ‘treatment’ and ‘time’ as within subject factors. Systolic and diastolic blood pressure and heart rate were analyzed as changes from baseline. Differences in blood glucose were analyzed as absolute values. The maximum fall in blood pressure was defined as the greatest
mean change from baseline for a treatment at any given time point. All APD pressure data, with the exception of the number of APD PWSs, are expressed as change from baseline. For the number and amplitude of antral PWs, duodenal PWs and IPPWs, basal pyloric pressures and number of APD PWSs, baseline values were calculated as the mean of values obtained between $t = -15 - 0$ min [28]. The number and amplitude of antral PWs, duodenal PWs (Channels 10-16) and IPPWs and basal pyloric pressures are expressed as mean values for the 60 minute intraduodenal glucose infusion period (ie $t = 0 - 60$ min). The number and amplitude of duodenal PWs (Channel 16) are expressed as mean values for 15 minute periods during the entire 120 minute duodenal infusion period (ie $0 - 15$ min, $15 - 30$, ..., $105 - 120$ min) [28]. The number and amplitude of antral PWs, duodenal PWs (Channels 10-16) and IPPWs and basal pyloric pressures were analyzed with ‘treatment’ and the number and amplitude of duodenal PWs (Channel 16) with ‘time’ ($t = -15 - 0$, $0 - 15$, $15 - 30$, ..., $105 - 120$ min) and ‘treatment’ as factors [28]. APD PWSs are expressed as the total number of PWs traveling over 2 (ie 1.5cm), 3 (ie 3cm), ..., 15 (ie 21cm) channels during the 120 minute infusion period [28]. The number of APD PWSs was analyzed with length of propagation (1.5, 3, 4.5, ..., 21cm) and ‘treatment’ as factors [28]. Phase III activity was excluded from the data analysis. Systolic and diastolic blood pressure, heart rate, blood glucose concentration and the number and amplitude of duodenal PWs (Channel 16) were analyzed separately from $t = 0 - 60$ min and $t = 60 - 120$ min. The number and amplitude of antral PWs, duodenal PWs (Channels 10-16) and IPPWs and basal pyloric pressures were analyzed between $t = 0 - 60$ min. One-way ANOVAs were used to analyze the effects of ‘time’ from $t = 0 - 60$ min and $t = 60 - 120$ min on systolic blood pressure, diastolic blood pressure, heart rate, blood glucose concentrations, the number and amplitude of duodenal PWs (Channel 16) and the effects of ‘length of propagation’ of the number of APD PWSs. In all analyses, post-hoc comparisons of adjusted means were performed using Student’s t-tests. All analyses were performed using Statview (version 5.0; Abacus Concepts, Berkeley, CA, USA) and
SuperANOVA (version 1.11, Abacus Concepts, Berkeley, CA, USA). Data are presented as mean values ± standard error of the mean (SEM), and a P value < 0.05 was considered significant in all analyses.
RESULTS

The studies were well tolerated. Three of the ten subjects reported constipation after granisetron which, in all cases, had resolved within 48 hours of completion of the experiment.

The median score for autonomic nerve dysfunction was 1.2 (range: 0 - 3); one of the ten subjects had definite autonomic dysfunction. Two subjects (not including the one with autonomic neuropathy) had postprandial hypotension that was evident on both study days. In one subject, basal pyloric pressure data were not available because of technical difficulties.

Blood pressure and heart rate

There was no difference in blood pressure or heart rate at t = -25 min (ie prior to intravenous granisetron) between the two study days (control vs granisetron): systolic blood pressure (133.0 ± 5.6 mmHg vs 131.9 ± 4.5 mmHg, P = 0.64); diastolic blood pressure (69.9 ± 1.9 mmHg vs 70.5 ± 1.8 mmHg, P = 0.57) and heart rate (57.1 ± 2.4 bpm vs 58.3 ± 2.7 bpm, P = 0.43). Nor was there any difference in baseline (ie t = 0 min) blood pressure or heart rate between the two days (control vs granisetron): systolic blood pressure (133.2 ± 5.3 mmHg vs 130.8 ± 4.3 mmHg, P = 0.37); diastolic blood pressure (69.3 ± 2.8 mmHg vs 66.6 ± 2.2 mmHg, P = 0.27) and heart rate (57.3 ± 2.3 bpm vs 57.1 ± 2.7 bpm, P = 0.88). There was no effect of granisetron on systolic blood pressure (P = 0.46), diastolic blood pressure (P = 0.48) or heart rate (P = 0.68) prior to the commencement of intraduodenal glucose infusion (ie between t = -25 min and t = 0 min).

Systolic and Diastolic blood pressure (Figure 2)

Between t = 0 - 60 min there were falls in systolic and diastolic blood pressure on both the control day and after granisetron (P < 0.0001 for both) with no difference (P < 0.65) between the two days. Similarly, between t = 60 - 120 min, there was no difference in systolic or diastolic blood pressure between the two days (P < 0.87).
Heart rate (Figure 2)

Between t = 0 - 60 min there was a rise in heart rate both on the control day and after granisetron (P < 0.0001 for both) with no difference (P = 0.24) between the two days. Similarly, there was no difference (P = 0.53) in heart rate between t = 60 - 120 min between the two days.

Antropyloroduodenal (APD) pressures

There was no difference in the baseline (ie t = -15 - 0 min) number of antral PWs (control: 31.7 ± 9.0 vs granisetron: 45.9 ± 11.5, P = 0.34), number of IPPWs (control: 4.1 ± 1.3 vs granisetron: 5.5 ± 2.7, P = 0.61) and APD pressures between the two study days (control vs granisetron): amplitude of antral PWs (57.1 ± 16.1 mmHg vs 58.0 ± 15.3 mmHg, P = 0.95); basal pyloric pressure (6.6 ± 7.5 mmHg vs 6.6 ± 4.9 mmHg, P = 0.10) or amplitude of IPPWs (24.4 ± 8.1 mmHg vs 24.5 ± 9.0 mmHg, P = 0.10). Between t = 0 - 60 min there was no difference in the number (P = 0.70) or amplitude (P = 0.40) of antral PWs, nor was there any difference in basal pyloric pressure (P = 0.60), or the number (P = 0.52) and amplitude (P = 0.98) of IPPWs, between the two days (Table).

There was no difference in the baseline (ie t = -15 - 0 min) number of duodenal PWs involving Channels 10 - 16 (control: 129.9 ± 33.0 vs granisetron: 144.9 ± 34.0; P = 0.75) and Channel 16 (control: 20.1 ± 4.7 vs granisetron: 36.7± 11.4; P = 0.19) and duodenal pressures between the two days (control vs granisetron): amplitude of duodenal PWs, Channels 10 - 16 (28.1 ± 3.8 mmHg vs 22.9 ± 2.0 mmHg; P = 0.30) and Channel 16 (23.5 ± 1.8 mmHg vs 22.7 ± 1.5 mmHg; P = 0.68). Between t = 0 - 60 min there was no difference in the number (P = 0.40) or amplitude (P = 0.90) of duodenal PWs, in Channels 10 - 16, between the two days (Table).
There was an increase in the number of duodenal PWs in Channel 16 between baseline and t = 0 - 15 min on the control day (P = 0.03), but no change in the number of duodenal PWs in Channel 16 after granisetron (P = 0.19), and no difference between the two days (P = 0.89). Between t = 0 - 60 min, there was a decrease in the number of duodenal PWs in Channel 16 from baseline on both the control day (P < 0.05) and after granisetron (P < 0.001) and the magnitude of the reduction in the number of duodenal PWs in Channel 16 from baseline was greater (P < 0.05) after granisetron when compared with control (Figure 3a). Between t = 60 - 120 min there was no difference in the number of duodenal PWs in Channel 16 between the two study days (P = 0.12). Between t = 0 - 60 min, there was no overall change in the amplitude of duodenal PWs in Channel 16 on the control day (P = 0.11), however, the amplitude of duodenal PWs was decreased after granisetron (P < 0.001); the reduction in the amplitude of duodenal PWs in Channel 16 from baseline between t = 0 - 60 min was greater (P < 0.05) after granisetron when compared with control (Figure 3b). Between t = 60 - 120 min, there was no difference (P = 0.37) in the amplitude of duodenal PWs in Channel 16 between the two days.

Antropyloroduodenal sequences

The number of PWs sequences decreased with increasing length of propagation on both the control day and after granisetron (P < 0.0001 for both) without any significant difference (P = 0.17) between the two study days (data not shown).

Blood glucose concentrations (Figure 4)

There was no significant difference at t = -25 min in blood glucose (control vs granisetron) between the two days (6.3 ± 0.2 mmol/L vs 6.5 ± 0.2 mmol/L; P = 0.47), or at baseline (6.2 ± 0.2 mmol/L vs 6.3 ± 0.1 mmol/L; P = 0.72). There was a rise between t = -2 - 60 min in blood
glucose on both days ($P < 0.0001$ for both) with a subsequent fall between $t = 60 - 120$ min ($P < 0.0001$ for both). Between $t = 0 - 60$ min ($P = 0.27$) and $t = 60 - 120$ min ($P = 0.94$), there was no difference in blood glucose concentrations between the two study days.
DISCUSSION

The major observations in this study are that the 5-HT3 receptor antagonist, granisetron, when administered acutely to healthy older subjects in a dose of 10µg/kg has no effect on blood pressure, heart rate or antral and pyloric motor responses, but modulates the ‘local’ duodenal motor response, to intraduodenal glucose. Accordingly, in this group, the cardiovascular and antropyloric motor responses to enteral glucose do not appear to be influenced by 5-HT3 mechanisms, but 5-HT3 receptors appear to be involved in modulating the duodenal motor response to intraduodenal glucose.

Using oral glucose loads [4,6,7] and intraduodenal glucose infusions [5,8,9], we have established a relationship between the magnitude of the postprandial fall in blood pressure and rise in heart rate with the rate of nutrient delivery from the stomach to the small intestine in healthy older subjects; these effects were evident within 60 minutes of ingestion and infusion of glucose. The latter studies excluded the potential effects of gastric emptying/distension on blood pressure, hence, in the current study, we infused glucose directly into the small intestine for a period of 60 minutes and at a rate (ie 3 kcal/min) that has been shown to decrease blood pressure, in healthy older subjects [8] and approximate the normal rate of gastric emptying [16]. The dose of granisetron (ie 10µg/kg/intravenous) employed was comparable to that given in previous studies [26,30,31], and is the recommended dose for clinical use [30]. Enteral glucose induced a gradual fall in systolic and diastolic blood pressure and a rapid increase in heart rate, all of which were comparable to those observed previously [5,8,9]. Furthermore, in accordance with previous studies, on the control day, there was a transient increase in duodenal motility within the first 15 minutes of the commencement of the glucose infusion [11] as well as reductions in the number of antral,
and proximal, duodenal pressure waves and an increase in the frequency of isolated pyloric pressure waves [12].

In a recent study in healthy adult volunteers [30], granisetron (10µg/kg/intravenous) had no effect on systolic blood pressure or heart rate. However, it is unclear whether granisetron was administered in the postprandial or fasted state. We observed that granisetron had no effect on the systolic and diastolic blood pressure or heart rate responses suggesting that the stimulation of 5-HT3 receptors is not involved in modulating the effects of enteral glucose in healthy older subjects. It should be recognised that 5-HT is released with increasing intraluminal pressures in the small intestine [32,33]. Hence, there is a potential for 5-HT3 receptors to modulate distension-induced postprandial changes in blood pressure. In rodents, the decreases in diastolic blood pressure resulting from duodenal distension with intraluminal pressures of 10 - 75 cmH₂O are attenuated by intravenous granisetron in doses of 1 - 100µg/kg [34].

While the release of 5-HT is known to slow gastric emptying in rodents by activation of pathways containing 5-HT3 receptors [18,21-24], in humans, the reported effects of 5-HT3 antagonists on gastric emptying are unclear. 5-HT3 antagonists have been shown to have no effect on [35-39], accelerate [40] or delay [41] gastric emptying. A recent study [26] suggests that the suppression of antral waves by intraduodenal lipid infusion is mediated via a 5-HT pathway; intravenous granisetron (10µg/kg) attenuated the suppression of antral waves after intraduodenal lipid, but not intraduodenal glucose, in healthy young subjects. However, glucose (5ml of 25% dextrose) also failed to induce a significant duodenal motor response [26]. In the current study, while there were no apparent effects of granisetron in the motor response across all duodenal channels (ie Channels 10 - 16), granisetron suppressed the
increase in the number and amplitude of duodenal pressure waves from baseline, that were evident within the first 15 minutes of the commencement of intraduodenal glucose infusion, in the channel closest to the infusion port (ie Channel 16). These observations suggest that the ‘local’ duodenal motor response to glucose is mediated via 5-HT3 receptors and that enterochromaffin cells may potentially play a role by releasing 5-HT in response to the presence of glucose. While it would be of interest to determine whether topical anesthesia modifies the response to granisetron, the local anesthetic, benzocaine, does not appear to affect the effects of intraduodenal glucose on APD motility in healthy young subjects [42].

Acute changes in the blood glucose concentration, including deviations that are within the normal postprandial range, have been shown to have an impact on gastric motility and gastric emptying [43,44]. For example, in healthy young adults, hyperglycemia is associated with the stimulation of localized pyloric, and inhibition of antral, contractions [43]. Hence, it was important to monitor blood glucose levels in this study. That granisetron had no effect on the glycemic response to intraduodenal glucose tends to discount a role for glycemia in the observed effects of granisetron on duodenal motility, but this issue warrants formal evaluation.

In conclusion, in healthy older subjects, the falls in systolic and diastolic blood pressure and rise in heart rate induced by intraduodenal glucose infusion are unaffected by granisetron suggesting that the cardiovascular response to enteral glucose is mediated by mechanisms unrelated to the stimulation of 5-HT3 receptors. In contrast, granisetron suppressed the ‘local’ duodenal motor response to intraduodenal glucose, suggesting that 5-HT3 receptors are involved in modulating the effects of glucose on small intestinal motility.
**GRANTS**

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FIGURE LEGENDS

Table: Changes in the number and amplitude of antral, pyloric phasic and duodenal pressure waves and the change in the amplitude of basal pyloric pressure waves from baseline during intraduodenal glucose at a rate of 3 kcal/min after administration of control and granisetron (10µg/kg) at t = -25 min. Intraduodenal glucose was given between t = 0 - 60 min. Data are presented as control vs granisetron and are mean values ± SEM (n = 10).

Figure 1: Diagram of multi-lumen catheter used for intraduodenal glucose and saline infusion and measurement of antropyoroduodenal (APD) pressures.

Figure 2: Changes in (A) systolic blood pressure, (B) diastolic blood pressure and (C) heart rate from baseline during intraduodenal infusion of glucose (3 kcal/min) after administration of control (○) and granisetron (10µg/kg) (●) at t = -25 min. Intraduodenal glucose was given between t = 0 - 60 min and intraduodenal saline between t = 60 -120 min. Data are mean values ± SEM (n = 10). P values indicate ‘treatment’ effects between t = 0 - 60 min and t = 60 -120 min.

Figure 3: Change in the (A) number and (B) amplitude of duodenal pressure waves (Channel 16) from baseline during intraduodenal infusion of glucose (3 kcal/min) after administration of control (○) and granisetron (10µg/kg) (●) at t = -25 min. Intraduodenal glucose was given between t = 0 - 60 min and intraduodenal saline between t = 60 -120 min. Data are mean values ± SEM (n
Figure 4: Blood glucose concentrations during intraduodenal infusion of glucose (3 kcal/min) after administration of control (○) and granisetron (10µg/kg) (●) at t = -25 min. Intraduodenal glucose was given between t = 0 - 60 min and intraduodenal saline between t = 60 - 120 min. Data are mean values ± SEM (n = 10). P value indicates ‘treatment’ effect between t = 0 - 60 min and t = 60 - 120 min.
Table. Effects of control and granisetron (10 µg/kg iv) on the change in the number and amplitude of antropyloroduodenal pressure waves from baseline between t = 0 - 60 min during intraduodenal glucose infusion.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Granisetron</th>
<th>P value</th>
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<td></td>
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</tr>
<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>4.4 ± 4.6</td>
<td>-5.8 ± 20.0</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Phasic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>22.8 ± 11.4</td>
<td>12.5 ± 15.9</td>
<td>0.52</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>70.3 ± 61.0</td>
<td>68.6 ± 73.7</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Duodenal pressure waves</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Channels 10-16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>-113.0 ± 143.7</td>
<td>-285.0 ± 112.3</td>
<td>0.40</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>-16.3 ± 18.2</td>
<td>-19.3 ± 11.8</td>
<td>0.90</td>
</tr>
</tbody>
</table>
Figure 2

A

$\Delta$ Systolic blood pressure (mmHg)

<table>
<thead>
<tr>
<th>ID glucose</th>
<th>ID saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>granisetron</td>
</tr>
</tbody>
</table>

P = 0.65  P = 0.69

Time (min)

B

$\Delta$ Diastolic blood pressure (mmHg)

<table>
<thead>
<tr>
<th>ID glucose</th>
<th>ID saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>granisetron</td>
</tr>
</tbody>
</table>

P = 0.16  P = 0.87

Time (min)

C

$\Delta$ Heart rate (bpm)

<table>
<thead>
<tr>
<th>ID glucose</th>
<th>ID saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>granisetron</td>
</tr>
</tbody>
</table>

P = 0.24  P = 0.53

Time (min)
Figure 4

![Graph showing glucose and saline levels over time](image)

- **ID glucose**
- **ID saline**

- ○ control
- ● granisetron

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
</tr>
</tbody>
</table>

- P = 0.27
- P = 0.94

145x107mm (600 x 600 DPI)