Effects of intraduodenal glucose, fat, and protein on blood pressure, heart rate, and splanchnic blood flow in healthy older subjects

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ABSTRACT

Background: Postprandial hypotension frequently occurs in the elderly. The hypotensive response to a meal is triggered by the interaction of nutrients with the small intestine; information relating to the effects of different macronutrients on blood pressure (BP) is limited and inconsistent.

Objective: The objective of the study was to determine the effects of intraduodenal glucose, fat, and protein on BP, heart rate (HR), and superior mesenteric artery (SMA) blood flow in healthy older subjects.

Design: Eight subjects received intraduodenal glucose (64 g), fat (10% oil emulsion), protein (72 g whey), or saline (0.9%) at a rate of 2.7 mL/min for 90 min, followed by intraduodenal saline for 30 min. BP, HR, and SMA blood flow were measured.

Results: The falls in systolic BP during infusions of glucose, fat, and protein did not differ significantly (P = 0.97); however, the fall occurred significantly earlier during the glucose infusion; (18 ± 3.0 min) than during the fat (46 ± 11.0 min; P = 0.02) and protein 33 ± 7 min; P = 0.04) infusions. The increases in HR during glucose, fat, and protein infusions (P < 0.0001 for all) did not differ significantly. SMA blood flow increased significantly after all infusions (P < 0.001 for all), but the increase was significantly (P < 0.05) lower after protein than after the other infusions.

Conclusions: Intraduodenal glucose, fat, and protein decrease systolic BP in healthy older subjects, but the onset of the hypotensive response is earlier after glucose, and the effect of protein on SMA blood flow is less than that of the other nutrients. Am J Clin Nutr 2008;87:156–61.

KEY WORDS Postprandial hypotension, blood pressure, aging, nutrients

INTRODUCTION

Postprandial hypotension occurs frequently and is an important clinical problem, particularly in the elderly and in persons with autonomic dysfunction (1, 2), by predisposing these populations to numerous adverse sequelae, including syncope and cerebrovascular accidents (2–4). Current approaches to management are suboptimal. It has been suggested that, of the macronutrients, carbohydrate (particularly glucose) has the greatest suppressive effect on blood pressure (BP) (2, 5). Whereas oral ingestion of glucose (5), sucrose (6, 7), and starch (8) reduces BP in healthy older subjects and persons with autonomic failure, intravenous glucose has little, if any, effect (2), which indicates that the response is mediated by the gastrointestinal tract. The rate of glucose delivery from the stomach to the small intestine is a major determinant of the hypotensive response to enteral glucose (9, 10). For example, in healthy older subjects, the fall in systolic BP is substantially greater when glucose is infused intraduodenally at a rate of 3 kcal/min when it is infused at a rate of 1 kcal/min (9). Conversely, gastric distension attenuates the fall in BP (11–14).

Information relating to the effects of the other macronutrients—fat and protein—on BP is limited and inconsistent (5, 15–19), although these effects have fundamental implications for the dietary management of postprandial hypotension. It has been suggested that fat (5, 15, 16, 18) and protein (5, 16) have little effect on BP, but other studies have reported a substantial fall in BP after high-fat (17, 19, 20) and protein (15) meals. Glucose (21), fat (22), and protein (23) slow gastric emptying; the slowing of gastric emptying by fat (24) and protein (23) is dependent on the lipolysis of fat to fatty acids (25) and the proteolysis of protein to amino acids (26), respectively.

The hypotensive response to a high-fat drink is later than that of carbohydrate (19), which may be attributable to the time taken to generate a significant amount of free fatty acids to trigger a hypotensive response. Fat also may layer to the top of stomach contents as a result of its low density (27), which slows the rate at which fat empties from the stomach. Because gastric distension (11, 14) attenuates the effects of intestinal nutrients on BP, variations in the rate of gastric emptying complicate previous comparisons between nutrients. Impaired regulation of splanchnic blood flow may be important in the pathophysiology of postprandial hypotension (28). As with information on BP, information relating to the effects of different macronutrients on superior mesenteric artery (SMA) blood flow, usually quantified by Doppler ultrasound, is inconsistent (16, 17, 29–33). In those
studies, glucose (16, 17, 29, 30, 33), fat (16, 17, 29, 30), and protein (16, 29, 30) were ingested orally, and, because gastric emptying was not quantified, differences in small intestinal nutrient delivery and gastric distension may have influenced the observations. Through the infusion of nutrients directly into the small intestine, the effects of gastric distension can be bypassed.

The aim of this study was to determine the effects of intraduodenal glucose, fat, and protein infusions on BP, heart rate (HR), and SMA blood flow in healthy, older subjects. The broad hypothesis to be addressed was that there would be differential responses to the 3 macronutrients and, in particular, that the hypotensive response to intraduodenal fat would not be significantly different in magnitude, but later than the response to glucose.

SUBJECTS AND METHODS

Subjects

Eight healthy older subjects (4 F, 4 M) with a median age of 74 y (range: 68–79 y) and body mass index (in kg/m²) of 24.5 (range: 21.2–28.2) who were recruited by advertisement were studied. We calculated that a minimum of 8 subjects would be required to detect a mean change in systolic BP of 15 mm Hg with a power of 0.80 and assuming significance at \( P < 0.05 \). All subjects were nonsmokers. None had a history of gastrointestinal disease or surgery; diabetes mellitus; significant respiratory, renal, hepatic, or cardiac disease; or alcohol abuse or epilepsy, and none were taking medication known to influence BP or gastrointestinal function.

All subjects provided written informed consent. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and all experiments were carried out in accord with the Declaration of Helsinki.

Protocol

Each subject was studied on 4 occasions, separated by at least 7 d, in single-blind, randomized order. On each study day, the subject attended the Discipline of Medicine, Royal Adelaide Hospital, University of Adelaide, at \( 0830 \) after a fast (10.5 h for solids; 8.5 h for liquids) (34). A silicone-rubber catheter (≈4-mm diameter) (Dentsleeve International Ltd, Mui Scientific, Mississauga, Canada), which included an infusion channel with a port located ≈10 cm distal to the pylorus (ie, in the duodenum) and 2 other channels, 1 positioned in the antrum (2.5 cm proximal to the pylorus) and the other positioned in the duodenum (2.5 cm distal to the pylorus), was introduced into the stomach via an anesthetized nostril (34). The latter 2 channels were perfused with normal saline (0.9%). The correct positioning of the catheter was maintained by continuous measurement of the transmucosal potential difference between the antral (−40 mV) and the duodenal (0 mV) channels (22). For this purpose, an intravenous cannula filled with sterile saline was placed subcutaneously in the left forearm and used as a reference electrode (22). The tip of the catheter was allowed to pass into the duodenum by peristalsis, which took between 30 and 90 min.

Once the catheter was in position, the subject was placed in the recumbent position and an automated BP cuff was placed around the left arm (34). Approximately 30 min after the catheter had been positioned correctly (at \( t = 0 \) min) an intraduodenal infusion of either glucose (64 g), fat (10% Intralipid; Fresenius Kabi AB, Uppsala, Sweden), protein [72 g; 97% whey protein concentrate containing 8.4% carbohydrate (mostly lactose); Perfect Protein; Aussie Bodies Pty Ltd, Port Melbourne, Australia], or saline (0.9%) in a total volume of 243 mL was begun and continued at a rate of 2.7 mL/min for 90 min. Intraduodenal infusions were given with a volumetric infusion pump (Gemini PC-1; IMED Corp, San Diego, CA) that could not be seen by the subject, to ensure that the subject was blinded to the study condition. The glucose, fat, and protein infusions all resulted in an energy delivery of 3 kcal/min. On all days, saline (0.9%) was infused intraduodenally at the same rate between \( t = 90 \) and 120 min. At \( t = 120 \) min, the catheter and the intravenous cannula were removed, the subject was given a light meal, and, soon afterward, he or she was allowed to leave the laboratory.

Measurements

Blood pressure and heart rate

BP (systolic and diastolic) and HR were measured with an automated oscillometric BP monitor (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI) at \( t = 9, 6, \) and 3 min before commencement of the intraduodenal infusion and, subsequently, every 3 min between \( t = 0 \) and 120 min. Baseline (ie, \( t = 0 \) min) BP and HR were calculated as the mean of measurements taken at \( t = 9, 6, \) and 3 min before commencement of the intraduodenal infusion. Postprandial hypotension was defined as a fall in systolic BP ≥ 20 mm Hg that was sustained for ≥30 min (2).

Superior mesenteric artery blood flow

SMA blood flow was measured by duplex ultrasonography (ie, B-mode and Doppler imaging) using an ultrasonography system (Logiq 9; GE Healthcare Technologies, Sydney, Australia), as described previously (35). The subject was scanned using a 3.5C broad-spectrum 2.5–4-MHz convex transducer (35) at \( t = −2 \) min, 5 min, and 10 min and then at 15-min intervals between \( t = 0 \) and 120 min. Blood flow (mL/min) was calculated instantaneously by using the following equation (35):

\[
\text{Blood flow (mL/min)} = \pi \times r^2 \times \text{TAMV} \times 60
\]

where \( r \) = the radius of the SMA, and TAMV is the time-averaged mean velocity.

Autonomic function

On one of the study days, after completion of the intraduodenal infusion, autonomic nerve function was evaluated by using standardized cardiovascular reflex tests (36). Parasympathetic function was evaluated by the variation (R–R interval) of the HR during deep breathing and the response to standing (30:15 ratio). Sympathetic function was assessed by the fall in systolic BP 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 (36).

Statistical analysis

Data were evaluated by using mixed-model repeated-measures 2-factor analysis of covariance, with treatment and time as the within-subject factors. Systolic and diastolic BP and
HR were analyzed as changes from baseline. SMA artery blood flow was analyzed as an absolute value. Data were analyzed from $t = -2$ to 90 min and from $t = 0$ to 90 min for SMA blood flow and from $t = 0$ to 90 min and from $t = 90$ to 120 min for systolic BP, diastolic BP, and HR to determine the effects (treatment and time) of intraduodenal glucose, fat, protein, and saline. One-factor analysis of variance was used to analyze the effects of time on systolic and diastolic BP, HR, and SMA blood flow. In all analyses, post hoc comparisons of adjusted means were performed by using Student’s paired $t$ test. The maximum fall in BP was defined as the greatest mean change from baseline in each subject at any given time point for each treatment. Data are presented as means ± SEMs, and statistical significance was set at 5%. All analyses were performed by a professional statistician using SAS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

The studies were well tolerated. Four of the 8 subjects experienced diarrhea soon after completion of the fat infusion, and 2 subjects reported diarrhea after completion of the protein infusion. One subject reported nausea just before the completion of the fat and protein infusions. In all cases, these symptoms had resolved within 3 h of the completion of each experiment. No subject had definite autonomic neuropathy; the median score was 2.5. Postprandial hypotension (ie, a fall in systolic BP of ≥20 mm Hg sustained for ≥30 min) was evident in one subject; this occurred during the fat infusion. In one subject, acceptable SMA blood flow measurements could not be obtained on the control (saline) study because the vessel was obscured by abdominal gas; these data were, accordingly, not included. In the subject who experienced nausea, data collection on the fat and protein infusion days was terminated at $t = 90$ min.

Blood pressure and heart rate

There was no significant difference in baseline (ie, $t = 0$ min) BP or HR between the 4 d. Systolic BP was $\approx 126.0 \pm 6.0$ mm Hg, diastolic BP was $\approx 67.0 \pm 3.0$ mm Hg, and HR was $\approx 60.0 \pm 3.0$ bpm.

Systolic blood pressure

Between $t = 0$ and 90 min, there was a significant ($P < 0.005$) fall in systolic BP during glucose infusion but no overall change during fat ($P = 0.59$) or protein ($P = 0.44$) infusions. In contrast, there was a modest but significant ($P < 0.05$) rise during the saline infusion. The maximum falls in systolic BP during the glucose (11.7 ± 2.8 mm Hg), fat (11.7 ± 4.8 mm Hg), and protein (11.0 ± 1.5 mm Hg) infusion did not differ significantly ($P = 0.97$); however, the maximum fall occurred significantly earlier during glucose infusion (18 ± 3 min) than during fat (46 ± 11 min; $P = 0.02$) and protein (33 ± 7 min; $P = 0.04$) infusions, although there was no significant ($P = 0.12$) difference in the time of maximum fall between fat and protein infusions. There was a significant ($P < 0.01$) treatment × time interaction for systolic BP on all study days. Systolic BP was significantly lower between $t = 0$ and 90 min during the glucose, fat, and protein infusions ($P < 0.05$ for all 3) than between $t = 0$ and 90 min during the saline infusion and significantly lower during glucose infusion than during fat and protein infusions ($P < 0.05$ for both). During the fat infusion, systolic BP was initially [eg, at $t = 24$ min ($P = 0.03$)] greater and subsequently [eg, between $t = 78$ and 90 min ($P < 0.05$)] lower than during the protein infusion (Figure 1).

Between $t = 90$ and 120 min, there were no significant changes in systolic BP during the glucose ($P = 0.72$), fat ($P = 0.18$), protein ($P = 0.21$), or saline ($P = 0.25$) infusion (Figure 1). Systolic BP was significantly lower between $t = 90$ and 120 min after the glucose and fat infusions ($P < 0.0001$ for both) than after saline infusion; however, there was no significant difference between protein and saline ($P = 0.34$). Systolic BP also was significantly ($P < 0.0001$) lower after glucose infusion than after protein infusion, but there was no significant difference ($P = 0.30$) between glucose and fat infusions. After the fat infusion, systolic BP was significantly ($P < 0.0001$) lower than after protein infusion (Figure 1).
Diastolic blood pressure

Between \( t = 0 \) and 90 min, there was a significant fall in diastolic BP during glucose (\( P < 0.05 \)) and protein (\( P < 0.01 \)) infusions but not during fat (\( P = 0.83 \)) or saline (\( P = 0.91 \)) infusions (Figure 1). The maximum falls in diastolic BP during the glucose (13.6 ± 1.9 mm Hg), fat (11.6 ± 2.6 mm Hg), and protein (11.3 ± 1.2 mm Hg) infusions did not differ significantly (\( P = 0.44 \)), and there was no significant difference in the time of the maximal fall in diastolic BP between the infusions (glucose: 64 ± 7 min; fat: 56 ± 9 min; protein: 59 ± 7 min; \( P = 0.17 \)). Between \( t = 0 \) and 90 min, diastolic BP was significantly less during glucose (\( P < 0.01 \)) and protein (\( P < 0.05 \)) infusions than during saline infusion, and there was a trend (\( P = 0.15 \)) for diastolic BP to be less during fat infusion than during the saline infusion. Diastolic BP was significantly (\( P < 0.05 \)) lower during glucose infusion than during protein infusion (Figure 1).

Between \( t = 90 \) and 120 min, there were no significant changes in diastolic BP after glucose (\( P = 0.42 \)) or saline (\( P = 0.46 \)) infusions; however, diastolic BP fell significantly after the fat and protein infusions (\( P < 0.05 \) for both; Figure 1). Diastolic BP was significantly lower between \( t = 90 \) and 120 min during glucose (\( P < 0.001 \)), fat (\( P < 0.05 \)), and protein (\( P < 0.05 \)) infusions than during saline infusion. Diastolic BP also was significantly lower after glucose infusion than after fat and protein infusions (\( P < 0.01 \) for both) but not significantly lower after fat infusion than after protein infusions (\( P = 0.84 \); Figure 1).

Heart rate

Between \( t = 0 \) and 90 min, there was a significant rise in HR during the glucose, fat, and protein infusions (\( P < 0.0001 \) for all) but no significant (\( P = 0.61 \)) change during the saline infusion (Figure 1). The maximum rise in HR during the glucose (15.7 ± 2.3 bpm), fat (17.2 ± 4.6 bpm), and protein (14.8 ± 2.7 bpm) infusions did not differ significantly (\( P = 0.72 \)), nor was there any significant difference in the time of the maximum heart response (glucose: 64 ± 9 min; fat: 54 ± 8 min; protein: 64 ± 7 min; \( P = 0.65 \)). There was a significant (\( P < 0.001 \)) treatment × time interaction for HR on all study days. HR was significantly greater between \( t = 0 \) and 90 min during the glucose, fat, and protein infusions (\( P < 0.05 \) for all) than during the saline infusion. There was no significant difference in HR between the glucose infusion and the fat or protein infusions. At \( t = 66 \) min, HR was significantly greater during the fat infusion than during the glucose and protein infusions (\( P = 0.02 \) for both; Figure 1).

Between \( t = 90 \) and 120 min, there were significant falls in HR after the glucose (\( P < 0.01 \)) and protein (\( P < 0.05 \)) infusions but not after the fat (\( P = 0.20 \)) or saline (\( P = 0.37 \)) infusions (Figure 1). Between \( t = 90 \) and 120 min, HR was significantly greater during the glucose, fat, and protein infusions (\( P < 0.001 \) for all) than during the saline infusion. In contrast, there were no significant differences in HR between the 3 nutrient infusions (Figure 1).

Superior mesenteric artery blood flow

There was no significant difference in baseline (ie, \( t = -2 \) min) SMA blood flow between the 4 d (\( =629.0 ± 89.0 \) mL/min) (Figure 2). Between \( t = -2 \) and 90 min, there was a significant rise in SMA blood flow during glucose (\( P < 0.0001 \)), fat (\( P < 0.001 \)), and protein (\( P < 0.001 \)) infusions, which was evident from \( t = 5 \) min during glucose (\( P = 0.03 \)) and from \( t = 15 \) min during fat (\( P = 0.004 \)) and protein (\( P = 0.03 \)) infusions. In contrast, there was no significant (\( P = 0.16 \)) change in SMA blood flow during the saline infusion (Figure 2). There was a significant (\( P < 0.001 \)) treatment × time interaction for SMA blood flow on all study days. SMA blood flow was significantly greater during the glucose (\( P < 0.01 \)), fat (\( P < 0.001 \)), and protein (\( P < 0.05 \)) infusions than during the saline infusion.

Similarly, SMA blood flow was significantly greater during both glucose (\( P < 0.05 \)) and fat (\( P < 0.01 \)) infusions than during protein infusions and significantly (\( P = 0.04 \)) greater during glucose infusions than during fat infusion (Figure 2).

Between \( t = 90 \) and 120 min, there were significant falls in SMA blood flow after the glucose (\( P < 0.01 \)) and protein (\( P < 0.05 \)) infusions but no significant change after the fat (\( P = 0.18 \)) or saline (\( P = 0.13 \)) infusions (Figure 2). SMA blood flow was significantly greater between \( t = 90 \) and 120 min after the glucose, fat, and protein infusions (\( P < 0.0001 \) for all) than after the saline infusion; however, there was no significant difference in SMA blood flow after glucose infusion than after fat (\( P = 0.35 \)) or protein (\( P = 0.16 \)) infusions and no significant (\( P = 0.64 \)) difference in SMA blood flow after fat infusion than after protein infusion (Figure 2). There were no significant relations between BP or HR and SMA blood flow (data not shown).

DISCUSSION

An understanding of the effects of different nutrients on postprandial BP has important implications for the dietary management of postprandial hypotension. This study establishes that, in healthy older subjects, isocaloric and isovolemic intraduodenal infusions of glucose, fat, and protein reduce systolic BP and increase HR and SMA blood flow. It also establishes that the magnitude of these responses does not differ significantly, but there are significant differences between the nutrients in the onset of the fall in BP, and the increase in SMA blood flow may be less after protein infusion than after glucose or fat infusion.

The hypotensive response to intraduodenal glucose is dependent on the rate of glucose delivery into the small intestine (9), and intragastric mechanisms related to gastric distension reduce
the postprandial fall in BP in healthy older subjects; thus, to determine the effects of enteral nutrients independent of gastric distension, we infused nutrients intraduodenally and at a rate that approximated normal gastric emptying (ie, 3 kcal/min) (21). The fat emulsion used slowed gastric emptying (22), and the whey (97%) protein concentrate has a low carbohydrate content, which had no effect on the BP response to a high-fat drink (19).

The magnitude of the postprandial fall in BP is dependent on meal composition, and it has been suggested that carbohydrate, particularly glucose, has the greatest effect (5, 7, 8, 37). However, there is much less information about the effects of fat and protein (5, 15–18, 20). It has been suggested that fat has relatively little effect (5, 15, 16, 18) in healthy older subjects, but the ingestion of a high-fat (88% fat) drink containing cream blended with milk (653 kcal) induced a fall in systolic BP (mean: ≈16 mm Hg) that did not differ significantly from that induced by an isocaloric glucose drink (75 g and 93 g in 300 mL water; Poly-Hg) that did not differ significantly from those induced by intraduodenal glucose, but the response to glucose occurs earlier. Hence, glucose, fat, and protein have the potential to contribute to postprandial hypotension. The mechanisms responsible for these changes remain unclear, but the relatively slower BP responses to fat and protein may reflect the time needed for the digestion of fat to free fatty acids and that of protein to amino acids. If this possibility proves to be the case, inhibition of fat and protein digestion may represent an approach to the treatment of postprandial hypotension.

In summary, in healthy older subjects, isocaloric and isovolemic intraduodenal infusions of glucose, fat, and protein result in falls in systolic BP that are not significantly different, yet the response to glucose occurs earlier. Hence, glucose, fat, and protein have the potential to contribute to postprandial hypotension. The mechanisms responsible for these changes remain unclear, but the relatively slower BP responses to fat and protein may reflect the time needed for the digestion of fat to free fatty acids and that of protein to amino acids. If this possibility proves to be the case, inhibition of fat and protein digestion may represent an approach to the treatment of postprandial hypotension.

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The authors’ contributions are as follows—DG: acquisition of subjects; collection, analysis, and interpretation of data; and preparation of manuscript; TH: collection of data and preparation of manuscript; JHM: concept and design of study and preparation of manuscript; IMC: preparation of manuscript; MH: concept and design of study and preparation of manuscript; and KLJ: concept and design of study, data interpretation, and preparation of manuscript. None of the authors had a personal or financial conflict of interest.

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