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Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycemia, and GLP-1 release in healthy older subjects

Lora Vanis, Diana Gentilcore, Christopher K. Rayner, Judith M. Wishart, Michael Horowitz, Christine Feinle-Bisset, and Karen L. Jones

University of Adelaide, Discipline of Medicine, Royal Adelaide Hospital and National Health and Medical Research Council Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, South Australia, Australia

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Vanis L, Gentilcore D, Rayner CK, Wishart JM, Horowitz M, Feinle-Bisset C, Jones KL. Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycemia, and GLP-1 release in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 300: R1524–R1531, 2011. First published March 9, 2011; doi:10.1152/ajpregu.00378.2010.—Postprandial hypotension is an important problem, particularly in the elderly. The fall in blood pressure is dependent on small intestinal glucose delivery and, possibly, changes in splanchnic blood flow, the release of glucagon-like peptide-1 (GLP-1), and sympathetic nerve activity. We aimed to determine in healthy older subjects, the effects of variations in small intestinal glucose load on blood pressure, superior mesenteric artery flow, GLP-1, and noradrenaline. Twelve subjects (6 male, 6 female; ages 65–76 yr) were studied on four separate occasions, in double-blind, randomized order. On each day, subjects were intubated via an anesthetized nostril, with a nasoduodenal catheter, and received an intraduodenal infusion of either saline (0.9%) or glucose at a rate of 1, 2, or 3 kcal/min (G1, G2, G3, respectively), for 60 min (t = 0–60 min). Between t = 0 and 60 min, there were falls in systolic and diastolic blood pressure following G2 and G3 (P = 0.003 and P < 0.001, respectively), but no change during saline or G1. Superior mesenteric artery flow increased slightly during G1 (P = 0.01) and substantially during G2 (P < 0.001) and G3 (P < 0.001), but not during saline. The GLP-1 response to G3 was much greater (P < 0.001) than to G2 and G1. Noradrenaline increased (P < 0.05) only during G3. In conclusion, in healthy older subjects the duodenal glucose load needs to be > 1 kcal/min to elicit a significant fall in blood pressure, while the response may be maximal when the rate is 2 kcal/min. These observations have implications for the therapeutic strategies to manage postprandial hypotension by modulating gastric emptying.

postprandial hypotension; heart rate; insulin; aging

POSTPRANDIAL HYPOTENSION IS an important, yet generally under recognized, clinical problem occurring frequently in the healthy elderly (~20%), nursing home residents (~30–40%), and patients with autonomic dysfunction often secondary to diabetes mellitus (25–40%) (23). Postprandial hypotension can lead to syncope, angina, and stroke (23, 33) and is associated with increased mortality (8). The mechanisms mediating postprandial hypotension are poorly understood; however, the rate of small intestinal nutrient delivery (28, 38), changes in splanchnic blood flow (23), the release of gastrointestinal hormones (47), and sympathetic nerve activity (7, 30) have been identified as possible pathophysiological mechanisms.

Address for reprint requests and other correspondence: K. Jones, Univ. of Adelaide, Discipline of Medicine, Royal Adelaide Hospital, North Terrace, ADELAIDE, SA, 5000, Australia (e-mail: karen.jones@adelaide.edu.au).

The magnitude of the fall in blood pressure induced by enteral glucose in both healthy older subjects (26, 38) and patients with type 2 diabetes (28, 44) is influenced by the small intestinal glucose load and apparently not its osmolarity (10). We have reported that when glucose was administered intraduodenally to healthy older subjects at rates within the normal physiological range of gastric emptying (3) the fall in blood pressure was much greater in response to 3 kcal/min compared with 1 kcal/min, without any change from baseline in response to 1 kcal/min, suggesting a threshold for the hypotensive response that is > 1 and < 3 kcal/min (38). We are aware that a significant limitation of this study was that there was no control arm. Hence, it could not be determined whether the 1 kcal/min infusion had any effect on blood pressure. Moreover, because only two intraduodenal glucose loads were evaluated, there was no information about the dose response relationship between the hypotensive response and the duodenal glucose load. Both of these issues are of potential relevance to the development of therapeutic strategies designed to manage postprandial hypotension by modulating gastric emptying.

Following a meal, there is a substantial increase in splanchnic blood flow (~20% of total blood volume) with an approximate doubling of superior mesenteric artery (SMA) blood flow (23). In healthy older subjects, small intestinal carbohydrate infusion at a rate of 3 kcal/min increases SMA flow and the magnitude of the increase is related directly to the fall in blood pressure (11, 49), indicative of a causal association. The relationship between the small intestinal glucose load and SMA blood flow has hitherto not been evaluated.

The rate of gastric emptying is also a major determinant of the glycemic, as well as the blood pressure, response to carbohydrate (18) and the release of the so-called incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (18, 25, 37), in healthy young adults (41) and patients with type 2 diabetes (32). In both groups, the relationship of glycemia and GLP-1 release with small intestinal glucose delivery is nonlinear, so that there is relatively little difference in the glycemic responses to intraduodenal glucose loads of 2 and 4 kcal/min, which is attributable to a much greater GLP-1 (and hence insulin) response to the latter. The relationship of glycemia and GLP-1 release with the small intestinal glucose load has hitherto not been evaluated in apparently healthy older subjects, in whom glucose intolerance occurs frequently. There is evidence in healthy young subjects that GLP-1 may increase blood pressure (5), and we have reported in healthy older subjects that the attenuation of the fall in blood pressure induced by oral sucrose, using the α-glucosidase inhibitor acarbose, which is

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known to slow gastric emptying and has been recently advocated for the use in the management of postprandial hypotension, is associated temporally with the secretion of GLP-1 (9). Both endogenous (4) and exogenous (31) GLP-1 are also known to slow gastric emptying. Given that the magnitude of the postprandial fall in blood pressure is dependent on gastric emptying (28, 38), GLP-1 may potentially be important in mediating the hypotensive response.

It has been suggested that the abnormally large fall in blood pressure after a meal in postprandial hypotension reflects, at least in part, the failure of the sympathetic nervous system to compensate adequately (7, 52). Plasma noradrenaline levels reflect sympathetic nerve activity, and in both young and older subjects plasma noradrenaline levels rise after a meal. This response is markedly attenuated in patients with postprandial hypotension (34, 52). It has been reported that in healthy young subjects there is no difference in the plasma noradrenaline response to two different oral glucose loads (42). In healthy subjects the rate of gastric emptying of carbohydrate is tightly regulated in a given individual, so that duodenal calroric delivery is constant and relatively unaffected by the intragastric load, as a result of small intestinal feedback (3). There is no information about the effects of variations in small intestinal glucose delivery on the plasma noradrenaline response.

The primary aim of this study was to determine in healthy older subjects the effects of variations in the small intestinal glucose load on blood pressure and heart rate. Secondary objectives were to evaluate effects on SMA blood flow, plasma GLP-1 release, and plasma noradrenaline.

We hypothesized that, in this group, intraduodenal glucose infusion at a rate of 1 kcal/min would not affect blood pressure and that the hypotensive response to 2 kcal/min would be less than that to 3 kcal/min and that these effects would be attributable to changes in SMA blood flow, plasma GLP-1, and plasma noradrenaline.

MATERIALS AND METHODS

Subjects

Twelve healthy older subjects (6 male and 6 female, recruited by advertisement) with a mean age of 68.7 ± 1.0 yr (range: 65–76 yr) and body mass index of 23.9 ± 0.7 kg/m^2 (range: 20.4–27.4 kg/m^2) were studied. All subjects were nonsmokers. None had a history of gastrointestinal disease or surgery; diabetes; significant respiratory, renal, hepatic, or cardiac disease; chronic alcohol abuse; epilepsy; or were taking medication known to influence blood pressure or gastrointestinal function.

Protocol

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 involvement. All experiments were carried out in accordance with the Declaration of Helsinki.

Each subject was studied on four occasions, separated by a minimum of 3 days, in randomized, double-blind order. Randomization was performed using the online Random Integer Set Generator program (www.random.org). On each day, the subject attended the University of Adelaide, Discipline of Medicine, Royal Adelaide Hospital, at 0800 h following an overnight fast (10 h for solids; 8 h for liquids) (49). At that time, a silicone catheter (external diameter, ~4 mm; Dentsleeve International, Mui Scientific, ON, Canada) was introduced into the stomach via an anesthetized nostril (38). The assembly included an infusion channel (internal diameter, ~1 mm) and was positioned by using measurements of transmucosal potential difference (16) so that the infusion port was located ~10 cm distal to the pylorus (i.e., in the duodenum) as well as two other channels that were positioned in the antrum (2.5 cm proximal to the pylorus) and duodenum (2.5 cm distal to the pylorus), respectively, and were perfused with 0.9% saline.

Once the tube was positioned correctly, an automated blood pressure cuff was placed around the left arm (38) and a 30-min blood pressure stabilization period occurred. At $t = 0$ min the subject received, for 60 min (i.e., between $t = 0$ and 60 min), an intraduodenal infusion of either: *1*) 1 kcal/min glucose (G1), *2*) 2 kcal/min glucose (G2), *3*) 3 kcal/min glucose (G3), or *4*) saline (0.9%), at a rate of 5 ml/min, in randomized order. On all 4 days, isovolumetric saline was infused between $t = 60$ and 120 min (38). Intraduodenal infusions were performed using a volumetric infusion pump (model Gemini PC-1; Imed, San Diego, CA). At $t = 120$ min, the catheter was removed and the subject then given a light meal and then allowed to subsequently leave the laboratory. On one of the study days, cardiovascular autonomic nerve function was evaluated immediately after the completion of the study (6, 40).

Measurements

Blood pressure and heart rate. Blood pressure (systolic and diastolic) and heart rate were measured using an automated oscillometric blood pressure monitor (model DINAMAP ProCare 100; GE Medical Systems, Milwaukee, WI) at $t = -9$, -6, and -3 min prior to commencement of the intraduodenal infusions and then every 3 min between $t = 0$ and 120 min (38). Baseline blood pressure and heart rate, i.e., $t = 0$ min, were calculated as the mean of measurements taken at $t = -9$, -6, and -3 min. Postprandial hypotension was defined as a fall in systolic blood pressure of ≥ 20 mmHg that was sustained for at least 30 min (23).

SMA blood flow. SMA blood flow was measured by Duplex ultrasonography (i.e., B-mode and Doppler imaging) using a Logiq 9 ultrasonography system (GE Healthcare Technologies, Sydney, Australia) (39). Subjects were scanned using a 3.5 C broad spectrum 2.5–4 MHz convex transducer before ($t = -2$ min) the commencement of the intraduodenal infusion and then at 15-min intervals between $t = 0$ and 120 min (11). Blood flow (ml/min) was calculated instantaneously using a previously reported method (39).

Blood glucose, serum insulin, plasma GLP-1, and plasma noradrenaline concentrations. Venous blood samples were obtained prior to the commencement of the intraduodenal infusion (i.e., $t = -2$ min) and at 15-min intervals between $t = 0$ and 120 min. Blood glucose concentrations were determined immediately by using a portable blood glucose meter (Medisense Prescision Q·I·D System; Abbott Laboratories, Medisense Products, Bedford, MA). Serum and plasma were separated by centrifugation at 3,200 rpm for 15 min at 4°C within 30 min of collection and stored at −70°C until analyzed. Serum insulin (mU/l) was measured by ELISA immunoassay (Diagnostics Systems Laboratories, Webster, TX). The sensitivity of the assay was 0.26 mU/l, and the coefficient of variation was 2.6% within and 6.2% between assays. Plasma GLP-1 (pmol/l) was measured by radioimmunoassay (model GLPIT-36HK; Linco Research, St. Charles, MO). The minimum detectable limit was 3 pmol/l, and the intra- and interassay coefficient of variation were 6.7% and 7.8%, respectively. Plasma noradrenaline was measured using HPLC coupled with electrochemical detection (Waters, Milford, MA) (17).

Autonomic function. Autonomic nerve function was assessed using standardized cardiovascular reflex tests (6, 40). 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 (6, 40).

Statistical Analysis

Systolic and diastolic blood pressure and heart rate were analyzed and presented as changes from baseline. SMA blood flow, blood glucose, serum insulin, and plasma GLP-1 were analyzed and presented as absolute values. One-way ANOVA was used to analyze the effects of time on the change from baseline values for systolic and diastolic blood pressure and heart rate, and absolute values of SMA blood flow, blood glucose, serum insulin, and plasma GLP-1 concentrations. The maximum falls in systolic and diastolic blood pressure and rise in heart rate, SMA blood flow, blood glucose, serum insulin, and plasma GLP-1 were defined as the greatest change from baseline in each subject at any given time point for each treatment. Areas under the curve (AUC) were calculated using the trapezoidal rule and analyzed by one-way ANOVA to evaluate a treatment effect between $t = 0$ and 60 min for systolic and diastolic blood pressure and heart rate, between $t = -2$ and 60 min for SMA blood flow, and between $t = -2$ and 120 min for blood glucose, serum insulin, and plasma GLP-1. We calculated that a minimum of eight subjects would be required to detect a mean difference in systolic blood pressure of ~10 mmHg with the power of 0.80 and at a significance level of $P < 0.05$ (38). All analyses were performed using the SPSS version 16.0.2 (SPSS, Chicago, IL). Systolic and diastolic blood pressure, heart rate, and plasma noradrenaline are shown as changes from baseline and means ± SE. SMA blood flow, blood glucose, serum insulin, and plasma GLP-1 data are shown as absolute values means ± SE. A P value < 0.05 was considered significant in all analyses.

RESULTS

The studies were well tolerated, and there were no adverse events. The mean score for autonomic nerve function was 0.73 (range: 0–2), i.e., no subject had evidence of autonomic nerve dysfunction. One subject exhibited postprandial hypotension (i.e., a fall in systolic blood pressure > 20 mmHg sustained for at least 30 min) during G2.

Systolic and Diastolic Blood Pressure and Heart Rate

There was no difference in baseline ($t = 0$ min) blood pressure or heart rate among the 4 days (saline vs. G1 vs. G2 vs. G3, respectively): systolic blood pressure (122 ± 5 mmHg vs. 118 ± 4 mmHg vs. 125 ± 5 mmHg vs. 122 ± 5 mmHg; $P = 0.16$); diastolic blood pressure (70 ± 2 mmHg vs. 67 ± 2 mmHg vs. 68 ± 2 mmHg vs. 69 ± 2 mmHg; $P = 0.17$); and heart rate (57 ± 2 beats/min vs. 61 ± 3 beats/min vs. 57 ± 2 beats/min vs. 59 ± 3 beats/min; $P = 0.09$).

Between $t = 0$ and 60 min, there was a fall in systolic blood pressure during G2 ($P < 0.001$) and G3 ($P = 0.003$) but not during saline ($P = 0.25$) or G1 ($P = 0.74$). The maximum falls in systolic blood pressure from baseline during G2 (15 ± 2 mmHg) and G3 (12 ± 2 mmHg) were not different ($P = 0.18$). There was a treatment effect ($P = 0.001$) for the AUC ($t = 0–60$ min) for the change in systolic blood pressure, so that systolic blood pressure was less during G2 ($P = 0.007$) and G3 ($P = 0.002$) but not during G1 ($P = 0.17$) compared with saline (Fig. 1*A*). Similarly, the fall in systolic blood pressure was greater during G2 ($P = 0.03$) and G3 ($P = 0.005$) compared with G1, but there was no significant difference between G2 and G3 ($P = 0.51$). At $t = 120$ min, systolic blood pressure was not different from baseline after G2 (122 ± 4 mmHg; $P = 0.94$) but was greater after saline (127 ± 6

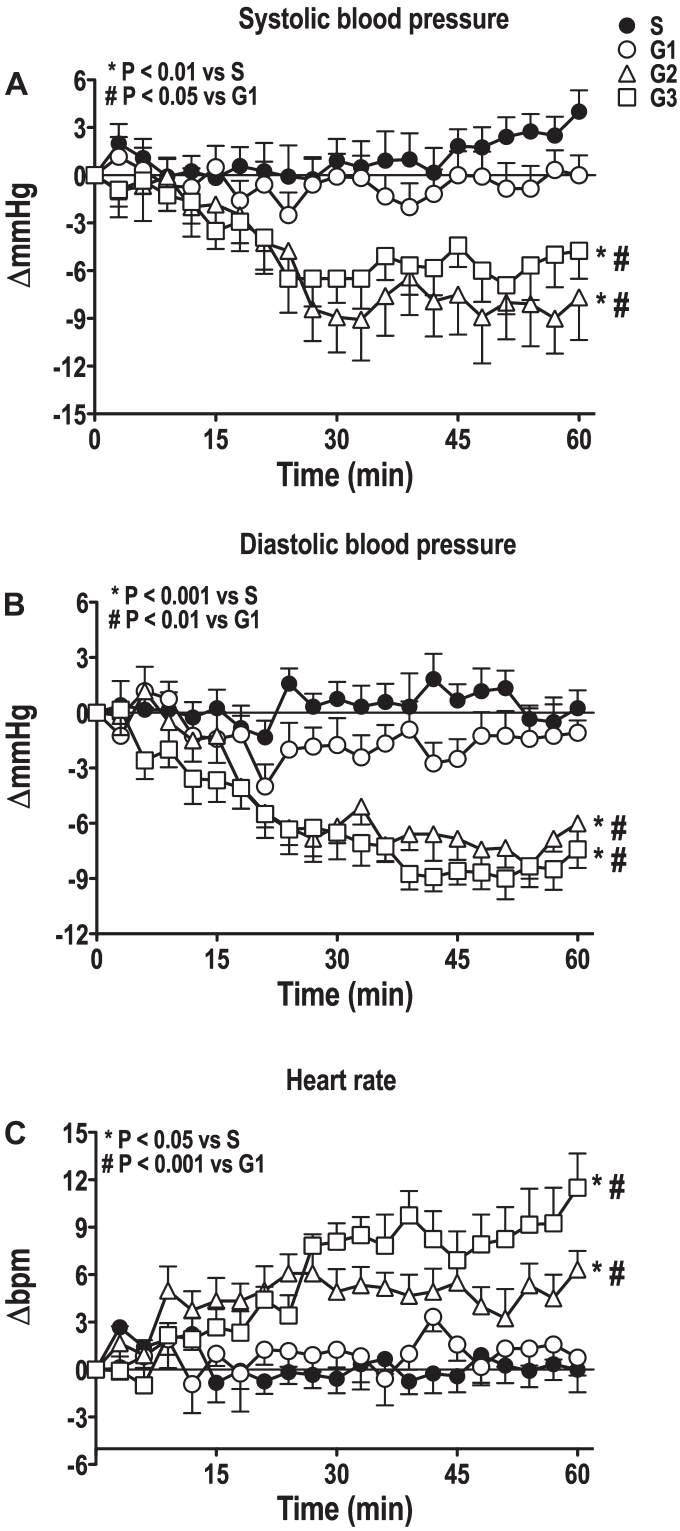

Fig. 1. Change in systolic blood pressure (*A*), diastolic blood pressure (*B*), and heart rate (*C*) from baseline in response to intraduodenal (ID) saline (S; ●) and glucose at a rate of either 1 kcal/min (G1; ○), 2 kcal/min (G2; △), or 3 kcal/min (G3; □) in healthy older subjects. Data are means ± SE ($n = 12$). Systolic blood pressure treatment effect: *$P < 0.01$ saline compared with G2 and saline compared with G3, #$P < 0.05$ G1 compared with G2 and G1 compared with G3; diastolic blood pressure treatment effect: *$P < 0.001$ saline compared with G2 and saline compared with G3, #$P < 0.01$ G1 compared with G2 and G1 compared with G3; heart rate: *$P < 0.05$ saline compared with G2 and saline compared with G3, #$P < 0.001$ G1 compared with G2 and G1 compared with G3.

mmHg; $P = 0.04$) and G1 (126 ± 5 mmHg; $P = 0.004$) and tended to be less following G3 (118 ± 4 mmHg; $P = 0.09$).

Between $t = 0$ and 60, there was a fall in diastolic blood pressure during G2 ($P < 0.001$) and G3 ($P < 0.001$) but not during saline ($P = 0.79$) or G1 ($P = 0.18$). The maximum falls in diastolic blood pressure from baseline were during G2 and G3 (11 ± 1 mmHg and 12 ± 1 mmHg, respectively) with no difference between the two ($P = 0.46$). There was a treatment effect ($P < 0.001$) for the AUC ($t = 0–60$ min) for the change in diastolic blood pressure so that diastolic blood pressure was less during both G2 ($P < 0.001$) and G3 ($P < 0.001$) and tended to be less during G1 ($P = 0.06$) compared with saline (Fig. 1*B*). Similarly, the fall in diastolic blood pressure was greater during G2 ($P = 0.002$) and G3 ($P < 0.001$) compared with G1, while there was no difference between G2 and G3 ($P = 0.21$). At $t = 120$ min, diastolic blood pressure was not different from baseline after saline (70 ± 3 mmHg; $P = 0.95$) and G3 (68 ± 3 mmHg; $P = 0.22$) but was greater after G1 (69 ± 2 mmHg; $P < 0.05$) and G2 (71 ± 2 mmHg; $P = 0.02$).

Between $t = 0$ and 60 there was a rise in heart rate during G2 ($P = 0.03$) and G3 ($P < 0.001$) but not during saline ($P = 0.28$) or G1 ($P = 0.45$). The maximum rise in heart rate from baseline was slightly greater ($P = 0.05$) after G3 (15 ± 4 beats/min) compared with G2 (11 ± 3 beats/min). There was a treatment effect ($P = 0.001$) for the AUC ($t = 0–60$ min) for the change in heart rate, so that heart rate was greater during G2 ($P = 0.01$) and G3 ($P = 0.01$) but not during G1 ($P = 0.67$) compared with saline (Fig. 1*C*). Heart rate was greater during G2 ($P < 0.001$) and G3 ($P < 0.001$) compared with G1 with no difference between G3 and G2 ($P = 0.17$). At $t = 120$ min, heart rate was not different from baseline after saline (60 ± 2 beats/min; $P = 0.16$), G1 (60 ± 3 beats/min; $P = 0.92$), and G2 (58 ± 2 beats/min; $P = 0.46$) but was higher following G3 (64 ± 2 beats/min; $P = 0.02$).

SMA Blood Flow

There was no difference ($P = 0.73$) in baseline ($t = -2$ min) SMA blood flow among the 4 days (saline vs. G1 vs. G2 vs. G3: 916 ± 50 ml/min vs. 977 ± 74 ml/min vs. 927 ± 69 ml/min vs. 965 ± 55 ml/min, respectively; $P = 0.73$) (Fig. 2).

Between $t = -2$ and 60, there was a rise in SMA blood flow during G1 ($P = 0.01$), G2 ($P < 0.001$), and G3 ($P < 0.001$) but no overall change during saline ($P = 0.15$). The maximum SMA blood flow during G1 (1,428 ± 107 ml/min) was greater than saline ($P = 0.04$); the maximum SMA flow during G2 (2,144 ± 133 ml/min) was greater than saline ($P < 0.001$) and G1 ($P < 0.001$), and the maximum SMA flow during G3 (2,797 ± 184 ml/min) was greater than saline ($P < 0.001$), G1 ($P < 0.001$), and G2 ($P = 0.001$). There was a treatment effect ($P < 0.001$) for the AUC ($t = -2–60$ min) of SMA blood flow, so that SMA blood flow was greater during G1 compared with saline ($P = 0.04$) during G2 compared with saline ($P < 0.001$) and G1 ($P < 0.001$) and during G3 compared with saline ($P < 0.001$), G1 ($P < 0.001$), and G2 ($P < 0.001$). At $t = 120$ min, SMA blood flow did not differ from baseline after saline (941 ± 60 ml/min; $P = 0.38$), G1 (903 ± 68 ml/min; $P = 0.29$), and G2 (927 ± 69 ml/min; $P = 0.99$) but was greater than baseline following G3 (1,125 ± 87 ml/min; $P = 0.04$).

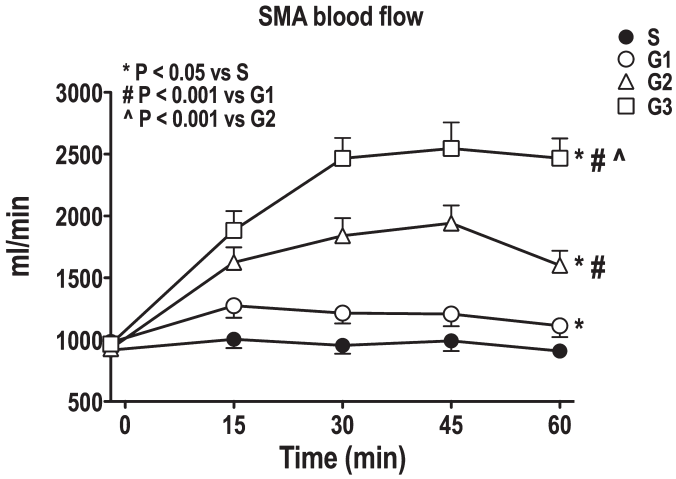

Fig. 2. Effects of intraduodenal saline (●) and glucose at a rate of either 1 cal/min (○), 2 kcal/min (△), or 3 kcal/min (□) on superior mesenteric artery (SMA) blood flow in healthy older subjects. Data are means ± SE ($n = 12$). *$P < 0.05$ saline compared with G1, saline compared G2, and saline compared with G3; #$P < 0.001$ G1 compared with G2 and G1 compared with G3; ^$P < 0.001$ G2 compared with G3.

Blood Glucose, Serum Insulin, and Plasma GLP-1

There was no difference ($P = 0.65$) in baseline ($t = -2$ min) blood glucose among the 4 days (saline vs. G1 vs. G2 vs. G3: 6.2 ± 0.1 mmol/l vs. 6.2 ± 0.2 mmol/l vs. 6.2 ± 0.1 mmol/l vs. 6.0 ± 0.1 mmol/l, respectively; $P = 0.65$). Between $t = -2$ and 120 there was a rise in blood glucose during G1 ($P < 0.001$), G2 ($P < 0.001$), and G3 ($P < 0.001$) but not during saline ($P = 0.22$). Maximum blood glucose during G1 (8.9 ± 0.3 mmol/l) was greater than saline ($P < 0.001$); maximum blood glucose during G2 (11.1 ± 0.3 mmol/l) was greater than saline ($P < 0.001$) and G1 ($P < 0.001$), and maximum blood glucose during G3 (12.2 ± 0.5 mmol/l) was greater than saline ($P < 0.001$), G1 ($P = 0.001$), and G2 ($P = 0.02$). There was a treatment effect ($P < 0.001$) for the AUC ($t = -2–120$ min) for the change in blood glucose, so that the rise in blood glucose during G1, G2, and G3 was greater compared with saline ($P \leq 0.001$, for all). Similarly, the rises in blood glucose during G2 ($P < 0.001$) and G3 ($P = 0.005$) were greater compared with G1, while there was no difference between G2 and G3 ($P = 0.32$). At $t = 120$ min, blood glucose did not differ from baseline after G1 (6.2 ± 0.2 mmol/l; $P = 0.83$), G2 (6.6 ± 0.3 mmol/l; $P = 0.30$), and G3 (5.6 ± 0.8 mmol/l; $P = 0.56$), but was less following saline (5.9 ± 0.1 mmol/l; $P = 0.01$) (Fig. 3*A*).

There was no difference ($P = 0.31$) in baseline ($t = -2$ min) serum insulin among the 4 days (saline vs. G1 vs. G2 vs. G3: 7.3 ± 0.8 mU/l vs. 6.9 ± 1.3 mU/l vs. 6.9 ± 0.9 mU/l vs. 6.1 ± 0.6 mU/l, respectively; $P = 0.31$). Between $t = -2$ and 120 min, there was an increase in serum insulin during G1 ($P < 0.001$), G2 ($P < 0.001$), and G3 ($P < 0.001$) but no change during saline ($P = 0.40$). Maximum serum insulin during G1 (21.0 ± 2.8 mU/l) was greater than saline ($P = 0.001$); maximum serum insulin during G2 (68.4 ± 11.7 mU/l) was greater than saline ($P < 0.001$) and G1 ($P < 0.001$); and maximum serum insulin during G3 (155.8 ± 25.9 mU/l) was greater than saline ($P < 0.001$), G1 ($P < 0.001$), and G2 ($P = 0.001$). There was a treatment effect ($P < 0.001$) for the AUC

(t = −2–120 min) for the change in serum insulin, so that the increase in serum insulin during G1, G2, and G3 was greater compared with saline ($P \leq 0.001$, for all). Similarly, the increase in serum insulin during G2 and G3 was greater compared with G1 ($P < 0.001$, for both) and greater during G3 compared with G2 ($P < 0.001$). At t = 120 min, serum insulin did not differ from baseline following G1 (8.1 ± 1.3 mU/l; P = 0.17), was less than baseline following saline (5.7 ± 0.7 mU/l; P = 0.005), and greater following G2 (10.8 ± 1.5 mU/l; P = 0.007) and G3 (18.1 ± 2.7mU/l; P = 0.001) (Fig. 3*B*).

There was no difference (P = 0.31) in baseline (t = −2 min) plasma GLP-1 among the 4 days (saline vs. G1 vs. G2 vs. G3: 14.4 ± 1.2 pmol/l vs. 14.5 ± 1.4 pmol/l vs. 15.8 ± 1.7 pmol/l vs. 15.9 ± 1.8 pmol/l, respectively; P = 0.23). Between t = −2 and 120 min, there was an increase in plasma GLP-1 during G1 ($P < 0.001$), G2 ($P < 0.001$), and G3 ($P < 0.001$) but no change during saline (P = 0.17). Maximum plasma GLP-1 during G1 (19.4 ± 2.1 pmol/l) was not greater than saline (P = 0.58); maximum serum GLP-1 during G2 (28.3 ± 3.4 pmol/l) was greater than saline (P = 0.004) and G1 (P = 0.01), and maximum plasma GLP-1 during G3 (62.0 ± 5.7 pmol/l) was greater than saline ($P < 0.001$), G1 ($P < 0.001$), and G2 ($P < 0.001$). There was a significant treatment effect ($P < 0.001$) for the AUC (t = −2–120 min) for the change in plasma GLP-1, so that the rise in serum GLP-1 was greater during G2 (P = 0.02) and G3 ($P \leq 0.001$) and tended to be greater during G1 (0.07) compared with saline. Similarly, the increase in plasma GLP-1 during G2 (P = 0.005) and G3 ($P \leq 0.001$) was greater compared with G1, and during G3 compared with G2 ($P \leq 0.001$). At t = 120 min, plasma GLP-1 did not differ from baseline following saline (15.5 ± 1.6 pmol/l; P = 0.21), G1 (13.7 ± 1.7 pmol/l; P = 0.63), G2 (12.7 ± 1.4 pmol/l; P = 0.13), or G3 (20.0 ± 2.2 pmol/l; P = 0.13) (Fig. 3*C*).

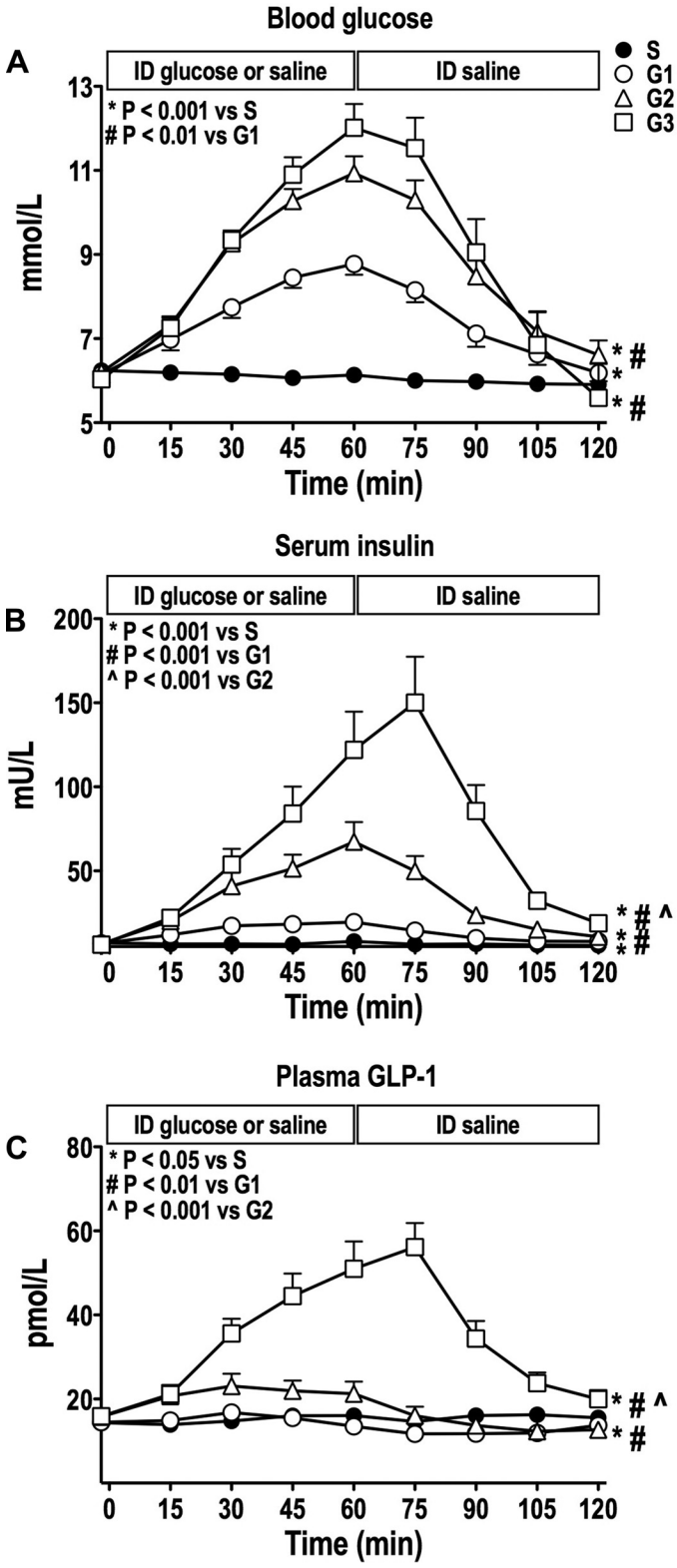

Fig. 3. Effects of intraduodenal saline (●) and glucose at a rate of either 1 cal/min (○), 2 kcal/min (△), or 3 kcal/min (□) on blood glucose concentration (*A*), serum insulin concentration (*B*), and plasma glucagon-like peptide-1 (GLP-1) concentration in healthy older subjects (*C*). Data are means ± SE (n = 12). Blood glucose: *$P < 0.001$ saline compared with G1, saline compared with G2 and saline compared with G3, #$P < 0.01$ G1 compared with G2 and G1 compared with G3; serum insulin: *$P < 0.001$ saline compared with G1, saline compared with G2 and saline compared with G3, #$P < 0.001$ G1 compared with G2 and G1 compared with G3, ^$P < 0.001$ G2 compared with G3; plasma GLP-1: *$P < 0.05$ saline compared with G1, saline compared with G2 and saline compared with G3, #$P < 0.01$ G1 compared with G2 and G1 compared with G3, ^$P < 0.001$ G2 compared with G3.

Plasma Noradrenaline Concentrations

Plasma noradrenaline levels were available in 10 of the 12 subjects. Baseline (t = −2 min) plasma noradrenaline levels were slightly different among the 4 days (saline vs. G1 vs. G2 vs. G3: 1.4 ± 0.2 nmol/l vs. 1.3 ± 0.3 nmol/l vs. 2.1 ± 0.3 nmol/l vs. 1.3 ± 0.2 nmol/l, respectively; P = 0.013) so that baseline G2 was greater than both G1 (P = 0.05) and G3 (P = 0.03). Between t = −2 and 60, there was a significant increase in plasma noradrenaline only after G3 (P = 0.02), which then fell (P = 0.03) between t = 60 and 120 min, so that there was no difference between t = −2 and t = 120 min (P = 0.12) (Fig. 4).

DISCUSSION

This study establishes that in healthy older subjects intraduodenal glucose infusion at a rate of 1 kcal/min has no effect on blood pressure, whereas there is no difference in the hypoten-

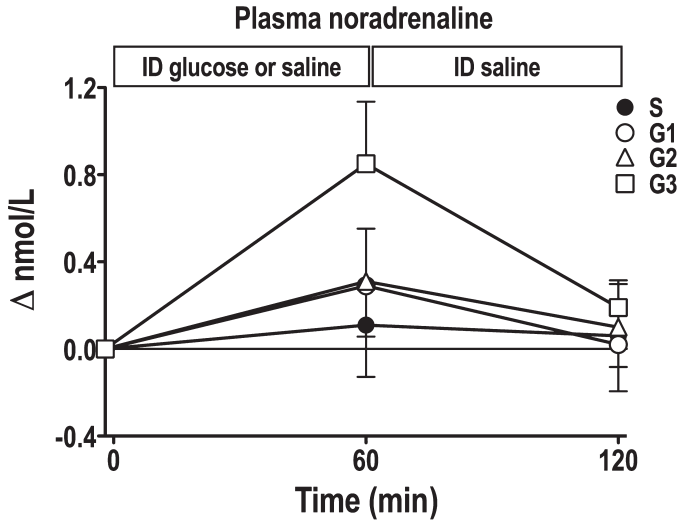

Fig. 4. Effects of intraduodenal saline (●) and glucose at a rate of either 1 cal/min (○), 2 kcal/min (△), or 3 kcal/min (□) on plasma noradrenaline levels in healthy older subjects. $*P < 0.05$: $t = 60$ min compared with $t = -2$ and $t = 120$ min for G3 only.

sive responses to infusions of 2 and 3 kcal/min. In contrast, the 1 kcal/min glucose infusion results in a slight increase in SMA blood flow, and the stimulation of SMA blood flow by the 3 kcal/min infusion is greater than that induced by the 2 kcal/min infusion. The GLP-1 responses are consistent with those observed in healthy young subjects (41) and patients with diet-controlled type 2 diabetes (32) so that there was substantially greater stimulation of GLP-1 by the 3 kcal/min infusion, which is likely to account for the greater insulinemic response and potentially the lack of difference in the blood pressure responses to the 2 and 3 kcal/min infusions. The latter may also reflect the significant plasma noradrenaline response to the 3 kcal/min infusion, but not the two other duodenal glucose loads.

In healthy older subjects, the fall in systolic blood pressure and rise in heart rate induced by glucose are known to be load dependent (27, 38) rather than concentration dependent (10), so that the hypotensive response to intraduodenal glucose infusion at a rate of 3 kcal/min is much greater than to 1 kcal/min (38), whereas there is no difference in the response to 3 kcal/min infusions of varying osmolarity (10). We have now shown that intraduodenal glucose at a rate of 1 kcal/min has no effect on blood pressure in this group i.e., we would anticipate that if gastric emptying occurred at a rate of 1 kcal/min or less, there would be no fall in blood pressure, particularly as gastric distension attenuates the postprandial fall in blood pressure (13, 43, 46, 49). That the falls in blood pressure and rise in heart rate induced by 2 and 3 kcal/min intraduodenal glucose were comparable, indicates that the response to the 2 kcal/min infusion was close to maximal and establishes that the dose response curve is narrow within the physiological range for gastric emptying (3).

Previous studies by our group have shown that SMA flow increases during intraduodenal nutrient infusion (11, 14, 49). In healthy older subjects, when glucose is infused intraduodenally at a rate of 3 kcal/min, there is a prompt rise in SMA flow (11, 49). Similarly, intraduodenal infusion of sucrose at a rate of 3 kcal/min is associated with a fall in blood pressure and an increase in SMA flow, which are related (15). The present study establishes that intraduodenal glucose infused at rates of 1, 2, and 3 kcal/min increases SMA blood flow from ~15 min, and that in contrast to blood pressure there is a modest response to the 1 kcal/min infusion and the response to the 3 kcal/min infusion is substantially greater than to 2 kcal/min so that the maximum response remains uncertain. It is not surprising that the infusion of intraduodenal saline did not affect SMA blood flow as nutrients are required to elicit this response (11, 49).

The effects of different intraduodenal glucose loads on blood glucose, serum insulin and plasma GLP-1 concentrations have been evaluated in healthy young subjects (41) and patients with type 2 diabetes (32). In these groups, in response to infusion of glucose at 1, 2, or 4 kcal/min for 120 min, there is little if any difference between the glycemic responses to 2 and 4 kcal/min glucose, which is attributable to the substantially greater GLP-1 and insulin responses to the latter (32, 41). Hence, the current observations in healthy older subjects illustrate that there is a rise in blood glucose following 1, 2, and 3 kcal/min intraduodenal glucose infusion, the responses to 2 and 3 kcal/min are comparable, and the insulin and GLP-1 responses to the latter are much greater, is not surprising. The implication is that if gastric emptying of carbohydrate does not exceed 1 kcal/min, there will only be a modest glycemic response and that the incretin (GLP-1) effect is of greater relevance when rates of small intestinal glucose entry are higher.

Studies in humans (5) and animals (1) suggest that acute, administration of exogenous GLP-1 increases blood pressure. The α-glucosidase inhibitor acarbose, which is used frequently in the management of type 2 diabetes, appears to be of benefit in the management of postprandial hypotension (9, 24, 45). We have reported that acarbose slows gastric emptying and attenuates the fall in blood pressure induced by oral (9) and intraduodenal (15) sucrose in healthy older subjects and that the former effect is temporally associated with a marked stimulation of endogenous GLP-1, supporting a potential role for GLP-1 in the management of postprandial hypotension. If this proves to be the case, it is possible that DDP-4 inhibitors, which increase plasma levels of active GLP-1, and GLP-1 agonists, such as exenatide and liraglutide, may be therapeutically useful (35). Studies using GLP-1 agonists (exenatide and liraglutide) in the management of type 2 diabetes suggest that long-term use may be associated with a fall in blood pressure (2), but the latter was not measured postprandially. We would speculate that the increased GLP-1 response for the 3 kcal/min compared with the 2 kcal/min duodenal glucose infusion accounts for the absence of differential effects on blood pressure. While insulin has vasodilatory properties (21), both glucose and insulin are unlikely to play a major role in postprandial hypotension given that intravenous glucose has little, if any, effect on blood pressure (20, 21) and postprandial hypotension occurs in type 1 patients who are insulin-deficient (22). In the present study, the insulinemic response to the 3 kcal/min infusion was much higher than to 2 kcal/min, but there was no difference in the hypotensive response.

Oral glucose is known to increase plasma noradrenaline in humans and that this effect is more pronounced in the elderly (29, 52). In contrast, in patients with postprandial hypotension, there is a marked attenuation or absence of the postprandial rise in plasma noradrenaline (29, 34), indicative of failure of the sympathetic nervous system to compensate to maintain blood

pressure after a meal. The rise in plasma noradrenaline observed in the elderly is not evident with intravenous insulin or glucose (36), indicating that this effect is mediated by the gastrointestinal tract. In the present study, we observed a rise in noradrenaline only after intraduodenal infusion at 3 kcal/min, establishing that the rise in noradrenaline is dependent on the rate of nutrient delivery. In a previous study of healthy young subjects, two different oral glucose loads (0.5 and 1.0 g/kg of body wt) failed to increase plasma noradrenaline (42). Given our observations, this is not surprising because in healthy subjects, gastric emptying is tightly regulated between 1 and 3 kcal/min (3); hence, different carbohydrate loads empty from the stomach in comparable rates and in the majority of subjects this rate is < 3 kcal/min. We speculate that the noradrenaline response to the 3 kcal/min, but not 2 kcal/min, infusion observed in our study, may contribute to the observed lack of difference in blood pressure responses.

The mechanisms responsible for the effects of glucose on blood pressure are uncertain. While we did not include a mannose control, other carbohydrates, that do not activate glucose sensors, such as fructose (51) and xylose (50) have minimal, if any, effect on blood pressure, suggesting that the effects are relatively specific to glucose. The effects of enteral glucose on blood pressure may potentially reflect the neurotransmitter 5-hydroxytryptamine (5-HT) (54). However, in healthy older individuals, the 5-HT3 antagonist granisetron in a dose of 10 μg/kg, had no effect on the blood pressure and heart rate response to intraduodenal glucose (12). A role for intestinal taste receptors, which have been linked to GLP-1 release (19, 53), warrants evaluation as is the case for the portal TRPv4 channel (35).

In evaluating our observations, it should be recognized that we studied healthy older subjects and assessed the responses to intraduodenal, rather than intragastric, glucose loads. This approach bypassed the potential effects of gastric distension. Preliminary studies suggest that patients with postprandial hypotension may be more sensitive to small intestinal nutrients i.e., the hypotensive response to a given intraduodenal glucose load is substantially greater (48), and it will be important to define thresholds and load responses in this group given the therapeutic implications. It would also be of interest to know whether intraduodenal water (in the absence of gastric distension) has a significant effect on blood pressure or SMA flow compared with intraduodenal saline.

In summary, in healthy older subjects, intraduodenal glucose infusion at a rate of 1 kcal/min has no effect on blood pressure, whereas infusions at 2 and 3 kcal/min induce comparable, and substantial, falls. The implication is that at a rate of gastric emptying or small intestinal nutrient delivery of ~1 kcal/min, there is likely to be minimal postprandial fall in blood pressure.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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