Effects of variations in duodenal glucose load on blood pressure, heart rate, superior mesenteric artery blood flow and plasma noradrenaline in healthy young and older subjects

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ABSTRACT

PPH (postprandial hypotension), leading to increased morbidity and mortality, is an important clinical problem, particularly in the elderly and individuals with autonomic dysfunction. The magnitude of the postprandial fall in BP (blood pressure) appears to be dependent on the rate of nutrient entry into the small intestine and may be related to changes in splanchnic blood flow and sympathetic nerve activity. We aimed at determining the comparative effects of different ID (intraduodenal) glucose loads on BP, HR (heart rate), SMA (superior mesenteric artery) flow and vascular conductance and plasma NA (noradrenaline) in ‘young’ and ‘older’ subjects. A total of 12 ‘young’ (six male and six female; age, 22.2 ± 2.3 years) and 12 ‘older’ (six male and six female; age, 68.7 ± 1.0 years) subjects, the latter who have been studied previously [Vanis, Gentilcore, Rayner, Wishart, Horowitz, Feinle-Bisset and Jones (2011) Am. J. Physiol. Regul. Integr. Comp. Physiol., 300, R1524–R1531], had measurements of BP, HR, SMA flow and plasma NA before, and during, ID infusions of glucose at 1, 2 or 3 kcal/min (‘G1’, ‘G2’ and ‘G3’) (where 1 kcal ≈ 4.184 J), or ‘S’ (saline) for 60 min. In ‘young’ subjects, there was no change in BP during any of the four infusions. In contrast, in ‘older’ subjects, SBP (systolic BP) fell during ‘G2’, and ‘G3’ ($P < 0.005$ for both), but not during ‘S’ or ‘G1’. In ‘young’ and ‘older’ subjects HR increased during ‘G2’ ($P < 0.05$) and ‘G3’ ($P < 0.001$), a response that was greater ($P < 0.05$) in the young, but not during ‘S’ or ‘G1’. The rise in SMA flow and vascular conductance in response to ID glucose were load-dependent in both ‘young’ and ‘older’ subjects ($P < 0.001$ for all), with no difference between them. Plasma NA rose in response to ‘G2’ and ‘G3’ ($P < 0.05$) in the young, but in ‘G3’ ($P < 0.05$) only in the ‘older’ subjects, with no difference between them. Hence, in response to small intestinal glucose infusions at 1, 2 and 3 kcal/min, ‘older’, but not ‘young’, subjects exhibit a comparable fall in BP in response to the two higher glucose loads, which may reflect an inadequate, compensatory, rise in HR, in the ‘older’ subjects, but not a greater increase in SMA conductance.

INTRODUCTION

PPH (postprandial hypotension), defined as a fall in SBP [systolic BP (blood pressure)] ≥ 20 mmHg within 2 h of a meal, is an important clinical problem, particularly in the elderly and individuals with autonomic dysfunction [1,2]. Current therapies are suboptimal [1].

Key words: aging, autonomic dysfunction, blood pressure, heart rate, postprandial hypotension.

Abbreviations: AUC, area under the curve; BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; ID, intraduodenal; NA, noradrenaline; PPH, postprandial hypotension; SV, stroke volume; SMA, superior mesenteric artery; SBP, systolic blood pressure; TPR, total peripheral resistance; TMPD, transmucosal potential difference.

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Despite its high prevalence, the pathophysiological mechanisms underlying PPH are poorly understood. Gastric distension [3,4], the rate of small intestinal nutrient delivery [5,6], splanchnic blood flow [1] and neural and hormonal mechanisms [2] have all been implicated. Carbohydrates, such as glucose, have a highly depressive effect on BP when administered orally [7], or intraduodenally [8], and the magnitude of the fall in BP induced by oral glucose in healthy ‘older’ subjects and patients with Type 2 diabetes is greater when gastric emptying is relatively faster [5]. In contrast, gastric distension attenuates the fall in BP [9]. Gastric emptying of glucose is regulated closely to be in the range of 1–4 kcal/min (where 1 kcal of glucose is regulated closely to be in the range of 19.1–24.2 kg/m²), recruited by advertisement, were studied. All subjects were non-smokers and none had a history of cardiovascular, hepatic, renal or gastrointestinal disease, epilepsy, diabetes or chronic alcohol abuse. No subject was pregnant, breast feeding or taking medication known to influence gastrointestinal function or BP. Four of the subjects had participated previously in research studies involving gastrointestinal intubation.

Results were compared with those obtained in 12 healthy ‘older’ subjects [six female and six male; mean age, 22.2 ± 2.3 years (range, 19–26 years), mean BMI (body mass index), 21.8 ± 2.2 kg/m² (range, 19.1–24.2 kg/m²), recruited by advertisement, were studied. All subjects were non-smokers and none had a history of cardiovascular, hepatic, renal or gastrointestinal disease, epilepsy, diabetes or chronic alcohol abuse. No subject was pregnant, breast feeding or taking medication known to influence gastrointestinal function or BP. Four of the subjects had participated previously in research studies involving gastrointestinal intubation.

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Subjects
A total of 12 healthy ‘young’ subjects (six female and six male; mean age, 22.2 ± 2.3 years (range, 19–26 years), mean BMI (body mass index), 21.8 ± 2.2 kg/m² (range, 19.1–24.2 kg/m²), recruited by advertisement, were studied. All subjects were non-smokers and none had a history of cardiovascular, hepatic, renal or gastrointestinal disease, epilepsy, diabetes or chronic alcohol abuse. No subject was pregnant, breast feeding or taking medication known to influence gastrointestinal function or BP. Four of the subjects had participated previously in research studies involving gastrointestinal intubation.

Changes in sympathetic nerve activity may also play a role in determining whether or not PPH occurs [13,16]. In both ‘young’ and ‘older’ subjects, plasma NA (noradrenaline) levels were shown to rise after a meal, but this response was reported to be markedly attenuated in patients with PPH [16,17]. Gastric distension is known to increase muscle nerve sympathetic nerve activity – the so-called ‘gastrovascular reflex’ [3], and this may be impaired in the elderly [14]. In healthy ‘older’ subjects, an ID glucose load of 3 kcal/min was shown to increase plasma NA [12], whereas in healthy ‘young’ subjects, there is no difference in the plasma NA response to oral glucose at two loads of 0.5 and 1.0 g/kg of body weight [18], which would be expected to empty from the stomach at comparable rates [10]. However, there is neither information about the effects of the ID glucose load on the plasma NA response in healthy ‘young’ subjects nor the relative effects in ‘young’ and ‘older’ subjects.

The primary aims of this study were to determine the effects of the small intestinal glucose load on BP, HR, SMA flow and conductance and plasma NA in healthy ‘young’ subjects. Secondary objectives were to compare these responses with those reported previously in healthy ‘older’ subjects [12]. We hypothesized that ID glucose would: (i) have minimal effect on BP in healthy ‘young’ subjects, irrespective of the glucose load, (ii) increase HR, SMA flow and NA in a load-dependent manner and (iii) lead to greater increase in HR in ‘young’ than in ‘older’ subjects.

Part of this work was presented at the Sixth International Academy on Nutrition and Ageing, held in Bologna on 14 April 2011, and subsequently published in abstract form [18a].

MATERIALS AND METHODS

Subjects
A total of 12 healthy ‘young’ subjects (six female and six male; mean age, 22.2 ± 2.3 years (range, 19–26 years), mean BMI (body mass index), 21.8 ± 2.2 kg/m² (range, 19.1–24.2 kg/m²), recruited by advertisement, were studied. All subjects were non-smokers and none had a history of cardiovascular, hepatic, renal or gastrointestinal disease, epilepsy, diabetes or chronic alcohol abuse. No subject was pregnant, breast feeding or taking medication known to influence gastrointestinal function or BP. Four of the subjects had participated previously in research studies involving gastrointestinal intubation.

Protocol
In each subject measurements of BP, HR, SMA flow and plasma NA were obtained on four occasions, with each study day separated by a minimum of 1 week. The order of treatments on the 4 study days was randomized and double-blind, being determined by an independent investigator immediately after the enrolment of the subject; this investigator prepared
Potential difference) between the antrum (continuous measurement of the TMPD (transmucosal potential difference)) and the pylorus, and were perfused continuously with 0.9 % 'S'. Correct positioning of the catheter was maintained by a silicone rubber nasoduodenal catheter (outer diameter ∼ 4 mm) (Dentsleeve International, Mui Scientific) was inserted into the stomach via an anaesthetized nostril and allowed to pass into the duodenum by peristalsis [6]. The catheter design was such that, when correctly positioned, an infusion channel (internal diameter ∼ 1 mm) was located 10 cm distal to the pylorus. Two other channels were located in the antrum (2.5 cm proximal to the pylorus) and in the duodenum (2.5 cm distal to the pylorus) and were perfused continuously with 0.9 % 'S'. Correct positioning of the catheter was maintained by continuous measurement of the TMPD (transmucosal potential difference) between the antral (∼ 40 mV), and the duodenal (0 mV), channels [6]. For the purpose of measuring TMPD, a 0.9 % 'S'-filled reference electrode (20-gauge intravenous cannula) was inserted subcutaneously into the subject’s forearm [6]. The subject was placed in a recumbent position, at an incline of ∼ 20°. After the catheter was positioned correctly, an intravenous cannula (20 gauge) was inserted into a left antecubital vein for blood sampling and an automated BP cuff (DINAMAP ProCare 100; GE Medical Systems) placed around the right arm [6]. The subject then remained in the recumbent position and was allowed to ‘rest’ for approximately 30 min.

Commencing at t = 0 min, the subject received an ID infusion of glucose at either 1, 2 or 3 kcal/min (‘G1’, ‘G2’, ‘G3’, respectively) or 0.9 % ‘S’ for 60 min (i.e. t = 0–60 min), followed by ID 0.9 % ‘S’ for 60 min (i.e. t = 0–60 min), followed by ID 0.9 % ‘S’ for 60 min (i.e. t = 0–60 min). All infusions were performed using an automated volumetric infusion pump (Gemini PC-1; IMED). At t = 120 min the nasoduodenal catheter and both cannulae were removed and the subject offered a light meal prior to them leaving the laboratory.

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

### Measurements

**BP and HR**

BP and HR were measured using an automated oscillometric BP monitor, every 3 min for 30 min prior to the commencement of the ID infusion, i.e. t = −30 to t = 0 min, and then every 3 min between t = 0 and 120 min [6]. ‘Baseline’ BP and HR were calculated as an average of the preceding three measurements taken immediately prior to the commencement of the ID infusion, i.e. t = −9, t = −6 and t = −3 min. PPH was defined as a fall in SBP ≥20 mmHg [1].

### SMA blood flow and vascular conductance

SMA flow was measured using duplex ultrasonography (i.e. B-mode and pulsed wave Doppler simultaneously), using a Logiq™ 9 ultrasound system (GE Healthcare Technologies) [12]. Scanning was conducted with a 3.5C broad-spectrum 2.5–4 MHz convex linear array transducer immediately before (i.e. t = −2 min) the commencement of the infusion, and then every 15 min from t = 0 to 120 min. Blood flow (ml/min) was calculated automatically using the equation: blood flow = π × r² × TAMV × 60, where r = the radius of the SMA and TAMV is the time-averaged mean velocity [8,19]. SMA vascular conductance was calculated as SMA blood flow at a given time point divided by MAP (mean arterial pressure = DBP (diastolic blood pressure) + 1/3 (SBP − DBP)) [15,20].

### Plasma NA

Venous blood samples (∼ 18.5 ml) were obtained immediately prior to infusion (i.e. at t = −2 min) and then at 60 and 120 min for measurement of plasma NA using HPLC coupled with electrochemical detection (FCD; Waters) [21].

### Statistical analysis

BP and HR data were analysed and presented as changes from baseline between t = 0 and 60 min, SMA flow was analysed and presented as absolute values between t = −2 and 60 min and plasma NA concentrations were analysed and presented as changes from baseline between t = −2 and 120 min. The maximum fall and rise in SBP and DBP, and HR were defined as the greatest change from baseline in each subject at any given time point for each treatment. Baseline values and the maximum rise, or fall, in the parameters were analysed using one-way repeated measures ANOVA. AUCs (areas under the curve) were calculated using the trapezoid rule, and analysed by one-way ANOVA, to evaluate effects of ‘treatment’ between t = 0 and 60 min for SBP, DBP and HR and between t = −2 and 60 min for SMA flow. A paired Student’s t test was used to compare the differences between mean baseline and AUC values in the ‘young’ and ‘older’ subjects, as well as the changes in plasma NA from baseline. On the basis of previous data [12], a sample size of 12 subjects was calculated to be required to detect a difference between the study days in the fall in SBP of 5 mmHg with 80% power to demonstrate P < 0.05. All analyses were performed using SPSS 17.0.0. Results are means ± S.E.M. P < 0.05 was considered significant in all analyses.

### RESULTS

The treatments and test procedures were well tolerated and there were no adverse events. PPH was not evident...
Table 1  Baseline variables (SBP, DBP, HR, SMA flow, SMA vascular conductance and plasma NA) on 4 study days in 'young' and 'older' subjects

Results are means ± S.E.M. (n = 12 'young' and n = 12 'older' subjects). Values were obtained immediately before ID glucose at rates of 1 kcal/min ('G1'), 2 kcal/min ('G2') and 3 kcal/min ('G3') or saline ('S').

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young subjects</th>
<th>Older subjects</th>
<th>P</th>
<th>P (young compared with older)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>'S'</td>
<td>'G1'</td>
<td>'G2'</td>
<td>'G3'</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>107 ± 3</td>
<td>108 ± 4</td>
<td>108 ± 3</td>
<td>107 ± 3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>60 ± 1</td>
<td>61 ± 1</td>
<td>61 ± 1</td>
<td>61 ± 1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>59 ± 2</td>
<td>60 ± 2</td>
<td>63 ± 3</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>SMA (ml/min)</td>
<td>931 ± 59</td>
<td>931 ± 57</td>
<td>980 ± 62</td>
<td>1002 ± 111</td>
</tr>
<tr>
<td>SMA conductance (ml/mmHg per min)</td>
<td>12.4 ± 0.9</td>
<td>12.1 ± 0.8</td>
<td>12.9 ± 0.8</td>
<td>13.1 ± 1.5</td>
</tr>
<tr>
<td>NA (mmol/l)</td>
<td>1.7 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
</tbody>
</table>

In the 'older' subjects, as reported [12], there was no difference in baseline (i.e., t = 0 min) BP or HR between the four treatments (Table 1) and between t = 0 and 60 min there were falls in SBP during 'G2' (P < 0.001) and 'G3' (P < 0.005), but not 'S' (P = 0.25) or 'G1' (P = 0.74). The maximum falls in SBP from baseline 'G2' (15 ± 2 mmHg) and 'G3' (12 ± 2 mmHg) were not different (P > 0.05) but not during 'S' (P < 0.79) or 'G1' (P < 0.18) (Figure 1E). Similarly, between 'G1' and 'G2' (P < 0.001) there was a fall in DBP during 'G2' and 'G3' (P < 0.001) so that HR was greater during 'G2' and 'G3' (P < 0.001 for both) but not during 'S' (P < 0.79) or 'G1' (P < 0.18) (Figure 1E). Between t = 0 and 60 min there was no change in HR during 'S' (P = 0.04) or 'G1' (P = 0.04), whereas for the AUC during 'G1' (i = 0.04 min) there was an effect of treatment (P < 0.001) for the change in HR during 'G2' and 'G3' (P < 0.001 for both) and between 0 and 60 min there was a fall in DBP during 'S' (P = 0.04) or 'G1' (P = 0.04) and a slight increase in DBP during 'G2' (P < 0.001) and 'G3' (P < 0.001) (Figure 1A). At 120 min the maximum increase in DBP during 'G2' (i = 1 ± 1 mmHg) and 'G3' (i = 1 ± 1 mmHg) was not different from baseline (results not shown).
was greater ($P < 0.05$) during ‘G3’ (15 ± 4 beats/min) compared with ‘G2’ (11 ± 3 beats/min; Figure 1F).

Comparison between ‘young’ and ‘older’ subjects
Baseline SBP ($P < 0.05$) and DBP ($P < 0.001$) were higher in the ‘older’ subjects (Table 1). There was an effect of treatment ($P < 0.05$) for the AUC ($t = 0–60$ min) for the changes in SBP and DBP, so that these were greater (and negative) in the ‘older’, when compared with the ‘young’, subjects. There was an effect of treatment ($P < 0.05$) for the AUC ($t = 0–60$ min) for the change in HR, so that the magnitude of the rise in HR was greater in the ‘young’, compared with the ‘older’, subjects.

SMA blood flow and vascular conductance

‘Young’ subjects
There was no difference in baseline ($t = 0$ min) SMA flow between the four treatments (Table 1). Between $t = 0$ and 60 min there was a rise in SMA flow during ‘G1’, ‘G2’ and ‘G3’ ($P < 0.001$ for all), but no change after ‘S’ ($P = 0.87$). There was an effect of treatment ($P < 0.001$) for the AUC ($t = 0–60$ min) for SMA flow, with a trend for greater SMA flow during ‘G1’ compared with ‘S’ ($P = 0.08$), whereas ‘G2’ and ‘G3’ were higher than ‘G1’ ($P < 0.05$ for both) and ‘S’ ($P < 0.001$ and $P < 0.01$, respectively; Figure 2). At $t = 120$ min SMA flow was slightly higher than baseline ($P < 0.05$) after ‘G3’ (results not shown).

There was also no difference in baseline ($t = 0$ min) SMA conductance between the four treatments (Table 1). Between $t = 0$ and 60 min there was a rise in SMA conductance during ‘G1’, ‘G2’ and ‘G3’ ($P < 0.001$ for all), but no change after ‘S’ ($P = 0.45$). There was an effect of treatment ($P < 0.001$) for the AUC ($t = 0–60$ min) for SMA conductance, with greater SMA conductance during ‘G1’ ($P < 0.05$), ‘G2’ ($P < 0.001$) and ‘G3’ ($P < 0.005$) compared with ‘S’, greater during ‘G3’ and ‘G2’ ($P < 0.05$ for both) compared with ‘G1’, whereas there was no difference between ‘G3’ and ‘G2’ ($P = 0.71$) (Figure 3A).

‘Older’ subjects
As reported [12], there was no difference in baseline ($t = 0$ min) SMA flow between the four treatments (Table 1). Between $t = 0$ and 60 min there was a rise

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**Figure 1** Changes in SBP, DBP and HR from baseline in healthy ‘young’ (A–C) and ‘older’ (D–F) subjects, during ID saline (‘S’) and glucose at rates of 1 kcal/min (‘G1’), 2 kcal/min (G2’) or 3 kcal/min (G3’). Results are means ± S.E.M. (n = 12 ‘young’ and n = 12 ‘older’ subjects). Panels (D–F) were reproduced from Vanis, L., Gentilcore, D., Rayner, C.K., Wishart, J.M., Horowitz, M., Feinle-Bisset, C. and Jones, K.L (2011) Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycaemia and GLP-1 release in healthy older subjects, Am. J. Physiol. Regul. Integr. Comp. Physiol., 300, R1524–R1531 and are used with permission. © (2011) American Physiological Society.
Changes in SMA flow in healthy ‘young’ subjects during ID saline (‘S’) and glucose at rates of 1 kcal/min (‘G1’), 2 kcal/min (‘G2’) or 3 kcal/min (‘G3’)

Results are means ± S.E.M. (n = 12 ‘young’).

There was a rise in SMA flow during ‘G1’ (P < 0.01), ‘G2’ (P < 0.001) and ‘G3’ (P < 0.001), but no change after ‘S’ (P = 0.15). There was an effect of treatment (P < 0.001) for the AUC (t = −2 to 60 min) for SMA flow, i.e., there was no difference in magnitude of change in SMA flow between the ‘young’ and ‘older’ subjects in response to the different treatments. Likewise, there was no difference in baseline SMA vascular conductance between the ‘young’ and ‘older’ subjects, although mean values were higher in the young (P = 0.15) (Table 1). There was no effect of treatment (P = 0.60) on the AUC (t = −2–60 min), for SMA conductance, i.e., there was no difference in the magnitude of the change in SMA vascular conductance between the ‘young’ and ‘older’ subjects in response to the different treatments.

**Comparison between ‘young’ and ‘older’ subjects**

There was no difference in baseline SMA flow between the ‘young’ and ‘older’ subjects (Table 1). There was no effect of treatment (P = 0.92) on the AUC (t = −2–60 min), for SMA flow, i.e., there was no difference in magnitude of change in SMA flow between the ‘young’ and ‘older’ subjects in response to the different treatments. Likewise, there was no difference in baseline SMA vascular conductance between the ‘young’ and ‘older’ subjects, although mean values were higher in the young (P = 0.15) (Table 1). There was no effect of treatment (P = 0.60) on the AUC (t = −2–60 min), for SMA conductance, i.e., there was no difference in the magnitude of the change in SMA vascular conductance between the ‘young’ and ‘older’ subjects in response to the different treatments.

**Plasma NA concentrations**

‘Young’ subjects

There was no difference in baseline (t = −2 min) plasma NA between the four treatments (Table 1). Between t = −2 and 60 min there was a rise in plasma NA during ‘G2’ (P < 0.01) and ‘G3’ (P < 0.05), with no change during ‘S’ (P = 0.33) or ‘G1’ (P = 0.18). There was no difference in the magnitude of the rise in plasma NA at 60 min between ‘G2’ and ‘G3’ (P = 0.46), however, ‘G2’ was greater than ‘S’ (P < 0.05) and there was a trend for ‘G2’ to be greater than ‘G1’ (P = 0.06) (Figure 4). At t = 120 min, plasma NA was not different from baseline (results not shown).

‘Older’ subjects

As reported previously [12], plasma NA levels were available in ten of the 12 subjects. Between t = −2 and 60 min there was a rise in plasma NA during ‘G3’ (P < 0.05), with no significant change during ‘S’ (P = 0.66), ‘G1’ (P = 0.25) or ‘G2’ (P = 0.23).
Comparison between ‘young’ and ‘older’ subjects

There was no difference in baseline plasma NA between the ‘young’ and ‘older’ subjects ($P = 0.51$), nor any difference ($P = 0.73$) in the change of plasma NA at 60 min between the two groups.

**DISCUSSION**

The present study establishes that, in healthy ‘young’ subjects, ID glucose infusion at rates within the physiological range for gastric emptying, has no significant effect on either SBP or DBP, but increases HR, SMA flow and conductance and plasma NA. In the ‘young’, there was no difference in the magnitude of the HR response to the 2 and 3 kcal/min infusions, whereas the increase in SMA flow was load-dependent. These observations are in contrast with those reported previously in healthy ‘older’ subjects, particularly in relation to the substantial fall in BP evident in response to the highest glucose load, in contrast to the 2 and 3 kcal/min infusions in this group [12].

Moreover, our ‘older’ subjects were not ‘very’ old, i.e., mean age $\sim$ 69 years [12]. It should also be recognized that plasma NA concentrations in the forearm venous circulation are primarily an index of sympathetic nerve activity supplying the forearm musculature [23]. That in the older subjects an increase in plasma NA was only evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load.

The observed changes in forearm venous plasma NA may be consistent with this proposal. Our study establishes that, in both healthy ‘young’ and ‘older’ subjects, ID glucose infusion has the capacity to increase plasma NA. Hence, gastric distension is not a prerequisite for this effect. It has been reported that oral glucose increases plasma NA in healthy humans, that the response is greater in the elderly and that fasting plasma NA increases moderately with age [16,22]. It has also been reported that, in patients with PPH, there is no postprandial rise in plasma NA [17,22]. Fasting plasma NA levels have been reported to be moderately increased with age [22]. In the current study, the plasma NA response was only assessed at one time point, i.e. 60 min, and the number of subjects was relatively small, hence, our observations should be viewed circumspectly. Moreover, our ‘older’ subjects were not ‘very’ old, i.e., mean age $\sim$ 69 years [12]. It should also be recognized that plasma NA concentrations in the forearm venous circulation are primarily an index of sympathetic nerve activity supplying the forearm musculature [23]. That in the older subjects an increase in plasma NA was only evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load.

In our ‘older’ subjects baseline BP was predictably higher than in the ‘young’ subjects, which may have contributed to, but seems most unlikely to account for, our observations. Rather, the discrepant effects of duodenal glucose on BP in the ‘young’ and ‘older’ groups may, at least in part, reflect the adequacy of the compensatory rise in HR, given that the HR response was greater in the healthy ‘young’, than in the ‘older’, subjects. Clearly, we did not evaluate SV (stroke volume) or TPR (total peripheral resistance) both of which may influence BP. Thus, it is difficult to deduce whether the ability to maintain, or increase, SV or TPR, was also blunted in the older subjects. However, we speculate that, in the healthy ‘young’ subjects, the presence of nutrients in the small intestine initially stimulates specialized glucose receptors leading to mesenteric vasodilation and a trend for a fall in BP, so that arterial baroreceptors in the carotid sinus and aortic arch are stimulated to increase cardiac sympathetic activity and a rise in HR sufficient to maintain BP [2]. Although none of the ‘older’ subjects had evidence of autonomic nerve dysfunction, as determined by cardiovascular reflex tests [12], this does not exclude the possibility that subtle changes in autonomic function that occur during normal aging [2], may have been important.

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The present study establishes that, in healthy ‘young’ subjects, ID glucose infusion at rates within the physiological range for gastric emptying, has no significant effect on either SBP or DBP, but increases HR, SMA flow and conductance and plasma NA. In the ‘young’, there was no difference in the magnitude of the HR response to the 2 and 3 kcal/min infusions, whereas the increase in SMA flow was load-dependent. These observations are in contrast with those reported previously in healthy ‘older’ subjects, particularly in relation to the substantial fall in BP evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load, in contrast to the substantial fall in BP evident in response to the highest glucose load.
with the young, perhaps suggests that the increase in sympathetic vasoconstrictor activity to skeletal muscle may have been less in the older subjects. If such an effect was generalized through limb muscles it could also contribute to the demonstrated fall in BP and would be consistent with previous observations [16].

In the ‘young’ subjects SMA flow increased in response to all three glucose loads, as has been reported to occur in response to ID infusions of fat and glucose, and to a lesser extent, protein, in healthy ‘older’ subjects [8]. SMA flow does not rise during ID infusion of ‘S’ [12], indicating the requirement for nutrients to elicit this response. Our study establishes that, in both healthy ‘young’ and ‘older’ individuals, the rise in SMA flow is load-dependent, and that the responses are comparable in the two groups. Moreover, baseline SMA flow was not different between the two groups. That the increase in SMA flow in the ‘older’ subjects occurred in the face of a fall in BP was intuitively attributable to an increase in mesenteric vascular conductance, and this was shown to be the case. However, the magnitude of the increase in conductance was comparable between the two groups, indicating that it did not contribute to the discrepant BP responses.

The present study evaluated the response to ID, as opposed to intragastric, glucose loads to exclude the variable of ‘gastric distension’. The latter, even at low volumes, reduces the postprandial fall in BP [4] and increases sympathetic nerve activity [3] so that it attenuates the hypotensive effects of ID glucose, when infused at 3 kcal/min, in the healthy elderly [3,4,9]. Observations relating to the effects of ID glucose in patients with PPH are hitherto limited to only two subjects, but suggest that they may be more ‘sensitive’ to the effects of small intestinal glucose [14], i.e. the hypotensive response to a given ID load is substantially greater, but this has not been formally studied. Given the potential therapeutic implications for this group, this issue represents a priority for future studies.

In summary, in healthy ‘young’ subjects, small intestinal glucose at loads of 1, 2 and 3 kcal/min do not reduce BP, in contrast with ‘older’ subjects who exhibit a comparable fall in BP in response to the two higher glucose loads. This may potentially be attributable to an inadequate rise in HR, reflecting a smaller increase in sympathetic activity in the ‘older’ subjects, but not a greater increase in SMA conductance.

**AUTHOR CONTRIBUTION**

Laurence Trahair and Karen Jones collected, analysed and interpreted the data. Lora Vanis collected the data. Diana Gentilcore collected and analysed the data, and Kylie Lange analysed and interpreted the data. Christopher Rayner, Michael Horowitz, Karen Jones, Kylie Lange and Laurence Trahair drafted and prepared the paper. Karen Jones conceived and designed the experiments. All authors approved the final version of this manuscript.

**FUNDING**

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia and an NHMRC Career Development Award (to K.L.J.). The purchase of the Logiq™ 9 ultrasound system was supported by an Equipment Grant from the NHMRC of Australia, funds from the University of Adelaide and GE Medical Systems, Australia.

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Received 23 May 2011/22 September 2011; accepted 27 September 2011
Published as Immediate Publication 27 September 2011, doi:10.1042/CS20110270