Fasting and post-prandial splanchnic blood flow is reduced by a somatostatin analogue (octreotide) in man

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SUMMARY

1. The effects of the subcutaneous administration of a long-acting somatostatin analogue (octreotide) or of placebo on the splanchnic blood flow response to a mixed solid meal has been examined in eight normal subjects by using a transcutaneous Doppler ultrasound technique. Each subject was studied on two occasions more than 1 week apart.

2. On the control day, feeding had a pronounced effect on both superior mesenteric artery and portal venous blood flows, causing a peak rise of 82% in superior mesenteric artery blood flow at 15 min and of 75% in portal venous blood flow at 30 min post-prandially ($P<0.001$). Blood flows remained elevated 2 h after the meal. Pulse and blood pressure showed no significant changes from baseline.

3. Octreotide reduced fasting superior mesenteric artery blood flow by 59% ($P<0.05$) and portal venous blood flow by 49% ($P<0.01$) and blunted the normal post-prandial rise. Pulse and blood pressure did not change in response to either the injection or the ingestion of the meal.

4. Octreotide suppressed the release of insulin, glucagon and pancreatic polypeptide in response to feeding and resulted in post-prandial hyperglycaemia.

5. The mechanism of action of octreotide on splanchnic blood flow is uncertain. It may be mediated via a direct vascular effect or it may act via suppression of vasoactive intestinal hormones.

Key words: Doppler ultrasound, somatostatin (octreotide), splanchnic blood flow.

Abbreviations: BP, blood pressure; MAP, mean arterial pressure; PV, portal venous; SMA, superior mesenteric artery.

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INTRODUCTION

Somatostatin is a tetradecapeptide that is widely distributed in the central nervous system, gastrointestinal tract and pancreas. This hormone has widespread effects, including marked inhibition of the secretion of many hormones [1]. It is also known to reduce human portal venous (PV) pressure and splanchnic blood flow when given by constant intravenous infusion [2–4]. Its short half-life of 3 min limits its clinical use, but a longer-acting analogue (octreotide; Sandostatin) has been synthesized. Octreotide has been shown to possess similar actions to somatostatin, and previous invasive studies have confirmed a reduction in fasting splanchnic blood flow in dogs [5] and in man [6–9]. Kooner *et al.* [10] have shown by Doppler ultrasound in man that the normal rise in post-prandial superior mesenteric artery (SMA) blood flow is abolished by the subcutaneous administration of octreotide 30 min before a liquid meal. However, PV blood flow and the neuroendocrine response to the meal were not reported. In the present study the responses of both SMA blood flow and PV blood flow to feeding have been examined by transcutaneous Doppler ultrasound with and without the administration of octreotide. In addition, blood levels of glucose and plasma levels of insulin, pancreatic polypeptide, glucagon and gastrin were measured.

METHODS

Subjects and protocol

Eleven healthy, non-obese, non-diabetic volunteers (five females, six males), with a mean age of 25.5 years (range 20–43 years), gave informed consent for the study. In three subjects intestinal gas obscured adequate visualization of the SMA and thus data are available only in eight subjects. Each was studied unblinded on two occasions at least 1 week apart with or without a 50 μg subcutaneous injection of octreotide before a standard meal. Smoking and alcohol were not permitted in the

preceding 24 h, and patients arrived at the laboratory at 09.00 hours after 12 h of fasting. The study was approved by the local Hospital Ethical Committee.

An intravenous cannula was inserted into the left antecubital fossa and the subjects were rested in the supine position for at least 30 min. Baseline measurements of pulse rate, blood pressure (BP) (sphygmomanometer), and PV and blood SMA flows (Doppler ultrasound) were made. Mean arterial pressure (MAP) was calculated as diastolic BP plus one-third (systolic BP minus diastolic BP). Baseline venous blood samples were taken for measurement of glucose, insulin, glucagon, gastrin and pancreatic polypeptide. On the control day, 1 ml of saline (150 mmol/l NaCl), and on the study day 50 μg of octreotide, was then administered subcutaneously into the anterior abdominal wall. Repeat blood flow measurements were made after 15 min and repeat blood samples were taken after 25 min. Each subject then received a standard mixed solid and liquid meal consisting of 70 g of wholemeal bread, 40 g of cheddar cheese, 16 g of butter, 40 g of ice-cream, 150 g of tinned peaches and 150 ml of orange juice [19 g of protein, 32 g of fat and 112 g of carbohydrate; energy content 778 kcal (3255 kJ)]. The meal was consumed in the sitting position over 10 min, the time being noted when the subjects finished their meal. They then rested supine, and repeat haemodynamic, glucose and hormone measurements were made for a further 120 min post-prandially.

Analytical methods

Venous blood was collected into fluoride oxalate tubes for glucose assay by a glucose oxidase method and was analysed between 6 and 18 h later. Insulin was measured by r.i.a. in stored plasma. Fifty microlitres of aprotinin (Trasylol) was added to 8 ml of blood and centrifuged for 4 min. Plasma was collected and frozen at -20°C until assayed for glucagon, gastrin and pancreatic polypeptide by r.i.a.s [11].

Doppler ultrasound technique

Splanchnic blood flow was measured by the transcutaneous Doppler ultrasound technique using a duplex scanner (ATL 500; Squibb Medical Systems) [12, 13]. The duplex scanner consisted of a 3 MHz pulsed Doppler flowmeter and a real-time two-dimensional mechanical sector scanner. The portal vein was imaged beyond the confluence of the splenic and superior mesenteric veins and just before its bifurcation into the right and left portal veins. The SMA was imaged close to its origin. The lateral and antero-postero diameters of the SMA and the portal vein were measured serially by examining these vessels in cross-section. Blood flow was calculated from the Doppler equation [14] using the formula $Q = V_{mean} \times A$, where Q = blood flow, V_{mean} = mean velocity of blood and A = the cross-sectional area of the blood vessel. The angle of insonation (the angle between the Doppler beam and the longitudinal axis of the blood vessel) was maintained at below 40°. Comparison with a continuous flow model *in vitro* in our laboratory has shown a high correlation for blood flows between 300 and 3500 ml ($r > 0.9$) [13]. Short-term reproducibility *in vivo* for the PV blood flow was determined in two subjects examined for 30 min on 5 consecutive days and was found to be 11%. The day-to-day reproducibility was taken as the variation in the average daily measurement and was 8%. Short-term reproducibility for the SMA blood flow was 6.3% and day-to-day variation was approximately 9%. The accuracy of the system calipers for on-screen measurement of vessel diameter was better than 1 mm and the angle measuring cursor was accurate to within ± 1°.

Statistical methods

Results are expressed as means (SEM), and 95% confidence intervals are given where indicated. The overall differences between the responses to the meals were analysed by calculating the area under the curve (by the trapezoid method) for that variable divided by the duration of the time zone [15]. This gave an overall summary statistic for each subject for the whole study period, which was corrected for the baseline value. A paired Student's t-test was then used to assess the differences between meals. Changes within each group were analysed by analysis of variance.

RESULTS

The meal was completed by all subjects. When given octreotide, all subjects complained of short-lived pain at the injection site and two subjects developed mild diarrhoea 24 h after the study.

Splanchnic blood flow

Fasting basal SMA blood flow in the control group did not differ significantly from that in the octreotide-treated group [control, 513 (29) ml/min; octreotide, 553 (25) ml/min; P = not significant; Fig. 1]. Similarly, there was no significant difference in fasting basal PV blood flow [control, 791 (89) ml/min; octreotide, 667 (87) ml/min; P = not significant]. After food ingestion on the control day there was an 82% rise in post-prandial SMA blood flow and a 75% rise in PV blood flow, reaching a peak after 15 min in the SMA [849 (77) ml/min; $P < 0.001$] and after 30 min in the portal vein [1310 (147) ml/min; $P < 0.001$]. This gradually reduced with time, but remained significantly above baseline in both the SMA and the portal vein at 120 min post-prandially.

Octreotide injection elicited a 59% fall in fasting SMA blood flow from 553 (25) ml/min to 388 (53) ml/min ($P < 0.001$) and in fasting PV blood flow from 667 (87) ml/min to 379 (58) ml/min ($P < 0.01$; Fig. 1). After food ingestion in this group there was a small rise in SMA blood flow, which peaked at 30 min after the meal [before the meal, 388 (53) ml/min; 30 min after the meal, 476 (33) ml/min; $P = 0.05$], but blood flow remained signifi-

cantly below baseline at all times after the meal. There was a significant difference in the post-prandial rise in SMA blood flow over the 120 min of study between the control and the octreotide-treated groups [control, +190 (40) ml/min; octreotide, +47 (46) ml/min; $0.001 < P < 0.01$ using area under the curve summary data].

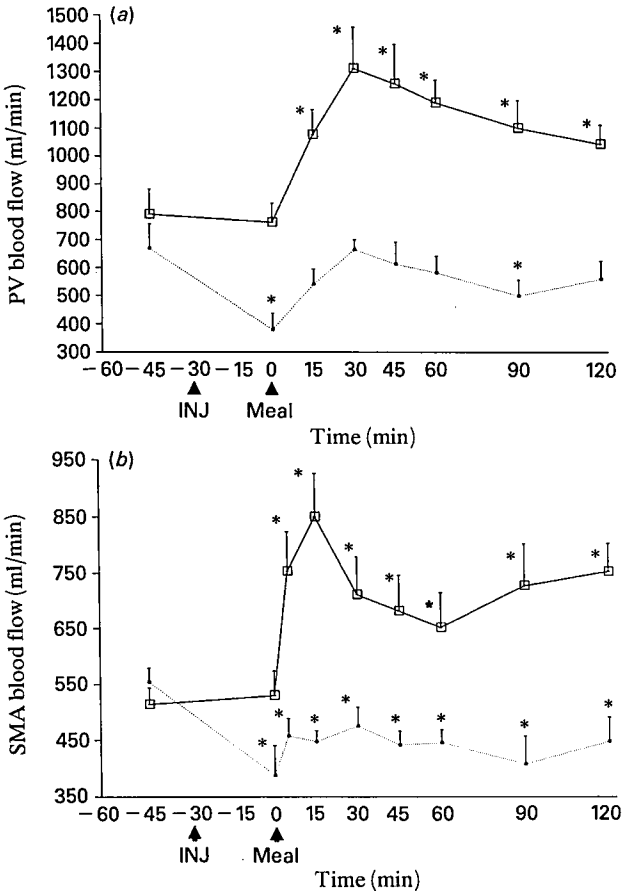

Fig. 1. Splanchnic blood flow in response to feeding in eight subjects after the administration of saline (□——□) or octreotide (50 μg; ■···■) subcutaneously. (*a*) PV blood flow. (*b*) SMA blood flow. Values are means with bars indicating SEM. Statistical significance: $^*P < 0.05$ compared with baseline values. Abbreviation: INJ, subcutaneous injection of saline or octreotide. The meal was consumed over 10 min.

Post-prandial PV blood flow showed a significant rise in the subjects given octreotide, with a peak rise occurring 30 min after the meal [before the meal, 379 (58) ml/min; 30 min after the meal, 664 (35) ml/min; $P = 0.001$]. However, the rise over the 120 min after the meal was blunted in comparison with the control day [control, +328 (72) ml/min; octreotide, +150 (44) ml/min: $0.05 < P < 0.1$, using area under the curve summary data].

Pulse and MAP

Baseline and post-prandial pulse and MAP values for the control and octreotide-treated groups are shown in Table 1. Baseline pulse and MAP were not significantly different between the groups. There was no significant difference in pulse rate over the 120 min of monitoring between the two groups and there was no significant change with time in either group. There was no significant difference in MAP over the 120 min of monitoring between the two groups. MAP fell significantly after the meal only in the control group and only at 90 min post-prandially [basal, 77 (2) mmHg; 90 min post-prandially 73 (2) mmHg; $P = 0.04$]. MAP did not change after the meal in the octreotide-treated group.

Changes in blood levels of glucose and plasma levels of hormones

Blood levels of glucose and plasma levels of insulin are shown in Fig. 2 and the overall differences over the 120 min of study are given in Table 2. Blood glucose levels showed an initial rise after the meal in the control group, returning to basal levels after 1 h. Blood glucose rose to hyperglycaemic levels in the octreotide-treated group. The normal post-prandial rise in plasma insulin levels was abolished by octreotide.

Plasma levels of glucagon and pancreatic polypeptide increased post-prandially in the control group (Fig. 3). Plasma glucagon levels showed an initial post-prandial fall and later returned to basal values in the octreotide-treated

Table 1. MAP and pulse rate after the administration of octreotide (50 μg) or saline (control) and the ingestion of a mixed solid meal in eight subjects

Values are means with SEM in parentheses. Statistical significance: $^*P = 0.04$ compared with baseline value. Abbreviation: NS, not significant.

Time (min) ...	−45	−15	+15	+30	+60	+90	+120	*P* value for the difference between groups
Pulse rate (beats/min)								
Control	64(3)	65(3)	62(1)	63(3)	61(3)	64(4)	66(3)	NS
Octreotide	60(2)	60(3)	58(3)	57(2)	61(4)	61(3)	62(4)	
MAP (mmHg)								
Control	77(2)	77(2)	74(2)	77(2)	76(2)	73(2)*	74(2)	NS
Octreotide	77(2)	79(2)	77(2)	76(2)	76(3)	75(2)	78(2)	

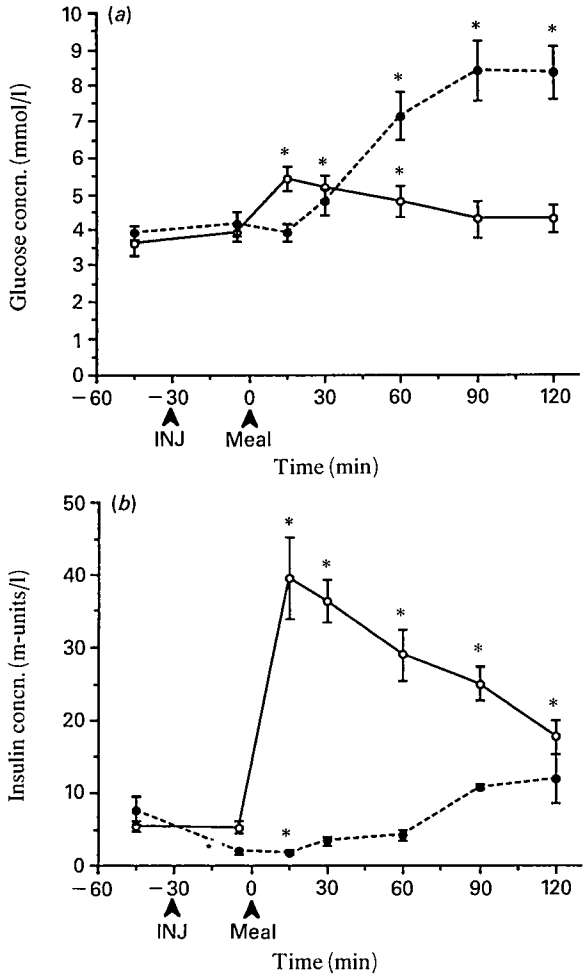

Fig. 2. Post-prandial blood concentrations of glucose (*a*) and plasma concentrations of insulin (*b*) in response to feeding in eight subjects after the administration of saline (o——o) or octreotide (50 μg; ●- - -●) subcutaneously. Values are means ± SEM. Statistical significance: $^*P < 0.05$ compared with baseline value. Abbreviation: INJ, subcutaneous injection of saline or octreotide.

group. Plasma levels of pancreatic polypeptide fell in this group and showed no post-prandial rise. The overall difference in response over the 120 min of study between the two groups was highly significant for both hormones (Table 2). Post-prandial plasma levels of gastrin rose transiently in the control group, but the octreotide-treated group showed a greater overall post-prandial rise (Table 3 and Fig. 3).

DISCUSSION

Native somatostatin is found in the upper gastrointestinal tract, pancreatic islets and widely throughout the central, peripheral and autonomic nervous systems. It has diverse actions that are mainly inhibitory and is known to decrease the plasma levels of many hormones, including glucagon, gastrin, growth hormone, insulin and pancreatic polypeptide [1, 9, 16, 17]. Its long-acting analogue, octreotide, is known to suppress hormone levels for as long as 6 h after subcutaneous injection [9]. Intestinal motor activity is inhibited, resulting in reduced gastric and duodenal motility, increased mouth-to-caecum transit time [18] and decreased gall-bladder emptying. In addition, octreotide is known to delay absorption of carbohydrate, amino acid and triacylglycerol from the upper small-intestine [18]. These diverse actions have prompted trials of somatostatin analogues in the treatment of gastrointestinal apudomas (vipoma and carcinoid syndrome) and in the treatment of acromegaly.

Numerous studies have shown that native somatostatin and its analogues reduce both portal pressure and splanchnic blood flow in rats [19], dogs [5] and human subjects [6–9]. Furthermore, the reduction in fasting splanchnic blood flow in man persists for at least 3 h after intravenous or subcutaneous administration of octreotide [6, 9] and the effect is largely independent of the dosage used or the route of administration. These studies have used invasive methods to directly measure portal pressure trans-hepatically and splanchnic blood flow via indocyanine dye clearance curves. This reduction in portal

Table 2. Overall summary statistic (area under the curve divided by 120 min, i.e. mean change) and 95% confidence intervals for the responses of blood levels of glucose and plasma levels of insulin, glucagon, pancreatic polypeptide and gastrin to a mixed solid meal in eight subjects when saline (control) or octreotide (50 μg) was injected subcutaneously before the meal

	Control	Octreotide	Mean difference (control minus octreotide)	*P* value for the difference between groups
Glucose (mmol/l)	0.80 (0.06 to 1.65)	2.41 (1.18 to 3.63)	−1.6 (−2.04 to −1.20)	0.06
Insulin (m-units/l)	21.4 (16.9 to 25.9)	4.3 (0.8 to 7.7)	18.2 (15.6 to 19.7)	<0.001
Glucagon (ng/l)	13.8 (−0.04 to 27.5)	−10.0 (−32.4 to −12.4)	29.3 (15.6 to 31.9)	<0.006
Pancreatic polypeptide (ng/l)	123 (59 to 187)	−6.3 (−24.5 to 11.9)	127 (111 to 148)	<0.004
Gastrin (ng/l)	10.7 (1.7 to 19.8)	29.8 (16.1 to 43.5)	−17 (−23.7 to −14.5)	0.02

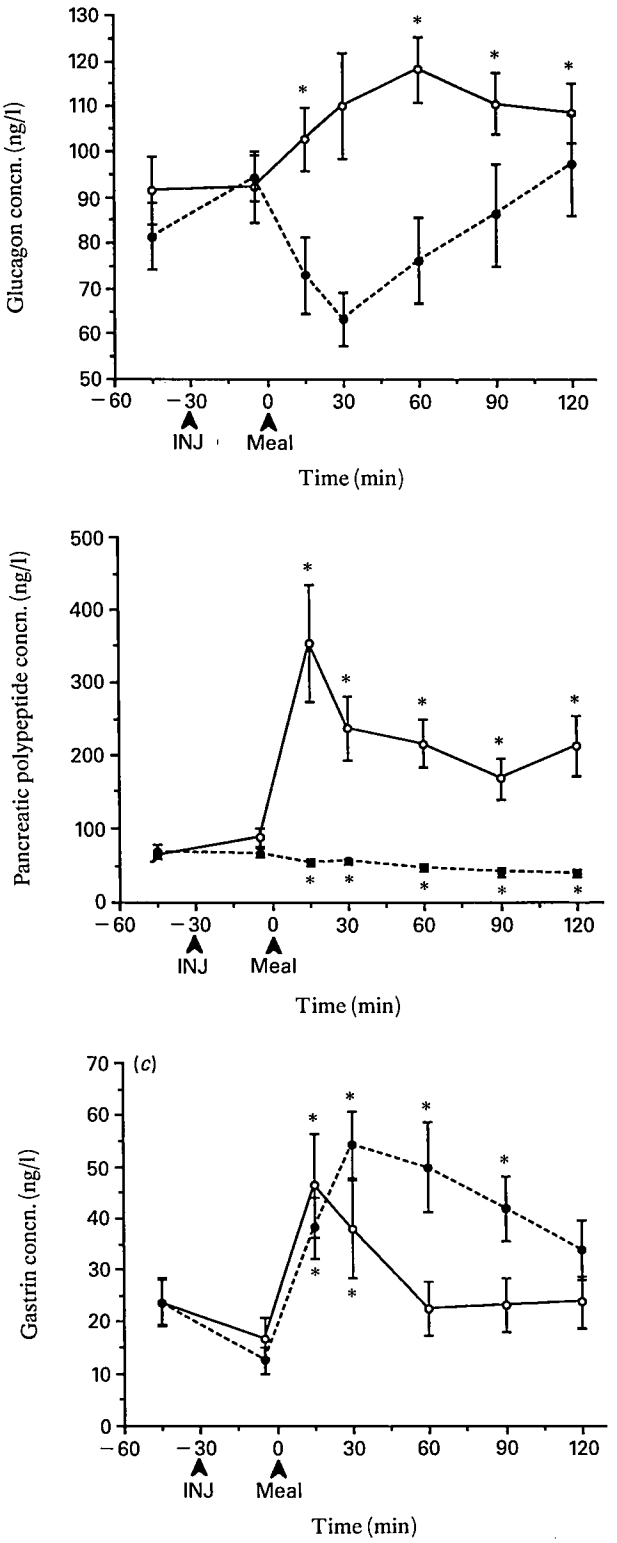

Fig. 3. Post-prandial plasma concentrations of glucagon (*a*), pancreatic polypeptide (*b*) and gastrin (*c*) in response to feeding in eight subjects after the administration of saline (○——○) or octreotide (50 μg; ●---●) subcutaneously. Values are means ± SEM. Statistical significance: *$P<0.05$ compared with baseline values. Abbreviation: INJ, subcutaneous injection of saline or octreotide.

pressure and splanchnic blood flow induced by somatostatin has potential importance in the treatment of bleeding oesophageal varices owing to portal hypertension and in modifying post-prandial hypotension in autonomic neuropathy [20–23]. The efficacy of somatostatin in the treatment of bleeding oesophageal varices is, however, controversial [24, 25].

The present study has measured splanchnic blood flow non-invasively, and the results obtained correlate well with previous invasive and ultrasound-measured values for human splanchnic blood flow [10, 12, 13, 26]. The administration of octreotide significantly lowered fasting SMA and PV blood flows and attenuated the post-prandial rise. Post-prandial blood flow in the SMA over 120 min was significantly lower in the octreotide-treated group compared with the control group, but just failed to achieve statistical significance in the portal vein. This may be due to the small sample size, but may possibly reflect differential effects of octreotide on the splanchnic circulation. Approximately 45% of fasting PV blood flow returns via the superior mesenteric vein, with 30% from the splenic and 25% from the inferior mesenteric veins [26a]. The changes in splenic and inferior mesenteric arterial blood flow and their corresponding venous flows are poorly understood and thus their relative contributions to post-prandial portal flow are unknown. It is possible, therefore, that octreotide exerts differential effects on the mesenteric and splenic responses to a meal with an enhanced effect on the superior mesenteric arterial system.

We failed to demonstrate any post-prandial change in MAP or pulse rate. Previous workers have shown little or no systemic vascular effects of somatostatin or its analogues [7, 10, 21, 27] in normal subjects and thus it may have specific haemodynamic effects on the splanchnic circulation. These may contribute to the improvement in post-prandial and postural hypotension noted in patients with autonomic neuropathy given octreotide [20, 22, 23]. Kooner *et al.* [10] were the first to report detailed non-invasive haemodynamic (including SMA) changes after the administration of octreotide and a liquid meal in eight subjects, and the results of the present study are in a broad agreement with theirs. However, the present study has shown a small, but significant, rise in SMA and PV blood flows after the ingestion of the meal in the octreotide-treated group (but less than in the control group), whereas Kooner *et al.* [10] showed no rise in SMA blood flow after the meal in the octreotide-treated group. This may relate to the differing meal types (liquid versus solid), energy content and composition of the meals (66 g of carbohydrate, 22 g of fat and 18 g of protein [10] compared with 112 g of carbohydrate, 32 g of fat and 19 g of protein in the present study). Furthermore, Kooner *et al.* [10] showed a post-prandial rise in pulse rate in the control group which was prevented by octreotide, but MAP did not differ between the two groups. We, however, have failed to show a change in either pulse rate or MAP in either group in response to the meal. The results of previous studies on post-prandial BP and pulse rate changes in the young are conflicting and may be due

to differing methods of data collection or of meal types. Some studies [28, 29] have shown no change in pulse rate or MAP after a glucose drink but others [30, 31] have shown a small, but significant, change in heart rate. Robertson *et al.* [30] also observed a rise in MAP after a mixed meal. Heseltine *et al.* [32] showed in young subjects that a high-carbohydrate meal resulted in a significant overall rise in both supine and erect (6 beats/min) heart rate, but no such changes occurred after a high-fat meal. Neither meal produced any significant changes in BP.

The mechanism of the action of octreotide on post-prandial splanchnic blood flow is not understood, but it may involve an indirect mechanism via suppression of vasoactive gut peptides or a direct vasomotor action on the splanchnic vasculature. We have shown that the release of pancreatic polypeptide, glucagon and insulin is suppressed by octreotide, in agreement with previous work [1, 17]. Glucagon is a potent mesenteric vasodilator. In dogs it produces a near doubling in SMA blood flow after intravenous or intra-arterial infusion [33], and it is implicated in the splanchnic hyperaemia of portal hypertensive rats [34]. Furthermore, it increases splanchnic blood flow in patients with well-compensated cirrhosis when given by intravenous infusion [35]. Its suppression by octreotide could therefore be a factor in the inhibition of post-prandial hyperaemia in this study.

Bolus supra-physiological doses of intravenous insulin cause a fall in BP in diabetic patients with autonomic neuropathy [36] and may cause a rise in pulse rate in normal volunteers independently of the effects of changes in blood glucose level [37]. Furthermore, euglycaemic hyperinsulinaemia has cardiovascular effects, including a fall in systemic BP in diabetic autonomic neuropathy [38], suggesting a vasoactive role of insulin that is independent of changes in the blood glucose level. Its effects on splanchnic blood flow are largely unknown, but the suppression of the post-prandial rise in plasma insulin levels by octreotide in this study would be consistent with a role for insulin in regulating splanchnic blood flow. However, octreotide may additionally have a direct action on splanchnic blood vessels; thus the BP in patients with autonomic neuropathy pretreated with octreotide remains normal despite a bolus dose of intravenous insulin [20]. The early fall in blood glucose levels after octreotide treatment in the present study is in agreement with the known decrease in hepatic glucose output after octreotide administration [9]. The late post-prandial hyperglycaemia seen in the octreotide-treated group possibly relates to a combination of a delay in intestinal absorption [18], altered plasma levels of glucagon and insulin, and possibly direct effects of octreotide on glucose disposal in the periphery [9].

Plasma levels of gastrin were unexpectedly higher post-prandially in the octreotide-treated group in comparison with the control group. In a previous study, post-prandial suppression of gastrin release by octreotide was not effective when octreotide was given more than 30 min before the meal [39] as in the present study. The post-prandial rise in plasma levels of gastrin was only modest in both groups, reflecting the mixed nature of the meal: gastrin is released especially in response to a protein-rich meal. Other potentially vasoactive hormones, such as motilin and neurotensin, are released in response to feeding, but we have not examined the effects of octreotide on these hormones. Further studies are required to delineate more exactly the effects of octreotide on post-prandial splanchnic vasodilatation in man.

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