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Splanchnic blood flow regulation in humans

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Effects of meal and incretins in the regulation of splanchnic blood flow

Endocrine CONNECTIONS

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Abstract

Objective: Meal ingestion is followed by a redistribution of blood flow (BF) within the splanchnic region contributing to nutrient absorption, insulin secretion and glucose disposal, but factors regulating this phenomenon in humans are poorly known. The aim of the present study was to evaluate the organ-specific changes in BF during a mixed-meal and incretin infusions.

Design: A non-randomized intervention study of 10 healthy adults to study splanchnic BF regulation was performed.

Methods: Effects of glucose-dependent insulinotrophic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) infusions and mixed-meal were tested in 10 healthy, glucose tolerant subjects using PET-MRI multimodal imaging technology. Intestinal and pancreatic BF and blood volume (BV) were measured with ^{15}O-water and ^{15}O-carbon monoxide, respectively.

Results: Ingestion of a mixed-meal led to an increase in pancreatic and jejunal BF, whereas duodenal BF was unchanged. Infusion of GIP and GLP-1 reduced BF in the pancreas. However, GIP infusion doubled blood flow in the jejunum with no effect of GLP-1.

Conclusion: Together, our data suggest that meal ingestion leads to increases in pancreatic BF accompanied by a GIP-mediated increase in jejunal but not duodenal blood flow.

Introduction

The splanchnic region is a crucial regulator of metabolic homeostasis; and disturbances in the function of gut and pancreas predispose to impaired glucose regulation in the postprandial state (1, 2, 3). After a meal, blood flow (BF) is redistributed in the splanchnic region to accommodate the absorption of nutrients in the gut, glucose delivery and insulin drainage to and from the pancreatic islets,

and hepatic metabolism (4, 5, 6). In healthy humans, an increase of about 50–100% has been reported in the celiac (CA) and superior mesenteric artery (SMA) flow following meal ingestion (7), but it is not known how this increase in perfusion is distributed between the splanchnic organs.

After a meal plasma levels of several potential vasoactive substances increase (8). In rodents,

experimental hyperglycemia increases and hypoglycemia decreases pancreatic islet perfusion (9). Moreover, incretins have been shown to regulate BF in the splanchnic and systemic circulation. When Kogire and co-workers (10) injected GIP to healthy dogs, they observed increased BF in SMA but not in CA, suggesting that GIP contributes to the redistribution of BF after a meal. Similar results have been reported for GLP-1 (11). However, the effects of incretin hormones on splanchnic BF distribution have not previously been studied in humans, most likely due to a lack of appropriate methods.

The measurement of BF distribution in the splanchnic area has now been overcome by a multimodal imaging approach with positron emission tomography (PET) which enables the assessment of splanchnic BF and blood volume (BV) in an organ-specific manner in humans (12). We used PET/MRI with ^{15}O-water and ^{15}O-carbon monoxide tracers to assess intestinal and pancreatic BF and BV, respectively. The present study was conducted to evaluate the physiological vascular changes occurring in the gut and pancreas after a mixed-meal and after intravenous infusions GIP and GLP-1.

Subjects and methods

Subjects

A total of 10 healthy subjects were recruited (Table 1). The subjects had a body-mass index (BMI) of 18–27 kg/m^2, fasting plasma glucose was below 6.1 mM and they were aged between 18 and 60 years. Subjects were generally in good health, as determined by physical examination, screening laboratory measurements and medical history. Smoking was considered as an exclusion criterion for the study. Subject body weight was stable between the experiments and none of the subjects had experienced rapid weight change three months prior to the enrollment.

Study approval

The Ethics Committee of the Hospital District of Southwestern Finland approved the studies (ClinicalTrials. gov Identifier NCT01880827), and all subjects gave their written informed consent before participation.

Research design

We measured changes in splanchnic BF and BV after a mixed-meal test, GIP infusion, and GLP-1 infusion

Table 1 Subject characteristics.

Parameter	Median (IQR) $n = 10$
Anthropometrics	
M/F	2/8
Age (years)	46 (46–52)
Weight (kg)	63.57 (59.3–66.5)
BMI (kg/m^2)	23.1 (21.8–24.1)
Body fat (%)	25.6 (23.8–30.0)
Systolic BP (mmHg)	136 (124–139)
Diastolic BP (mmHg)	88.4 (83.8–93.8)
Smoking (n (%))	0 (0)
Diabetes (n (%))	0 (0)
Biochemical data	
Fasting glucose (mM)	5.1 (4.9–5.2)
2-h glucose (mM)	6.1 (5.3–6.9)
HbA1c (mmol/mol)	33.0 (30.0–33.9)
Fasting insulin (U/L)	4.5 (3.0–5.8)
Insulin sensitivity indices	
HOMA$_{IR}$ (fraction)	1.0 (0.7–1.3)
2-h OGIS (mL/min/m^2)	458 (429–481)
β-Cell function parameters	
Basal ISR (pM/min/m^2)	66.9 (54.1–77.0)
Glucose sensitivity (pM/min/m^2/mM)	82.9 (63.1–91.8)
Potentiation factor ratio (dimensionless)	1.6 (1.2–3.2)

2-h OGIS, oral glucose insulin sensitivity index; GIP, glucose-dependent insulinotrophic peptide; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin; HOMA$_{IR}$, homeostatic model assessment for insulin resistance; ISR, insulin secretion rate.

(Supplementary Fig. 1, see section on supplementary data given at the end of this article). Prior to PET-studies a routine 75-g 2-h OGTT was performed to all subjects. Subjects were imaged in the supine position with a combined PET/MRI scanner Philips Ingenuity (Philips Healthcare) with 38×38 cm axial field-of-view (13) after an overnight fast. Two peripheral catheters were placed in the antecubital veins: one for blood sampling and the other one (in the contralateral arm) for incretin infusions and ^{15}O-water bolus injections. The lines were flushed with constant saline infusion. Baseline ^{15}O-water and ^{15}O-carbon monoxide PET-acquisition and whole-body MRI preceded the experiments. During the PET-studies, plasma levels of glucose, insulin, C-peptide, FFA, GIP and GLP-1 were measured at time points 0, 15, 30, 45, 60 and 90 min. Blood pressure and clinical well-being were monitored throughout the studies.

To assess pancreatic and gut BF, a dynamic PET scanning of 310 s (with variable frame times) was performed following an intravenous bolus injection of ^{15}O-water. Effective radiation dose per ^{15}O-water injection was 0.47 mSv. The total injected amount of radioactivity was 491 (462–515) MBq and radiochemical purity of the

radiotracer always exceeded 95%. To study the changes in pancreatic and gut BV, subjects inhaled room air mixed with 0.14% ^{15}O-labeled carbon monoxide (CO) through a three-way inhalation flap-valve. The inhalation lasted for two minutes, the total radioactivity dose being 0.57 mSv, and the total administered amount of radioactivity was 726 (688–770) MBq. After the administration, another two minutes was allowed for the CO to combine with hemoglobin before the 4-min static PET scan (Supplementary Fig. 2).

Pancreatic and gut BF were calculated from ^{15}O-water derived data by using a one-tissue compartment model (Fig. 1F) (14). Intestinal TACs were corrected for a delay between arterial and target tissue radioactivity, whereas delay correction was not considered necessary for pancreas.

Pancreatic and gut BVs were calculated from ^{15}O-carbon monoxide derived data using the following mathematical formula:

$$V_B = 100 \times C_{PET} \times \left(C_{BLOOD} \times \rho_{tissue} \times 0.85 \right)^{-1}$$

wherein V_B is the BV of the tissue region (in mL 100/g), C_{PET} and C_{BLOOD} are the radioactivities in the tissue and blood (in Bq/mL), respectively, ρ_{tissue} is the tissue density (1.045, 1.047 and 1.042 g/mL for pancreas, duodenum and jejunum, respectively) and 0.85 represents the tissue-to-large vessel hematocrit ratio (15). BF and BV values were corrected to the organ volume. Pancreatic volume was measured in a manual fashion from abdominal MR images whereas conventional values of 556.6 mL and 57.3 mL were used for jejunum and duodenum, respectively (15).

Mixed-meal testing

After baseline scans, a mixed-meal solution was administered orally during a 10-min period in a supine position. The mixed-meal (Nutridrink, Nutricia Advanced Medical Nutrition, Amsterdam, Netherlands) contained 250 kcal energy, and consisted of 40, 6 and 9 g of carbohydrates, fat and protein, respectively. During the 90-min time period ^{15}O-water and ^{15}O-carbon monoxide PET-scans were repeated twice (Supplementary Fig. 2A): at 20 and 50 min postingestion for ^{15}O-water and at 40 and 70 min postingestion for ^{15}O-carbon monoxide, respectively.
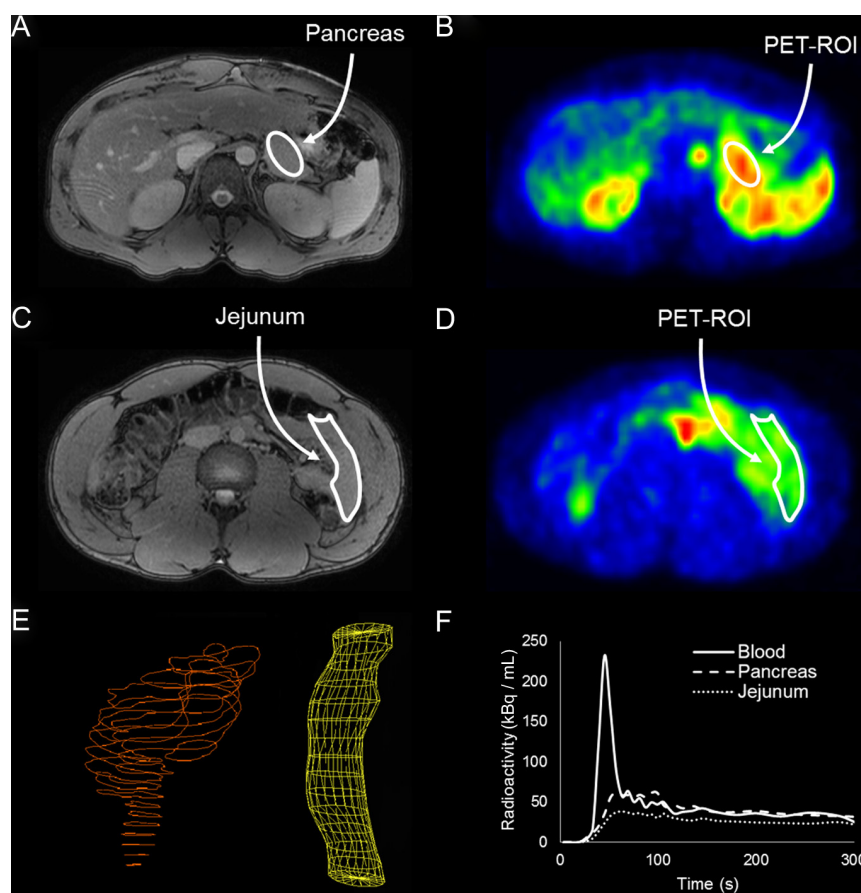

Figure 1
Non-invasive estimation of splanchnic blood flow (BF) at baseline and during the experiments using positron emission tomography (PET). (A, B, C and D) An example of co-registered abdominal MRI and ^{15}O-water PET image at the levels of second and fifth lumbar vertebrae, respectively. Pancreas and gut were identified from MRI image and the regions-of-interest (ROI) were reproduced into PET image. (E) Tissue-specific time-activity curves (TAC) were extracted from 3-dimensional ROIs in a manual fashion. Pancreatic ROI, orange polygon; gut ROI, yellow cylinder. (F) Pancreatic and intestinal BFs were calculated using one-tissue compartment analysis with an image-derived input function from abdominal aorta.

Incretin infusion experiments

Incretins were dissolved in sterilized water with 2% human serum albumin in the hospital pharmacy and were administered into the peripheral vein via a cannula with syringe pumps after baseline PET-scans. For GIP infusion, after baseline scans a constant 75-min GIP_{1-42} (Bachem Holding AG, Bubendorf, Switzerland) infusion was started at a rate of 4.0 pmol/kg/min and the rate was halved at the 15-min time point [16]. The variation in infusion rate was performed with the intention to reproduce physiological concentrations of GIP normally present in the splanchnic circulation after the meal ingestion. For GLP-1 infusion, after baseline scans a constant 75-min GLP-1 (Bachem Holding AG) infusion was started at the rate of 0.75 pmol/kg/min and the rate was maintained throughout the experiment [17]. ^{15}O-water and ^{15}O-carbon monoxide PET-scans were performed as described above.

Image processing, PET and MRI analysis

All data were corrected for dead time, decay and measured photon attenuation and reconstructed in a 256×256 matrix. Regional time-activity curves (TAC) were obtained from the 3-dimensional regions-of-interest (ROIs) drawn manually in the pancreatic parenchyma, duodenum and jejunum (Fig. 1A, B, C, D and E) using the Carimas 2.9 software (Turku PET Centre, downloadable at http://turkupetcentre.fi). An image-derived input function was obtained from the abdominal aorta, as described previously [18]. For reliable analysis, MRI scans were used as an anatomical reference [19].

Quantitation of insulin sensitivity and secretion

Homeostatic model assessment for insulin resistance ($HOMA_{IR}$) was calculated as Gluc × Ins: 22.5 from fasting samples. Moreover, insulin sensitivity was expressed as 2-h oral glucose insulin sensitivity index (OGIS) reflecting glucose clearance during hyperinsulinemic conditions [20]. Basal and total (absolute) insulin secretion rate (ISR) during meal-testing was derived from deconvolution of C-peptide kinetics [21], and β-cell function modeling (*glucose sensitivity*, *rate sensitivity* and *β-cell potentiation*) was applied to the data.

Biochemical analyses

During standard oral glucose tolerance test (OGTT) and experiments, blood was collected to lithium heparin and EDTA tubes and was stored at –80°C until further analyses. Additional blood samples were collected in chilled EDTA tubes pretreated with 25 mg of DPP-IV inhibitor (Diprotin-A, Sigma-Aldrich); and 2000 KIE of trypsin inhibitor (Trasylol, Bayer AG) were added to chilled EDTA tubes before blood sampling. Determination of plasma glucose, insulin, C-peptide, FFA, HbA1c and cholesterol levels are described elsewhere [12]. Total plasma GIP and active GLP-1 was measured using an enzyme-linked immunosorbent assay (ELISA) from Merck Millipore. GIP and GLP-1 assays were performed according to the instructions provided by the manufacturers.

Statistics

The data are expressed as mean (interquartile range, IQR). Analyses of changes over time and between experiments (GIP infusion vs GLP-1 infusion) were performed using repeated measurements ANOVA; and Tukey–Kramer method was used to adjust the *P* values of paired comparisons. To investigate the association of independent factors and splanchnic flow during mixed-meal test, a linear regression analysis was performed. The differences in time-corrected AUCs between experiments were calculated using paired *t* test (within study arms) and Mann–Whitney *U* test (between study arms); and Bonferroni's method was used to adjust the *P* values of paired comparisons. The normality of residuals was checked for justification of the analyses. Pearson's or Spearman's correlation coefficients were calculated depending on the normality of the data. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SAS System for Windows, version 9.4 (SAS Institute, Cary, NC, USA).

Results

The metabolic effects of a mixed-meal test

Fifteen minutes after ingestion of the mixed-meal plasma glucose, serum insulin (Fig. 2A and B) and C-peptide were increased. Simultaneously, plasma GIP levels increased and reached a plateau at 30 min postingestion (Fig. 2C). In contrast, plasma GLP-1 (Fig. 2C) remained unchanged. In concert with increased insulin appearance, serum FFA levels decreased from 0.75 (0.53–0.96) to 0.36 (0.17–0.55) mM ($P = 0.007$) within 90-min.
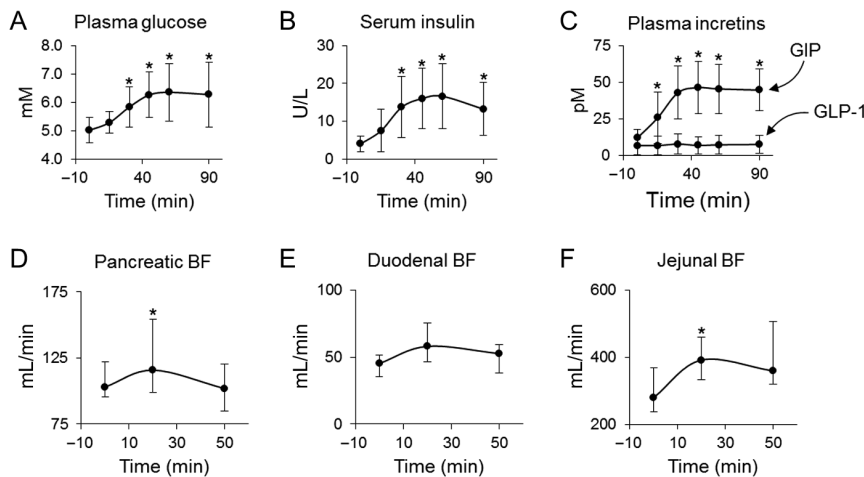
Figure 2
Metabolic and splanchnic vascular changes after mixed-meal ingestion. After ingestion of a mixed-meal, an increase in plasma levels of glucose (A) and insulin (B) was observed. Mixed-meal ingestion provoked a rapid and sustained increase in plasma GIP levels (C; black balls), whereas no change in plasma GLP-1 levels was observed (C; white balls). A significant increase in pancreatic (D) and jejunal (F) BF was seen 20-min postingestion whereas duodenal BF (E) was unaffected by mixed-meal ingestion. Both pancreatic (D) and jejunal (F) BF were normalized at 50-min postingestion. Data are median (IQR), $n = 10$, *$P < 0.05$ vs baseline in repeated measurements ANOVA with Tukey–Kramer correction.

The splanchnic vascular effects of a mixed-meal test

At baseline, the median (IQR) pancreatic, duodenal and jejunal BF were 1.57 (1.46–1.78), 0.79 (0.70–0.92) and 0.54 (0.43–0.66) mL/mL/min, respectively. Mixed-meal ingestion increased pancreatic and jejunal BF by 1.17- and 1.68-fold ($P = 0.016$ and 0.023 for time factor, respectively) at 20 min, whereas no change in duodenal BF was observed ($P = 0.307$ for time factor) (Fig. 2D, E and F). Pancreatic BF returned to baseline at 50 min despite plasma glucose concentrations still being elevated. In contrast, jejunal BF remained elevated during the whole test. Individual BF values in the pancreas but not in the intestine after the meal (both 20 or 50 min) correlated with baseline values (r_P range 0.92–0.97, $P < 0.001$). At baseline BV values were 14.2 (12.0–15.3), 16.9 (10.3–19.7) and 13.4 (9.53–17.4) mL 100 g in pancreas, duodenum and jejunum, respectively, and remained unchanged throughout the mixed-meal test.
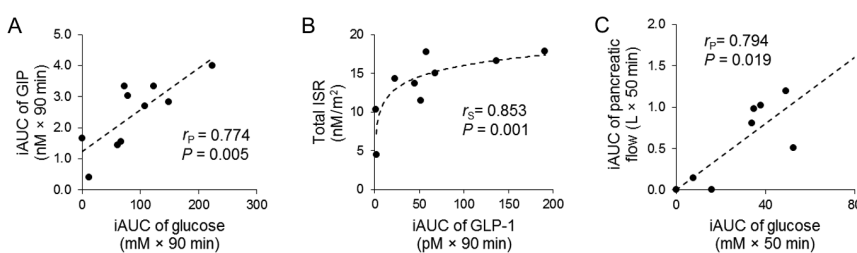
Interrelationships between metabolic and BF variables

During the mixed-meal test, incremental area under the curve (iAUC) of glucose during the 90-min mixed-meal test was positively correlated with iAUC of GIP (Fig. 3A)

confirming the glucose dependency of GIP-secretion. However, the same relationship was not observed between increase in glucose and GLP-1 ($r_P = 0.129$, $P = 0.722$), even though GLP-1 (iAUC) but not GIP response was positively correlated with glucose sensitivity ($r_P = 0.717$, $P = 0.030$) and with absolute insulin secretion rate (Fig. 3B). Neither total nor iAUC of pancreatic BF response during the mixed-meal test correlated with empirical- or model-derived parameters of β-cell function, or with insulin and C-peptide response. However, incremental glucose (Fig. 3C) and GIP ($r = 0.730$, $P = 0.040$) responses were positively correlated with pancreatic BF response, whereas neither glucose nor incretins were associated with intestinal BF responses.

The effect of infusion of GIP and GLP-1

Supraphysiological levels of plasma GIP and GLP-1 were reached within 15 min after the start of the corresponding infusions (Fig. 4A and B), respectively, and this was accompanied by a sharp and transient increase in serum insulin (Fig. 4C) and C-peptide concentrations (data not shown). Decrease in plasma glucose was evident only during the GLP-1 infusion, but not during the GIP infusion (Fig. 4D). Compared to baseline values, pancreatic BF decreased similarly during

Figure 3
Relationships between metabolic variables and pancreatic BF during a mixed-meal test. (A) Plasma GIP and glucose correlated supporting the bifunctionality (i.e. absorption and GIP-secretion) of the foregut ($n = 10$). (B) GLP-1 response was correlated with total insulin secretion rate (ISR) during the meal ($n = 9$). (C) Increment in pancreatic flow correlated with glucose response ($n = 8$). iAUC, incremental area under curve; ISR, insulin secretion rate.
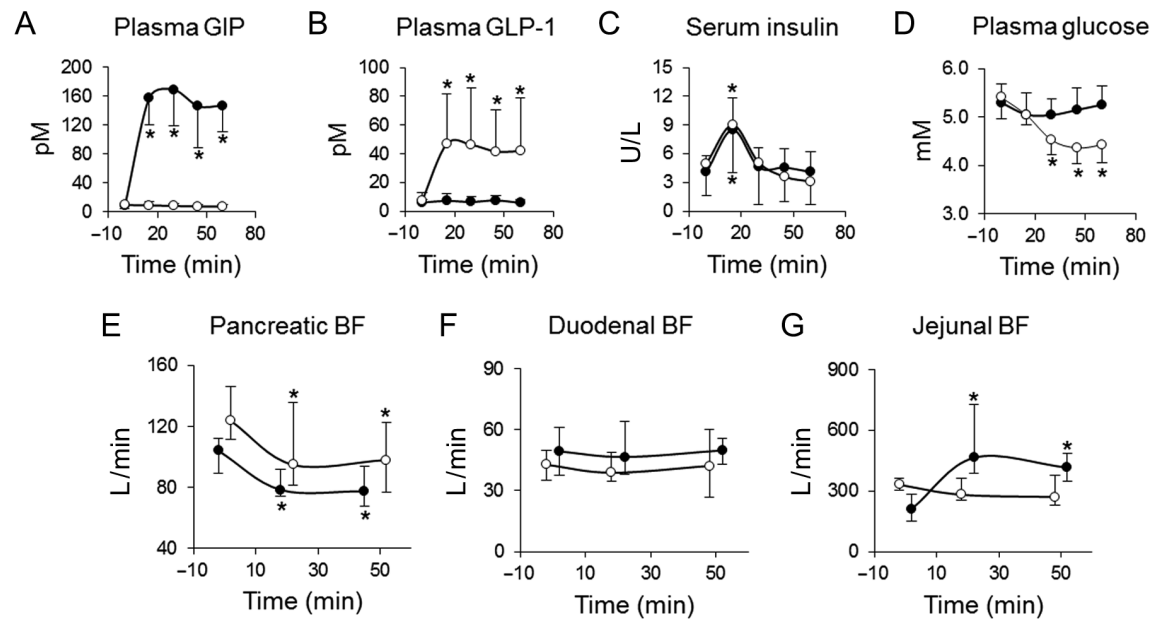
Figure 4

The effects of GIP (black dots) and GLP-1 (white dots) infusions on splanchnic BF. Supraphysiological concentrations of GIP (A) and GLP-1 (B) were reached within 15 min of start of the consequent infusion without affecting the levels of the uninfused incretin, respectively. Both incretins increased insulin levels transiently (C) whereas the decrease in plasma glucose was significant only during GLP-1 infusion (D). Infusion of GIP and GLP-1 led to a similar decrease in pancreatic BF rate (E). While infusions of GIP and GLP-1 unaltered duodenal BF (F), an increase in jejunal BF followed GIP but not GLP-1 infusion (G). Data are median (IQR), $n = 10$, $*P < 0.05$ vs baseline in repeated measurements ANOVA with Tukey–Kramer correction for individual interventions, $**P < 0.05$ vs baseline in repeated measurements ANOVA with Tukey–Kramer correction for pooled data.

GIP and GLP-1 infusion ($P < 0.001$ for time factor and $P = 0.745$ for time×intervention interaction, Fig. 4E). On the other hand, neither infusions had an effect on duodenal BF ($P = 0.756$ for time factor, and $P = 0.906$ for time×intervention interaction; Fig. 4F). Jejunal BF was increased by 2.4-fold during the GIP infusion ($P < 0.001$ for time factor, Fig. 4G) but it was unchanged during the GLP-1 infusion ($P = 0.691$ for time factor, $P < 0.001$ for time×intervention interaction). GIP and GLP-1 had no effect on pancreatic and intestinal BV. Decreases in plasma glucose after the GLP-1 infusions were not correlated with corresponding BF response in pancreas or intestine.

Discussion

The results of the present study demonstrate the adaptations in splanchnic BF during meal ingestion. Thus, a mixed-meal increased pancreatic and jejunal, but not duodenal BF. Infusion of GIP increased intestinal BF and reduced pancreatic blood flow. In contrast, infusion of GLP-1 diminished only pancreatic BF.

Here we utilized validated (12), cutting-edge molecular imaging methodology in ten healthy subjects and reported that jejunal and pancreatic BF *in vivo* are increased by approximately 70% and 20%, respectively, after a meal ingestion. In 1980s Chou and Kvietys coworkers (22, 23) described the hierarchy of nutrients inducing intestinal hyperemia and showed that lipid and fat in combination with bile are the most potent flow inducers followed by glucose and proteins. In healthy individuals, the rate of gastric emptying is tightly regulated by small intestinal feedback, wherein acute hyperglycemia and elevated levels of GLP-1 are mutually involved (24, 25). There are several differences in the magnitude of regulation of flow between gut and pancreas. First, pancreatic flow response seems to be dependent only on the levels of circulating vasoactive substances such as glucose and GIP, and on neural factors (26), while the postprandial response of the gut seems largely regulated by a direct interaction between luminal contents and the gut mucosa. Second, the stimulated gut BF accommodates absorption and metabolic processes, such as waste removal (27). In contrast to the jejunum, duodenal BF remained unchanged during the mixed-meal test, suggesting that the mucosal acid concentration might be the dominant flow regulator in the duodenum (28).

The incretin hormones GIP and GLP-1 are released from the enteroendocrine cells of the fore- and hindgut, respectively, upon chyme and bile salt contact with the

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mucosa, resulting in a potentiation of glucose-stimulated insulin secretion (GSIS) and control of appetite and food intake (29, 30). Both the GIP (31) and GLP-1 (32) receptors (GIPR and GLP-1R) have been identified in the endothelial and smooth muscle cells of the arterioles and GLP-1 has been ascribed cardioprotective role by endothelium-dependent vasodilation (32, 33). While previous studies in cultured cells (10, 34) and *in vivo* in canines have suggested that incretins may regulate splanchnic BF kinetics in the absorptive state, the involvement of the incretins in humans is somewhat unclear as the levels of active incretin hormones in the peripheral circulation are lower than the minimum doses required to produce vasodilatation (27). However, local tissue concentrations of these hormones, especially in the prehepatic vasculature (35), are high enough to exert their vasoactive properties. The doses of GLP-1 and GIP used in our study resulted in modestly pharmacological plasma levels and were well tolerated.

Interestingly, GIP infusion had a dual effect on BF, with a prominent increase in jejunal BF, paralleled by a decrease in pancreatic BF. Both of the incretin infusions transiently stimulated insulin secretion, consistent with previous findings (36). The results presented here suggest that in humans GIP may prepare the hindgut for the increases in metabolic demand, accompanied by a parallel increase in insulin secretion. The increase in jejunal BF elicited by GIP was in agreement with animal studies documenting augmentation of SMA flow after GIP bolus administration (10), confirming identical regulation in man. Previous studies in conscious animals failed to show any vasodilatation in the gut wall arterioles in response to postprandial incretin levels (27), indicating that the observed GIP-induced gut hyperemia is likely caused by the elevation in SMA BF.

The splanchnic vascular effects of GLP-1 were modest when compared with those of GIP, and were evident only as a decrease in pancreatic BF. In contrast after the mixed-meal test, GLP-1 was positively associated with jejunal but not with pancreatic or duodenal BF response. This is likely the result of the luminal stimulation of the gut leading to simultaneous upregulation of flow and hormonal secretion, rather than a causal relationship between incretins and gut BF. Of note, active GLP-1 levels remained in the baseline after mixed-meal ingestion (Fig. 2C), likely due to low amount of carbohydrates being insufficient for eliciting a response in GLP-1 secretion. The observation that GLP-1 does not regulate intestinal BF in the absorptive state is in line with a previous study in healthy Wistar rats (37). The same authors showed that GLP-1 attenuated pancreatic BF only after glucose administration but not during fasting conditions (37). In the study done by Trahair and coworkers the co-administration of GLP-1 infusion in humans further enhanced increase in SMA BF elicited by intraduodenal (ID) glucose infusion, whereas plain GLP-1 infusion without ID glucose infusion led to decrement in SMA BF (38). This is in line with our present study where GLP-1 leads to decrement in pancreatic BF, a tributary organ of SMA. However, why the jejunal BF remained unchanged despite the decrease in SMA BF cannot be answered on the basis of the present study but it may be linked to autoregulation in the mucosal vascular bed.

In interpreting these results some potential limitations should be recognized. We did not measure cardiac output, gastric emptying, sympathetic activity and atrial natriuretic peptide (ANP), which may be of relevance (39). It was not possible to differentiate islet BF from the exocrine pancreas BF due to the current PET resolution which equates 25-times the size of an average human islet (13). Consequently, the total pancreatic BF during the mixed-meal test may not reflect the exact vascular milieu in the islets. This may have curtained the link between islet BF, β-cell function, and insulin secretion during mixed-meal testing (5, 40). While the exocrine pancreatic BF is dependent on the afferent BF from the CA and its branches, islets have been shown to have more sophisticated vascular autoregulation (9, 11). Finally, two study subjects had IGT, which might have influenced the splanchnic flow. However, their splanchnic responses showed no statistical difference compared to non-insulin resistant study subjects.

In conclusion, the results of the present study demonstrate marked BF redistribution in the splanchnic vascular bed in response to a mixed-meal, due to an interaction of direct chyme contact, and elevations in plasma levels of glucose and incretin hormones, mainly GIP. Putative vascular effects of GLP-1 and GIP are likely to be more potent during postprandial and hyperglycemic conditions.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Endocrine Connections