IDENTIFICATION OF CONSTITUENTS OF CHYME RESPONSIBLE FOR POSTPRANDIAL INTESTINAL HYPEREMIA

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ABSTRACT

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By

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Blood flow to the splanchnic viscera increases after a meal. The purpose of the present study was: 1) to identify which constituents of chyme are responsible for the hyperemia and 2) to determine whether addition of amino acids to a glucose solution will increase the hyperemic effect of the solution when placed in the lumen of the jejunum. Two series of experiments were performed. In the first series, the vascular effects of luminal placement of the following solutions were compared: 1) undigested homogenized dog food diluted with 2 parts distilled water to 1 part food, 2) pancreatic enzyme preparation (Viokase^{R}) suspended in normal saline (187.5 mg/100 cc), 3) digested food, digested by the pancreatic enzyme preparation and diluted with 2 parts distilled water to 1 part food, 4) supernatant of the digested food, 5) precipitate of the digested food, 6) gallbladder bile diluted with 2 parts normal saline to 1 part bile, 7) equal parts of undiluted digested food, distilled water

and undiluted gallbladder bile, and 8) normal saline. These solutions were paired into the following six combinations: 1) digested food and undigested food, 2) supernatant and precipitate, 3) supernatant and digested food, 4) supernatant and enzyme, 5) gallbladder bile and normal saline, and 6) digested food plus bile and digested food. Venous outflow from two adjacent *in situ* canine jejunal segments were simultaneously measured; one segment contained one of the paired solutions and the adjacent segment contained the other such tnat the vasoactivity of the paired substances could be compared. As a control, normal saline was placed in both segments before and after the comparisons.

Luminal placement of digested food, its supernatant and the digested food plus bile solution significantly increased blood flow. Undigested food, precipitate, the pancreatic enzyme preparation, gallbladder bile (1:2 dilution) and normal saline, however, did not have any vascular effect. The hyperemic effect of digested food and its supernatant was quantitatively the same. Their vascular effects were significantly different from those of undigested food, precipitate and pancreatic enzyme, which did not increase blood flow. The addition of gallbladder bile to the digested food markedly augmented the hyperemic effect of the food. These studies indicate that the hyperemia induced by the presence of food in the lumen of the intestine requires the pancreatic

enzymes and that the hyperemia is enhanced by the addition of gallbladder bile. The substances responsible for post-prandial hyperemia are in the supernatant of the digested food and are likely to be the digestive products of food.

In the second series of experiments, the vascular effects of luminal placement of an isotonic glucose solution and a mixture of glucose and amino acids were determined and compared. The experiments were performed on two groups of dogs utilizing the double segment preparation. The glucose solution or the glucose-amino acids mixture was placed in one segment while normal saline was placed in the other as control. In the first group of dogs, the vascular effect of the isotonic glucose solution was studied. Venous outflow was obtained and vascular resistance calculated. These parameters were then compared with those obtained from the second group of animals in which the vascular effects of luminally placed isotonic glucose-amino acids mixture was tested.

Luminal placement of both the glucose and the glucose-amino acids mixture significantly increased blood flow and decreased vascular resistance. The glucose-amino acids mixture, however, had greater hyperemic effects than did the glucose solution alone. The study suggests that amino acids in the lumen enhance the hyperemic effect of glucose.

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Siu Po Sit

A THESIS

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To my parents

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CHAPTER I

INTRODUCTION

Many studies indicate that the cardiovascular system responds to feeding in two distinctly different phases. During presentation and ingestion of food, cardiac output, heart rate, aortic pressure and vascular resistance in various vascular beds are altered in a pattern which mimics an increase in sympathetic neural activity. Within 5-30 minutes following a meal, cardiac output, heart rate, aortic pressure and blood flow to the heart and kidney return to control levels while superior mesenteric arterial flow starts to rise and reaches a maximum in 30-90 minutes. A recent study further shows that this increase in mesenteric blood flow is confined only to the mucosal layer of that intestinal region which is exposed to food. The specific process triggering the intestinal hyperemic response to food is not known. Nor is it clear which of the constituents of intestinal contents are responsible for the hyperemia. It has been postulated that the digested products of food (i.e., fatty acids, amino acids, glucose etc.) and their absorptive processes may be involved in the local mesenteric hyperemia. Placement of each of these substances in the lumen of the small intestine

has been shown to increase venous outflow and decrease vascular resistance. The cumulative effect of these nutrients on mesenteric blood flow, however, has not yet been investigated.

The present study was undertaken to: 1) identify the constituents of chyme that are responsible for the postprandial hyperemia and 2) determine whether the intraluminal placement of two elementary nutrients, i.e., glucose and amino acids, as a mixture, have a cumulative effect on venous outflow of the jejunum.

CHAPTER II

LITERATURE REVIEW

Postprandial Hemodynamics

It is teleologically appealing to assume that blood flow through the mesenteric vascular bed increases postprandially because of an increase in digestive activities of the gastrointestinal tract following a meal. Likewise, the organs unrelated to digestion are expected to receive less blood flow following food intake. Fronek and Stahlgren (22) found that superior mesenteric blood flow increased after food intake by as much as 133% while the brachiocephalic and iliac arterial flows decreased to 86.5% and 74% of control, respectively. The experiments were performed on conscious dogs with implanted electromagnetic flow transducers around the ascending aorta, brachio-cephalic, superior mesenteric and iliac arteries. Blood flow and vascular resistance in these vessels along with systemic arterial pressure was recorded before a meal, during presentation and anticipation (of food), during ingestion, and 1 hour and 3 hours following food intake. During the anticipation and ingestion periods, cardiac output was observed to increase by 142% with a

concomitant rise in both blood pressure and heart rate. The changes in these parameters reached a maximum in the first minute after the beginning of ingestion and gradually declined back to control level 1 hour after feeding. Total peripheral resistance tended to drop during anticipation of food but increased modestly (5%) during ingestion. This slight increase persisted even after the completion of food intake. Brachiocephalic arterial flow increased during ingestion by 196% while the iliac arterial flow dropped to 75.4% of control level. Although there was a slight increase in superior mesenteric blood flow at this time, mesenteric regional resistance was found to increase by 28%. The authors suggested that there was a general sympathetic response to anticipation and actual ingestion of food. During digestion (1 and 3 hours after ingestion), blood pressure, cardiac output, heart rate and total peripheral resistance were not significantly different from control levels. However, there was a decrease in mesenteric regional resistance as indicated by the increase of blood flow through the superior mesenteric artery. There seemed to be a redistribution of blood flow to the splanchnic bed since both iliac and brachiocephalic arterial flows decreased significantly. The ratio of flow in the superior mesenteric artery to cardiac output was found to have increased from 9% at control to 13% three hours after food intake.

This finding of postprandial blood flow redistribution favoring the splanchnic bed, with cardiac output remaining unchanged was inconsistent with earlier reports (14,23,31, 44). These earlier studies showed that there was a concomitant rise in both cardiac output and splanchnic blood flow after food intake. Blood pressure, heart rate and blood flow to various other organs were also increased postprandially. The difference in the results between these early studies and that of Fronek and Stahlgren (22) may be due to differences in instrumentation, species, and methods used. For example, in 1929 Grollman (28) studied the effect of eating on cardiac output, pulse rate and blood pressure on conscious human subjects, but did not measure splanchnic blood flow. By employing the modified acetylene gas method to measure the vascular responses indirectly, he found an immediate increase in cardiac output after food ingestion that may last as long as five hours. Pulse rate was observed to increase transiently but systemic blood pressure was not significantly altered. Herrick et al. (31) utilized the thermostromuhr method of Rein to measure blood flow in trained dogs under local anesthesia (pantocaine). Blood flow was found to increase in the femoral, carotid and superior mesenteric arteries as well as the jugular vein following ingestion. However, neither systemic arterial pressure nor cardiac output were measured. Gladstone (23) measured the

effect of eating on cardiac output in conscious human subjects by using the ethylene gas method and found it increased by 25% of control. Dagenais et al. (14) studied the hemodynamic effects of carbohydrate and protein meals in man, measuring the changes in cardiac output, heart rate and blood pressure. Again mesenteric blood flow was not recorded. Heart rate was monitored by electrocardiograph and blood pressure by sphygmomanometer. A fine catheter was inserted percutaneously through an antecubital vein to the superior vena cava. Coomassie blue dye was injected through the catheter to measure cardiac output. A protein rich meal (filet mignon) brought a greater increment of cardiac output (+46%) than did a carbohydrate rich diet (fruit juice, ice cream, cake and syrup, 34%). There were comparable increases in both heart rate and systolic blood pressure in both instances. Maximal changes were reached in 1½ hours after the carbohydrate meal and much later (up to 3 hours) following the protein meal. Brandt and associates (5), unlike other investigators, estimated postprandial changes in splanchnic blood flow by the bromsulfalein (BSP) method in conscious human subjects. Protein feeding induced a 35% increase in the estimated splanchnic blood flow in 20-50 minutes while glucose feeding did not elicit any change. Cardiac output was not measured. Thus, the consensus among these early investigators was that cardiac output and mesenteric blood flow increased concomitantly after a meal.

Since the introduction of the redistribution hypothesis by Fronek and Stahlgren (22), many new studies have been performed to investigate this phenomenon. Most of them have made direct measurements on cardiac output, blood flow through the mesenteric and various other vascular beds with different types of flowmeters. Burns and Schenk (6) in 1969 measured cardiac output and blood flow through the superior mesenteric artery on conscious dogs following meal intake. Electromagnetic flowmeters were planted on the ascending aorta and the superior mesenteric artery to monitor blood flow. After consuming a standard meal of 15 oz. of horsemeat, mesenteric blood flow began to rise within 5 minutes and reached a plateau approximately 50 minutes later. The mean flow was still 50% above the control level 3 hours after feeding. Although there were occasional changes in cardiac output during ingestion, no detectable increment was observed during digestion. By using various flowmeters, Vatner et al. (57) found in conscious dogs that anticipation and ingestion of a meal caused increases in cardiac output, heart rate and aortic blood pressure. These increases returned to the control level within 10-30 minutes after food presentation and remained stable throughout the digestive period. Although mesenteric blood flow decreased (10%) transiently during anticipation, it began to increase during actual ingestion and reached the maximal values (115-300% of

control) within an hour. This increase in blood flow to the viscera may last up to 7 hours postprandially. The same group of investigators (56) found later that in addition to the above mentioned vascular changes, renal resistance increased by 24%, iliac and coronary resistances decreased by 33% and 62% respectively during the anticipation and ingestion period. During digestion, the increase in mesenteric flow was accompanied by a slight decrease (10%) in iliac flow while cardiac output, heart rate, renal and coronary vascular resistances returned to their control levels. This suggested that there was vasoconstriction in the muscular vascular bed to compensate for the increase in flow to the mesenteric vascular bed during digestion.

In 1974, Vatner et al. (58) studied the regional circulatory adjustments to eating and digestion in conscious primates. Doppler ultrasonic flow probes were used to measure blood flow changes in the mesenteric, renal, iliac and coronary arteries. Arterial pressure was measured by miniature gauges implanted in the thoracic aorta while heart rate was monitored continuously by cardio-tachometer. A total of eight baboons and one chimpanzee were used as experimental subjects. During ingestion of a meal consisting of different fruits, the baboons experienced an increase in both heart rate (82%) and arterial pressure (25%). Likewise, iliac and coronary flows were observed to increase by

84% and 152% respectively. There was a transient but significant decrease in both mesenteric (12%) and renal (4%) blood flow during this time. During digestion, mesenteric blood flow rose and reached a maximum in an hour. This increase in flow may last up to 4 hours and was accompanied by a significant decrease in iliac flow (31%). Heart rate, arterial pressure, coronary and renal blood flow remained at control levels throughout digestion. In the case of the chimpanzee, the response to feeding was similar to that of the baboons. However, mesenteric blood flow increased at 2 hours and reached a peak at 3 hours after eating, which was much later than those occurring in the baboons.

These recent studies have, therefore, shown that although cardiac output, heart rate and systemic pressure increase during the anticipation and ingestion of food, the changes are transient and decline to control levels during digestion (6,22,56,57,58). Mesenteric blood flow began to increase from 5 to 30 minutes after completion of food intake and the hyperemia may last up to 7 hours. This increase in mesenteric blood flow during digestion is accompanied by increased resistance in the brachiocephalic and iliac arteries (22,56,58). There is a postprandial redistribution of blood flow favoring the mesenteric vascular bed at the expense of the muscle and skin. Indeed, the ratio of blood flow in the superior mesenteric artery to cardiac output has

been observed to increase from 9% before meal to 13% during digestion (22).

These studies, however, have not determined the specific localization of the hyperemia within the mesenteric circulation. Fara et al. (18) observed that intraduodenal instillation of corn oil in cats caused increases of blood flow through the superior mesenteric, pancreatic and jejunal arteries while flow through the stomach and colon were not altered. Chou et al. (12) found in anesthetized dogs that the hyperemia through the various organs within the gastrointestinal tract seemed to follow the pattern of chyme movement. The flow through the celiac artery was observed to increase when food was introduced into the stomach but did not change when instilled into the duodenum. Superior mesenteric blood flow on the other hand, fell transiently but not significantly during intragastric placement of food; started to rise 30 minutes after the placement and remained increased for 3 hours. This is significant since the celiac artery supplies the stomach; whereas, the superior mesenteric artery supplies the small intestine. What this seemed to indicate then, was that blood flow may increase only in that region exposed to food and not indiscriminantly throughout the gastrointestinal tract.

This possibility was furthhr explored by these investigators when they infused food intraduodenally. In addition

to monitoring the superior mesenteric arterial flow, they measured venous outflow from an isolated *in situ* jejunal segment. As before, superior mesenteric blood flow was found to increase during the intraduodenal food infusion but venous outflow from the isolated jejunal segment which had no contact with food was not altered. When the same food was placed only into the isolated jejunal segment, the blood flow through the segment increased but that through the superior mesenteric artery did not. Subsequently venous outflows from two isolated adjacent *in situ* jejunal segments were measured simultaneously; one segment contained 10 ml of food and the other, the same amount of saline. The segment with food increased its flow while no change was observed in the control segment with saline. These findings suggested that the intestinal hyperemia that occurs during digestion is a local phenomenon. Radioactive microspheres were also used by these authors (12) to study the compartmental blood flow in the jejunum. Three isolated *in situ* jejunal segments were used, one was left empty and the other two contained either 10 ml of non-absorbable polyethylene glycol solution or the same amount of food. It was found that only the segment containing food significantly increased its total blood flow. The increase in the total wall flow resulted from an increase in mucosal flow; flow to the submucosa and the muscularis remain unchanged. Yu *et al.* (61) in a similar study using radioactive microspheres observed

that placement of 50% glucose solution in an isolated jejunal segment in dogs induced greater blood flow to the mucosa but not to the other two layers of the gut wall. Thus, the increase in the superior mesenteric blood flow during digestion may well be due to an increased flow in that portion of the intestine that is in contact with food. Furthermore, the increased flow is localized in the mucosal layer of the intestinal wall (12,61).

Mechanisms of Postprandial Hemodynamics

Although some information has surfaced in recent years concerning the mechanisms involving the cardiovascular responses to food intake, the overall picture is not entirely clear. Opinions are not always unanimous as to what mediates the local intestinal hyperemia during digestion. Nor is there a concensus as to what initiates the increase in flow to that part of the intestine that is in contact with food. Nonetheless, investigations have been done to elucidate the mechanisms of the postprandial responses. Among the mediators that have been implicated are: 1) the systemic and local neural pathways and 2) various humoral substances that are released into the blood stream during digestion.

Systemic and Local Nerves

The efferent parasympathetic system to the gastrointestinal tract originates in the pre-optic and supraoptic

nuclei of the hypothalamus. It synapses with the dorsal vagal nuclei and with cells in the second, third and fourth sacral segments (52). The vagal preganglionic fibers are connected directly and without interruption to the postganglionic neurons in the intrinsic plexus of the visceral organs, such as the liver, bile ducts, gallbladder, pancreas, stomach, small intestine and the proximal colon (46). The preganglionic neurons originate from the second, third and fourth sacral segments innervating the distal colon through the pelvic nerves (52).

The efferent sympathetic preganglionic fibers originate from the hypothalamic region, relay in the lower seventh or eighth thoracic segments (T_5 to T_{12}) and the upper lumbar segments (L_1 to L_3). The axons run via the splanchnic nerves to reach the postganglionic neurons in the celiac, superior, inferior mesenteric and the inferior hypogastric plexuses. The postganglionic fibers innervate the visceral blood vessels and the secretory glands. Stimulation of the sympathetic system causes vasoconstriction and inhibition of motility (46,52).

Autonomic preganglionic fibers and most parasympathetic postganglionic fibers to the gastrointestinal tract are cholinergic; in contrast, the sympathetic postganglionic fibers are known to be predominantly adrenergic (46).

There are two major intrinsic nerve plexuses within the gastrointestinal tract. the submucosal plexus of Meissner

and the myenteric plexus of Auerbach. The former plexus consists of unipolar and bipolar cells. It is situated between the muscularis mucosa and the circular muscles of the intestinal wall. The latter plexus is located between the longitudinal and circular muscle coats and its cells are mostly multipolar. The sensory endings of the visceral afferent fibers are dendrites from the submucosal plexus that may be situated in the mucosal epithelium, in the muscle layers or in the plexuses. They are chemical and mechanical receptors that respond to changes in the intestinal contents (peptides, amino acids, fats, pH and osmolality) and stretch or distension (15). The afferent impulses may be conducted centrally via the vagal and sympathetic fibers or be transmitted locally via the submucosal plexus to the myenteric plexus (15,46, 52).

Zamiatina (62) found that presence of food or its digestive products in the lumen of the gut can stimulate the receptors in the intestinal wall. Cats anesthetized with urethane were used in the study. Nerve branches of the afferent innervations from the small and large intestine were isolated and their impulses recorded by a cathode ray oscillograph. During digestion in animals that were fed with meat, high neural activity was seen from the afferent nerves of the jejunum, mesentery and pancreas but not of the colon. This was also true with glucose and amino acid

solutions infused into the gut. Glucose (4-10%) solution had a stimulating effect on the upper part of the jejunum; whereas, amino acid mixtures intensified the neural activities in the jejunum, mesentery and pancreas. In a similar experiment, Sharma and Nasset (48) have also been able to demonstrate that when glucose and amino acid solutions were perfused through the lumen of the small intestine, the frequency of firing from mesenteric nerves increased by as much as 400% from control.

Fronek and Stahlgren (22) characterized the increases in heart rate, blood pressure and cardiac output during anticipation and ingestion of food as a generalized sympathomimetic response. They cited as evidence the findings of Ehrlich et al. (16) that there was no increase in mean arterial blood pressure during ingestion in catecholamine-depleted dogs.

The roles played by the autonomic nervous system during anticipation, ingestion and digestion of food was examined in detail by Vatner et al. (57). The effects of food presentation, actual ingestion and digestion on cardiac output, heart rate, aortic pressure and mesenteric blood flow before and after adrenergic and cholinergic blockade in conscious dogs were investigated. Alpha and beta adrenergic blockade by phenoxybenzamine (15 mg/kg) and propranolol hydrochloride (3 mg/kg) respectively attenuated the increases in heart

rate, blood pressure and mesenteric resistance during the anticipation and ingestion periods. No effect was observed on the hyperemia in the mesenteric vasculature during digestion period. Cholinergic blockade by atropine (0.1-0.2 mg/kg) prevented the mesenteric vasodilation during digestion but bilateral thoracic vagotomy had no effect on the response. Fara et al. (17) also observed in cats that atropine (0.06-0.5 mg/kg, i.v.) blocked the increase in superior mesenteric blood flow seen after the intraduodenal instillation of milk, corn oil (fat), L-phenylalanine or hydrochloric acid. Bilateral splanchnicectomy or combined alpha and beta adrenergic blockades have no effect on the vasodilation. The important role played by the cholinergic fibers in the mesenteric hyperemia during digestion has also been demonstrated by Vatner et al. (58) in primates. They have shown that the mesenteric vasodilation in the baboon could be attenuated by prior cholinergic blockade with atropine (0.6 mg/kg). Again the blockade has no effect on the vascular responses seen in the early ingestion phase of a meal.

Thus, these findings seem to suggest that although the sympathetic nervous system may be involved in the anticipation and ingestion responses to food, it is the parasympathetic system that plays a major role in the mesenteric vasodilation during digestion. The fact that bilateral thoracic

vagotomy has no effect on the postprandial vascular response indicates that cholinergic influence may be at the local level; most likely involving the intramural nerve plexus.

Chen et al. (9) have demonstrated that dibucaine can attenuate the vascular effects of intraluminally placed hypertonic salt solutions. Before applying the local anesthetic, 1500 mOsm of NaCl, KCl, $MgCl_2$ or $CaCl_2$ salt solutions all increased blood flow in an in situ jejunal loop. However, after the mucosa of the segment had been exposed to 0.4% dibucaine, only $MgCl_2$ increased blood flow. Other solutions either lowered blood flow or had no effect on the jejunal vasculature. Chou et al. (10) showed that dibucaine can also attenuate the increase in blood flow evoked by hypertonic glucose solution in the lumen of the gut. Yu et al. (61) observed that the inhibitory effect of the local anesthetic on the vasodilation is limited to the mucosal layer of the luminal wall. Prior exposure to dibucaine attenuated the mucosal hyperemic response to hypertonic glucose solution in the lumen. Blood flow to the other two layers was not affected by the anesthetic.

As discussed above, the cardiovascular responses seen during the anticipation and ingestion of food may, in part, be mediated by the sympathetic fibers. The parasympathetic system, on the other hand, is likely to be involved in the postprandial hemodynamics. Local cholinergic plexuses have

been suggested to play a role in mediating the mesenteric hyperemia due to food. Precisely what are the neural mechanisms that lead to the vascular adjustments during digestion is not clear. It is likely that receptors in the gut wall continuously monitor the content of the chyme and provide vital information for the local reflex arc during the presence of food in the lumen. In turn, the intraluminal cholinergic plexus may either act on the blood vessels or release local vasoactive agents to produce the vascular responses to food intake.

Humoral Substances

Gastrointestinal hormones: The specific actions of the three gastrointestinal hormones, i.e., gastrin, secretin and cholecystokinin (CCK) on secretion, absorption, motility and metabolism of the gastrointestinal tract have long been under intense scrutiny. It was not until recently that attention has been given to their possible vascular effects. All three of these hormones are released from the upper gastrointestinal tract during digestion. They have been shown to have specific vascular effects on different organs.

Gastrin was first proven to exist by Grossman and colleagues (29) in a transplanted fundic pouch with a distended antrum. In 1964, Gregory and Tracy (27) succeeded in isolating the hormone which later was identified as a 17 amino acid peptide amide with a molecular weight of 2,114.

Species variation have been known to exist and the differences occur between residues 5 and 10 with the rest of the molecules being identical. Interestingly, all the physiological actions of the hormone can be reproduced by the C-terminal tetrapeptide amide of the molecule (15,34,52). A synthetic acyl derivative of the tetrapeptide called pentagastrin has long been available commercially for scientific research in both humans and animals. The antrum of the stomach is the main source of gastrin. The release of the hormone from the antrum may be stimulated by vagal stimulation, gastric distention or various chemicals (e.g., meat extracts, amino acids, histamine and alcohol) in the stomach. Inhibition of the release of the hormone occurs when the antral pH drops below 3.5 (34).

Chou et al. (11) observed in dogs that infusions of gastrin extracted from porcine antrum (0.2 mg/ml at 0.19-7.75 ml/min) into the superior mesenteric artery decrease the resistance of the vessel by 10 to 12%. They attributed the phenomenon to the hormone's vasodilating effect on the small vessels in the intestine. Laureta et al. (38) found local intra-arterial infusion of the same dose of the hormone at a slower rate to have similar effect on the canine stomach. It was concluded that gastrin may very well be vasoactive in both the gastric and mesenteric vascular beds. Swan and Jacobson (51) on the other hand, found that gastrin

had no effect on the total blood flow to a gastric pouch but did increase its mucosal blood flow. The effects of subcutaneous injection of gastrin extracted from porcine antrum were demonstrated by Burns and Schenk in dogs (6). Injection of 2 units/kg of the extract subcutaneously increased mesenteric blood flow within 5 minutes, flow reached a peak (45% above control) in 1 to 2 hours and remained elevated for up to 3 hours. In addition to its effects on the gastric and mesenteric vasculature, gastrin has also been shown to increase pancreatic secretion and blood flow (24) as well as decrease hepatic vascular resistance (42). Whether these vascular effects of the hormone resulted from a direct influence on the visceral blood vessels or indirectly through the release of intermediary agents is still not clear. Fasth et al. (19) observed in cat small intestine that atropine (1 mg/kg, i.v.) can attenuate the increase in intestinal motility but not the increase in blood flow induced by the intra-arterial infusion of the hormone (3 ug/kg/min). Bowen et al. (4) recently found that cholinergic blockade by atropine (0.5 mg/kg) abolished the vasodilating effect of pentagastrin (0.5 ug/kg/min, i.a.) in the canine distal ileum. Thus, depending on the species, the hormone's actions on both motility and blood flow may well be mediated through cholinergic receptors.

Secretin was first isolated by Mutt and Jorpes (40) and synthesized by Bodanszky et al. (3). The hormone is a polypeptide containing 27 amino acid residues in which all are required for activity. It has a molecular weight of 3,056. It is believed that secretin is produced by villus epithelial cells in the duodenum (15,34). Hydrogen ions in the duodenum are the most effective stimulant for the release of the hormone. Intraduodenal instillation of fatty acids and amino acids have also been shown to cause the release of the peptide (34). Secretin is most effective in stimulating the secretion of bicarbonate and fluid in the pancreas and pepsin in the stomach (15,34,45).

The vascular effects of secretin in the gastrointestinal vasculature have been studied in cats (17,45), dogs (4,11, 24,38) as well as in humans (54). Chou et al. (11) and Laureta et al. (38) did not observe any change in vascular resistance when they infused the hormone intra-arterially into the canine superior mesenteric artery (1 ug/ml) and the stomach (0.133 ug/ml) at various rates (0.19-7.75 ml/min). Goodhead et al. (24) used radioactive rubidium (^{85}Rb) to measure cardiac output and blood flow to various organs in the canine gastrointestinal tract. Secretin infusion (5 units/kg, i.v.) only caused increases in pancreatic and duodenal blood flow and not in other organs. Recently Bowen et al. (4) observed in dogs that high doses of synthetic

secretin (0.03 ug/kg/min and 0.3 ug/kg/min for 10 minutes) administered intra-arterially into a loop of distal ileum did not elicit any response. Burns and Schenk (6) on the other hand, found in dogs that intravenous injection of 1.5 units/kg of an impure extract of secretin increased mesenteric blood flow within 5 minutes. This increment reached a maximum (38% above control) in 2 hours. Ross (45) examined the effects of a natural secretin extract on arterial pressure as well as on blood flows through the femoral, hepatic and superior mesenteric arteries in cats. Rapid injection (1-10 units, i.a.) decreased resistance in the superior mesenteric and femoral arteries but not the hepatic artery. These changes were accompanied by a prolonged increase in blood pressure. Fara et al. (17) observed that intravenous administration (0.4-10.3 units) of a pure, natural secretin into cats increased the superior mesenteric, pancreatic and jejunal arterial blood flow. Uden (54) observed in humans that secretin injection increased the radius of the portal vein but not the hepatic artery. Thus, substantial disagreement exists as to the vascular effects of secretin in the stomach and the small intestine. This may stem from the fact that most studies were conducted with purified secretin rather than the synthetic one. Naturally obtained extracts of the hormone are known to contain various other vasoactive substances such as

CCK or plasma kinin. These contaminants may have contributed to many of the vasodilating effects of secretin. Only Bowen and associates (4) have used synthetic secretin in their studies. Unfortunately, they did not examine the vascular effects of the hormone in the entire gastrointestinal tract.

Ivy and Oldberg's cholecystokinin (33) and Harper and Raper's pancreozymin (30) have been proven to be one single hormone (36) whose structure was discovered by Mutt and Jorpes recently (39). It is a polypeptide consisting of 33 amino acids. Its C-terminal pentapeptide is identical to the minimal active fragment of gastrin and thus, the action of the two hormones are quite similar (34,39). There are, however, quantitative differences between the two agents. Unlike gastrin, CCK is a strong stimulant of gall bladder contraction and a weak stimulant of gastric secretion. In fact, CCK has been shown to antagonize the action of gastrin on gastric acid secretion. The mechanism is thought to be through competitive inhibition (34). Although amino acids, fatty acids and hydrogen ions in the duodenum all stimulate the release of CCK from the upper small intestine, vagal stimulation has little or no effect on the release of the hormone (34).

Fara et al. (18) was able to mimic the vascular effects of intraduodenal fat by intravenous infusion of CCK. In cats, infusion of 4.7 units/kg/hour of the partially

purified hormone increased both superior mesenteric blood flow and duodenal motility. It was postulated that CCK may be the mediator of fat-induced vasodilation in the duodenum. Fasth et al. (19) found that local intra-arterial infusion of the hormone (4.3 units/kg/min.) into the cat's small intestine caused an immediate but short lasting increase of blood flow through the superior mesenteric artery. Both the vascular and metabolic effects of CCK were examined by Fara et al. (17) in cats. Between the dosage of 1.1-4.3 units/kg/hour, i.v., at constant infusion, CCK increased blood flow and O_2 consumption in the jejunum and pancreas. These effects were not blocked by atropine (0.5 mg/kg, i.v.) or vagotomy. Bowen et al. (4), however, observed in canine ileum that the increases in superior mesenteric blood flow and O_2 consumption after infusion of CCK (0.1 ug/kg/min for 10 minutes) can be blocked by atropine (0.5 mg/kg, i.v.). Route of infusion and dosage of the hormone as well as species difference may account for the contrasting results.

Fara et al. (17) suggested that the mesenteric vasodilation caused by CCK may have been the consequence of the release of local vasoactive agents triggered by the hormone. Their in vitro studies have shown that CCK could not modify the active vascular tension on a strip of the superior mesenteric artery. Thus, it is unlikely that the hormone has any direct vascular effect on the mesenteric vasculature.

Biber et al. (2) observed in cats that blocking the vascular effects of 5-hydroxytryptamine (5-HT), a vasodilator, by an α-receptor antagonist (dihydroergotamine) can abolish the intestinal vascular responses to CCK infusion. It was suggested that 5-HT, may be the intermediary vasoactive agent for the mesenteric vasodilation elicited by CCK. Hilton and Jones (32) perfused the cat's pancreas with CCK and found increases in both pancreatic blood flow and secretion. In addition, they found that the activity of the active kinin-forming enzyme 'kallikrein' in the perfusate had increased about fourfold. This led them to speculate that plasma kinin may play a prominant role in the functional vasodilation of the pancreas during CCK infusion.

In summary, all three hormones have been shown to be vasoactive in the gastrointestinal vasculature. Infusion (both i.a. and i.v.) of gastrin in dogs and cats produced vasodilation in the superior mesenteric, pancreatic and hepatic arterial blood flows (6,11,24,38,42). Whether this hormone acts directly or through other vasoactive agents is not known. Findings concerning the vascular effects of secretin are controversial. There is conflicting evidence as to whether or not the hormone is vasoactive in the small intestine (4,6,11,17,38,45). Its vasodilating effect on the pancreas, however, has been well-established (20,24,41,54). CCK is known to decrease vascular resistance in the small

intestine (2,4,11,17,18,53), stomach (38), pancreas (24,32, 41) as well as in the portal vein (42,53). It was suggested that the hormone's action may be mediated by 5-hydroxytryptamine (2) and kallikrein (32).

It must be emphasized that much of the vascular effects of the hormones cited in this review were obtained from pharmacological doses. Thus, any extrapolation from these data must be treated with caution. Chou* recently found that of the 3 hormones, only CCK is able to exert its vascular effects at physiological doses (2-8 μ units/ml). This is compatible with the observation of Fara et al. (17) in cats that infusion of low doses of CCK mimicked the vascular response induced by intraduodenal fat. Furthermore, atropine, which prevents the release of CCK (59), has been shown to prevent postprandial mesenteric vasodilation (17,56,58). What these findings seem to suggest then, is that the mesenteric vasodilation could be a consequence of the release of CCK. It is unlikely, however, that CCK is the sole vasoactive agent involved since mesenteric blood flow has been shown to increase by as much as 300% of control postprandially (56,58). The average increase of flow in the superior mesenteric artery after CCK infusion (even at pharmacological doses) is less than 100% (2,4,17).

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*Personal communication with Dr. C. C. Chou.

Other vasoactive substances: Many other substances have been shown to be vasoactive in the mesenteric vasculature. Unfortunately, their exact role in postprandial hyperemia have not been determined. Both 5-hydroxytryptamine (2) and kallikrein (32) have been suggested as possible mediators for the vascular effects of CCK in the small intestine and the pancreas (2,32). Intra-arterial infusion of high carbon dioxide tension blood, ATP, ADP, AMP, bradykinin, prostaglandins, acetylcholine or histamine in the dog causes intestinal vasodilation (15,25,52). What role these substances play in postprandial hemodynamics, however, has not been elucidated. Thus, besides the three gastrointestinal hormones, little is known concerning the possible role of other endogenous humoral substances in eliciting the local increase of mesenteric blood flow.

Initiation Factors in Postprandial Hemodynamics

If the role played by various endogenous vasoactive substances during postprandial hyperemia is poorly understood, much less is known about the food constituents that are responsible for the vasodilation. Very little information is available concerning the initiating process of the vascular responses after eating. It has been observed by Dagenais et al. (14) that the time of maximal change of the vascular response to food was comparable to the time of

maximal absorption of carbohydrates and proteins. The site for transmembrane transport of water, electrolytes and other nutrients is located in the mucosal layer (15). That the hyperemia is confined only to this layer of the intestine would certainly lead one to speculate that the digestive products of food and their absorptive processes may be involved in the initiation of postprandial hyperemia (12). Whether digestion of food is necessary for the increase in mesenteric blood flow, however, has not been determined. Although various digestive products have been shown to be capable of increasing blood flow when placed in the lumen of the intestine (10,17,55,61), their role in the initiation process has yet to be elucidated.

The purpose of this present study was twofold: 1) to identify the constituents of chyme that are responsible for the postprandial intestinal hyperemia and 2) to determine whether the intraluminal placement of two elementary nutrients, i.e., glucose and amino acids, as a mixture, have a cumulative effect on venous outflow of the jejunum.

CHAPTER III

METHODS

Surgical Procedures

Mongrel dogs (15-25 kg) of either sex were fasted for twenty-four hours, anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and ventilated with a positive pressure Harvard respiration pump (Model #607, Dover, Mass.) to achieve normal arterial pH. Systemic arterial pressure (mm Hg) was monitored by a Statham pressure transducer (Model #P23Gb, Hato Ray, Puerto Rico) via a cannula (PE 280) inserted into the femoral artery, and continuously recorded on a four channel Sanborn oscillograph (7700 series, Waltham, Mass.).

The abdominal cavity was exposed through a midline incision and a loop of the jejunum about 30 cm distal to the ligament of Treitz was exteriorized and divided into two segments of equal length. The vein draining each segment was cannulated with a polyethlene tubing (PE 240) after an intravenous administration of sodium heparin (6 mg/kg). The venous outflow was collected in a reservoir initially containing 200 ml of 6% dextran in normal saline.

The venous blood was returned to the animal continuously with a Holter pump (Model RE 161, Extracorporeal Medical Specialties, Inc., King of Prussia, Pa.) via a femoral vein at rates equal to the rates of the total venous outflow. A rubber tube (i.d. = 0.3 cm; o.d. = 0.5 cm) was introduced into the lumen of each segment for the placement of the test substances. The tubes were connected to a Statham pressure transducer (P23Gb) for the measurement of the intestine luminal pressure when the solutions were in the lumen. Both ends of each segment were tied and the mesentery cut to exclude collateral flow. The two segment were then covered with a plastic sheet and kept at 37°C with a heat lamp.

Preparation of the Solutions Studied

The solutions studied were: 1) undigested food, 2) digested food, 3) the supernatant of the digested food, 4) the precipitate of the digested food, 5) the pancreatic enzyme preparation (Viokase^{R}, Viobin Co., Monticello, Ill.) used in the preparation of the digested food, 6) gallbladder bile, 7) digested food plus bile, 8) normal saline, 9) isotonic (5.4%) glucose solution, and 10) a mixture of glucose and 16 amino acids.

The food solutions were made from commercially available dog food (protein 12%, fat 7%, fiber 1.5%, ash 3%, linoleic acid 0.4%, moisture 78%) (Alpo Beef, Allen Products Co., Allentown, Pa.). A can of this dog food was homogenized in an electric blender, then the pH of the homogenate was adjusted to 7.0 by adding sodium bicarbonate. A part of the homogenate was retained to be used in the experiments as undigested food. To the other part of the homogenate a pancreatic enzyme preparation (187.5 mg/100 cc; Viokase, Viobin Co., Monticello, Ill) was added and the whole was gently mixed with a magnetic stirrer at room temperature for 5 hours to permit digestion. The digested food was then made near isotonic by adding 2 parts of distilled water to 1 part of the digested food. A part of this diluted digested food was retained to be used in the experiment as digested food while the other part was centrifuged (19,250 G) and divided into supernatant and precipitate. The mean $\pm$ S.E.M. osmolality of the supernatants of digested food made from six cans of dog food was 278 $\pm$ 29 mOsm/kg. The undigested food mixtures were also diluted 1:2 with distilled water and the whole was stirred for one hour with a magnetic stirrer at room temperature before the experiment. The osmolality of the supernatant of the diluted undigested food was 178 $\pm$ 12 mOsm/kg (mean $\pm$ S.E.M., N = 6). The higher osmolality of the digested food indicated that digestive products,

about 100 mOsm/kg, are produced after digestion by the pancreatic enzyme preparation *in vitro*. The pancreatic enzyme preparation was dissolved in normal saline (187.5 mg/100 cc) and its osmolality was 317 ± 17 mOsm/kg (mean ± S.E.M., N = 6).

Prior to each experiment bile was withdrawn from the animal's gallbladder with a needle and syringe. The volume of the bile obtained from each dog varied from 15 to 30 ml. The digested food plus bile solution was prepared by adding equal parts of undiluted digested food, distilled water and the gallbladder bile together. The whole was then mixed gently with an electric stirrer for about 15 minutes. The pH and osmolality of this solution was 6.3 ± 0.13 and 356 ± 30 mOsm/kg (mean ± S.E.M., N = 6) respectively. The bile to be placed in the lumen was diluted with 2 parts normal saline to 1 part bile. The diluted gallbladder bile had a pH of 7.0 ± 0.37 and an osmolality of 284 ± 2.4 mOsm/kg (mean ± S.E.M., N = 6).

The composition of the isotonic glucose-amino acids mixture is shown in Table 1. The mixture was prepared by first dissolving tyrosine and cystine in 1.2 cc of 3 M NaOH solution. This was necessary because these two amino acids do not dissolve in distilled water readily. The remaining 14 amino acids along with the glucose solution and an appropriate amount of distilled water were added to the solution to make a final mixture (Table 1). To ensure adequate

Table 1. Composition of the glucose-amino acids mixture.

Essential L - Amino Acids Mixture:	(mM)
1. Isoleucine	14.05
2. Leucine	21.14
3. Methionine	6.47
4. Phenylalanine	8.33
5. Threonine	13.19
6. Tryptophan	1.74
7. Valine	15.91
8. Lysine	13.34
Nonessential L - Amino Acids Mixture:	
1. Arginine	7.00
2. Aspartic acid	13.40
3. Cystine	1.07
4. Glutamic acid	18.93
5. Glycine	14.27
6. Histidine	3.13
7. Proline	11.50
8. Tyrosine	3.13
Glucose	100.00

mixing, this mixture was sonified (Ultrasonic Inc., Plainview, Long Island, N.Y.) and the pH was adjusted to approximately 7.0 with 3 M NaOH. The osmolality of the mixture was 303 ± 3 mOsm/kg (mean ± S.E.M., N = 6).

Experimental Procedures

Two series of experiments were performed. The protocol for the experiments of both series consisted of three 15-minute periods: pre-control, test and post-control. In the pre- and post-control periods, both segments contained 10 ml normal saline. The luminal contents in the test period, however, varied with each experiment (see below). During each 15-minute period, venous outflows from the two jejunal segments were simultaneously collected in three 3-minute samples followed by two 1-minute ones in graduated cylinders. There were one minute intervals between these collections. After each 15-minute period, the test solution or the normal saline were withdrawn and the lumens of the segments were washed gently with warm normal saline. The temperature of all solutions placed into the lumen was 37°C.

Series 1

In the first series of experiments the vascular effects of luminal placement of undigested food (1:2 dilution), digested food (1:2 dilution), supernatant and precipitate of

the digested food, the pancreatic enzyme preparation, gall-bladder bile (1:2 dilution), the digested food plus bile solution and normal saline were studied. The purpose was to identify the constituents of chyme that are responsible for the postprandial hyperemia. Thus, the solutions were paired into the following six combinations: 1) digested food and undigested food (N = 11), 2) supernatant and precipitate (N = 6), 3) digested food and supernatant (N = 6), 4) supernatant and the pancreatic enzyme (N = 6), 5) bile and normal saline (N = 6), 6) digested food plus bile and digested food (N = 9). During the test period, 10 ml of one of the paired solutions was placed into one segment and the same amount of the other solution was introduced into the adjacent segment. Since both segments were subjected to the same systemic influences at any given time, any difference in the vascular effects of the paired test solutions can reasonably be attributed to the variations in their vasoactive properties.

Series 2

In the second series of experiments, the vascular effects of luminal placements of the glucose-amino acids mixture and the isotonic glucose solution (300 mM glucose) were determined and compared. The purpose was to determine whether the digestive products glucose and amino acids, as

a mixture, have a cumulative hyperemic effect. A total of 12 dogs were used in this series and they were divided into two groups. In the first group (6 dogs), the vascular effects of the glucose solution was studied. During the test period, one segment contained 10 ml of the glucose solution and the other segment 10 ml of normal saline so that the vascular effects of this solution could be studied using saline as a control substance. In the second group (N = 6), the vascular effects of luminal placement of the glucose-amino acids mixture was studied and the mixture was placed in one segment while normal saline in the other segment during the test period.

Statistical Analysis of the Results

The Student's t-test modified for paired comparison was used for all analyses. In addition, the Student's group t-test for equal variance with unpaired but equal numbers of observation was used to compare the vascular effects of the isotonic glucose solution and the glucose-amino acids mixture. The statistical significance was set at p values less than 0.05.

CHAPTER IV

RESULTS

The mean ± S.E.M. systemic arterial pressure was 130 ± 2.0 mm Hg (N = 38) and was not significantly ($p < 0.05$) altered by the placement of various test and control solutions. The weights of the *in situ* jejunal segments ranged from 15 to 28 gm with an average of 20.2 ± 2.0 gm (mean ± S.E.M., N = 38).

Series 1

The effects of luminal placement of undigested food, digested food, supernatant and precipitate of the digested food, pancreatic enzyme preparation, gallbladder bile, digested food plus bile and normal saline on venous outflow, vascular resistance and luminal pressure are shown in Table 2. The flow values are collected during the last (14th to 15th minute) collection of blood flow in the 15 minute period. These values were chosen for presentation because venous outflow reached a steady state 10 to 15 minutes after placement of the test solutions. The flow obtained during the 8th to 11th minute collection period were not

Table 2. Effects of placing various constituents of chyme into the jejunal lumen on local blood flow (ml/min/100 gm), vascular resistance (mm Hg/ml/min/100 gm) and luminal pressure (mm Hg).

	Segment A			Segment B		
(N)	Precontrol	Test	Postcontrol	Precontrol	Test	Postcontrol
(11)	NaCl	Digested Food	NaCl	NaCl	Undigested Food	NaCl
Flow	56.9±5.0	63.3±5.5*	53.5±4.7	61.5±5.3	63.0±5.9	57.9±6.0
Resistance	2.54±.27	2.30±.23*	2.67±.26	2.36±.26	2.37±.28	2.52±.29
Luminal Pressure	3.6±2.0	2.8 ±0.8	2.5 ±0.8	2.2 ±0.8	1.8 ±0.3	2.9 ±1.1
(6)	NaCl	Supernatant	NaCl	NaCl	Precipitate	NaCl
Flow	51.0±6.0	56.0±6.0*	48.0±6.0	53.0±7.0	52.0±6.0	49.0±6.0
Resistance	2.76±.31	2.50±.26*	3.01±.37	2.78±.46	2.82±.44	3.05±.52
Luminal Pressure	2.5 ±0.8	2.3 ±0.9	3.4 ±1.5	2.9 ±1.1	2.5 ±0.5	3.9 ±1.1
(6)	NaCl	Supernatant	NaCl	NaCl	Digested Food	NaCl
Flow	48.0±6.0	53.0±6.0*	47.0±6.0	49.0±6.0	55.0±6.0*	48.0±5.0
Resistance	3.01±.37	2.67±.29*	3.08±.36	3.05±.52	2.63±.36*	3.02±.42
Luminal Pressure	3.4 ±1.5	2.5 ±1.1	2.6 ±1.0	3.9 ±1.1	2.4 ±0.9	2.1 ±1.1
(6)	NaCl	Supernatant	NaCl	NaCl	Enzyme	NaCl
Flow	54.0±7.0	62.0±7.0*	51.0±6.0	63.0±7.0	66.0±9.0	57.0±7.0
Resistance	2.69±.33	2.37±.34*	2.62±.26	2.29±.22	2.17±.26	2.41±.24
Luminal Pressure	2.1 ±0.3	2.30±1.2	3.2 ±1.0	3.8 ±2.0	4.0 ±1.2	3.4 ±1.0

Table 2--continued

	Segment A			Segment B		
(N)	Precontrol	Test	Postcontrol	Precontrol	Test	Postcontrol
(6)	NaCl	Bile	NaCl	NaCl	NaCl	NaCl
Flow	37.3±4.3	38.1±4.5	37.9±3.9	34.6±3.3	33.0±4.2	33.4±4.0
Resistance	4.07±.25	3.89±.24	3.78±.25	4.30±.20	4.50±.24	4.32±.27
Luminal Pressure	7.1 ±1.3	6.0 ±1.1	5.1 ±0.8	4.6 ±0.9	4.9 ±1.0	4.5 ±1.3
(9)	NaCl	Bile + Food	NaCl	NaCl	Digested Food	NaCl
Flow	42.6±3.8	65.4±7.2*	44.9±5.1	43.3±4.6	50.3±3.9*	44.6±4.0
Resistance	3.46±.30	2.31±.23*	3.35±.35	3.37±.27	2.64±.13*	3.32±.31
Luminal Pressure	8.1 ±1.7	12.1±2.5	6.6 ±1.2	6.1 ±1.5	6.8 ±2.5	8.1 ±2.5

*Values are statistically different from the precontrol values ($P < 0.05$, Student's t-test, pair comparisons).

statistically different from those obtained during the 14th and 15th minute period. As shown in Table 2, none of the solutions tested altered lumen pressure when placed into the lumen. The percent changes from precontrol of both flow and resistance produced by the paired test solutions are shown in Table 3. It also shows the difference (D = A-B) between the changes produced by the paired test solutions.

As shown in Table 2, luminal placement of digested food, its supernatant and digested food plus bile significantly increased blood flow as compared to precontrol. Undigested food, precipitate of the digested food, the pancreatic enzyme preparation and gallbladder bile, however, did not significantly alter venous outflow as compared to precontrol. When the vascular effects of digested food and supernatant were compared, digested food increased venous outflow by 13.4% and decreased vascular resistance by 11.7% (Table 3). Similar values, i.e., 11.3% increase in flow and 10% decrease in resistance, were obtained in the adjacent segment containing the supernatant of this digested food. There was no significant difference between the hyperemic effects of the two solutions. Addition of bile to digested food enhanced the hyperemic effects of the food (Table 2). While luminal placement of digested food plus bile solution increased blood flow by 54.8% and decreased vascular resistance by 32.4%, that of digested food alone increased flow by only

Table 3. Percent change from precontrol values of venous outflow and vascular resistance with paired solution in the lumen of the adjacent jejunal double segments.

(N)		Segment A	Segment B	
		Digested Food	Undigested Food	D = A-B
(11)	Flow	+11.5±1.8*	+2.0±2.3	9.4±1.5*
	Resistance	- 8.6±1.9*	- .32±2.5	9.0±1.4*
(6)		Supernatant	Precipitate	
	Flow	+11.3±4.4*	-1.4±4.0	12.7±4.2*
	Resistance	- 9.0±3.1*	+3.0±3.9	12.0±3.5*
(6)		Supernatant	Digested Food	
	Flow	+11.3±4.1*	+13.4±3.4*	2.1±2.1
	Resistance	-10.0±3.0*	-11.7±3.0*	1.7±1.5
(6)		Supernatant	Enzyme	
	Flow	+12.1±3.8*	+4.8±4.8	7.3±2.0*
	Resistance	-13.0±4.0*	-5.8±6.0	7.2±2.7*
(6)		Bile	NaCl	
	Flow	+ 1.1±2.6	-4.1±4.8	5.2±2.6
	Resistance	- 1.30±1.8	+4.97±5.4	6.3±3.8
(9)		Digested Food + Bile	Digested Food	
	Flow	+54.8±12.9*	+17.8±5.6*	37.0±10.3*
	Resistance	-32.4±5.0*	-13.9±3.9*	18.5±4.1*

D = A-B: the difference in changes produced by two paired solutions.

*Values are statistically significant at $P < 0.05$.

17.8% and decreased resistance by 13.9% (Table 3). The differences in blood flow (37%) and vascular resistance (18.5%) between the digested food plus bile solution and the digested food were statistically significant (Table 3). However, bile itself in the same concentration (1:2 dilution) in the lumen did not produce any significant vascular effect in the jejunal segment, i.e., +1.1% on blood flow and -1.3% in resistance (Table 3).

When the vascular effect of digested food was compared with undigested food, digested food again significantly increased blood flow (+11.5%) and decreased vascular resistance (-8.6%) (Tables 2 and 3). Undigested food, however, did not significantly alter jejunal blood flow or vascular resistance. The difference in changes produced by these two solutions was 9.4% in blood flow and 9.0% in vascular resistance (first row, Table 3) which was significant at $p < 0.05$. When tne hyperemic effects of supernatant and precipitate (both from the same digested food) were compared, the former again raised venous outflow but the latter did not (Tables 2 and 3). Supernatant increased blood flow 11.3% and decreased resistance by 9.0% while precipitate had no effect. The difference in their vascular effects was 12.7% for blood flow and 12.0% for vascular resistance. The pancreatic enzyme preparation did not have any significant effect on the jejunal vasculature (Table 2).

The following conclusion can be drawn from this series of experiments: 1) Digested food increased blood flow but undigested food did not. 2) Of the two constituents of digested food, only the supernatant raised blood flow and decreased vascular resistance; the precipitate did not have any vascular effect. 3) Intraluminal placement of digested food and its supernatant have similar effects on jejunal blood flow and resistance. Their vascular effects, however, were significantly different from those of the precipitate and undigested food. 4) The action of digested food and its supernatant was not likely due to the pancreatic enzyme preparation contained in these two solutions since the enzyme itself did not alter blood flow. 5) The addition of bile in the digested food potentiated the hyperemic effect of the food. Intraluminal placement of bile itself, however, did not have any effect on the jejunal segment.

Series 2

The vascular effects of the isotonic glucose solution and a mixture of glucose and amino acids were determined in this series of experiments. In each case the test solutions were placed in one segment while normal saline was placed in the other as a control. Table 4 shows mean $\pm$ S.E.M. venous outflow and vascular resistance during the control and experimental periods in the double segments and the percent

Table 4. Effects of luminal placement of the glucose solution and a mixture of glucose and amino acids on blood flow (ml/min/100 gm) and vascular resistance (mm Hg/ml/min/100 gm).

	Experimental Segment (E)			Control Segment (C)			D = E-C
(N = 6)	NaCl	Glucose	NaCl	NaCl	NaCl	NaCl	
Blood Flow	72.9±8.0	77.5±8.2*	71.0±7.6	69.6±0.9	68.7±8.6	69.2±9.4	
Δ%		+6.4±1.0**			-1.8±1.2		8.2±1.7**
Resistance	1.8±.20	1.72±.20*	1.96±.26	2.03±.30	2.08±.32	2.10±.35	
Δ%		-6.0±1.1**			+2.0±1.2		8.1±1.7**
(N = 6)	NaCl	Glucose-Amino Acid	NaCl	NaCl	NaCl	NaCl	
Blood Flow	57.0±5.0	66.0±5.0*	55.0±7.0	59.0±7.0	58.0±8.0	55.0±7.0	
Δ%		+16.7±4.5**			-0.7±4.3		17.4±5.2**
Resistance	2.6±.30	2.15±.16*	2.67±.29	2.69±.46	2.62±.37	2.75±.39	
Δ%		-15.6±3.4**			-0.45±4.4		+15.1±4.7**

Δ% = changes from precontrol values, in percent, with test or control solution in the lumen.

D = E-C = the difference in changes occurring simultaneously in the two segments.

**values are statistically significant at $P < 0.05$.

*values are statistically different from the precontrol values (p less than 0.05 student's test, pair comparisons).

change from precontrol of flow and resistance produced by the glucose and glucose-amino acids solutions. The flow values were collected during the last (14th to 15th minute) collection of blood flow in the 15 minute period. The table also contains the comparison of changes (from precontrol) that occurred in the experimental and control segments during placement of the test solutions (D = E-C, Table 4).

Luminal placement of both solutions significantly increased blood flow and decreased vascular resistance. When glucose was in the lumen, blood flow increased by 6.4% and resistance decreased by 6.0%. Venous outflow increased from a precontrol value of 72.9 $\pm$ 8.0 to 77.5 $\pm$ 8.2 ml/min/100 gm while resistance decreased from 1.83 $\pm$ 0.2 to 1.72 $\pm$ 0.2 mm Hg/ml/min/100 gm (Table 4). These values returned to control level during the postcontrol period after the glucose solution was withdrawn and normal saline was placed inside the lumen. The difference between the changes (from precontrol) that occurred in the experimental and control segments was 8.2% for blood flow and 6.7% for resistance. These values were significant at $p < 0.05$. Intraluminal placement of the glucose-amino acids mixture significantly increased blood flow from 57 $\pm$ 5.0 to 66 $\pm$ 5.0 ml/min/100 gm. This represents a 16.7% increase from precontrol. Vascular resistance on the other hand, decreased significantly from 2.60 $\pm$ 3.0 to 2.15 $\pm$ 0.16 mm Hg/ml/min/100 gm;

a 15.6% drop from precontrol. During the postcontrol period, blood flow returned to 55.0 $\pm$ 7.0 ml/min/100 gm while resistance was 2.67 $\pm$ 0.29 mm Hg/ml/min/100 gm; these values were not significantly different from the precontrol period (Table 4). The difference between the changes in the experimental and control segments (D = E-C, Table 4) was 17.4% for blood flow and 15.1% for resistance.

Although the glucose solution and the glucose-amino acids mixture both increased venous outflow and decreased vascular resistance when placed inside the lumen, the magnitude of these changes was found to be different (Student's group t-test, $p < 0.05$). Intraluminal placement of the glucose-amino acids mixture produced a greater hyperemic effect (+16.7%) on the jejunal vasculature than did the glucose solution (+6.4%). The presence of the amino acids mixture in the lumen thus seemed to have an additive effect on the hyperemia induced by the isotonic glucose solution.

CHAPTER V

DISCUSSION

Many studies indicate that blood flow through the splanchnic viscera increases during digestion (12,21,22,56, 57,58). Unfortunately, little is known concerning the constituents of intestinal chyme that are responsible for this postprandial mesenteric hyperemia. One of the objectives of the present study was to identify which of the constituents of chyme are responsible for the hyperemia. Thus, digested food, its supernatant and precipitate, undigested food, pancreatic enzyme preparation, gallbladder bile, digested food plus bile as well as normal saline were placed intraluminally into the in situ jejunal segments and their vascular effects determined and compared. These solutions were paired into the following combinations: digested food and undigested food; supernatant and precipitate; supernatant and digested food; supernatant and enzyme; gallbladder bile and normal saline; digested food plus bile and digested food alone. The two food solutions compared were individually placed in the two adjacent jejunal segments simultaneously. The testing of the vasoactivities of different food

solutions under the same systemic conditions allowed a fair comparison of their capacity to influence the intestinal vasculature.

The comparison between digested food and undigested food revealed that only the former was capable of increasing blood flow. The different responses from the two solutions were not due to changes in either aortic or luminal pressure since neither of these parameters were altered. Nor was it due to their different osmolalities--which for digested food was 278 $\pm$ 29 mOsm/kg and undigested food, 178 $\pm$ 12 mOsm/kg. Kvietys et al. (37) have recently shown that lumen osmolality within a range of 180 to 1,000 mOsm/kg is not a contributing factor in the increase in mesenteric blood flow when food is in the intestine. In their study, the digested food having an osmolality of 183 $\pm$ 5.8 mOsm/kg produced similar hyperemia as the one having an osmolality of 291 $\pm$ 5.3 mOsm/kg did.

The hyperemic effect of digested food was also not due to the pancreatic enzymes present in the food since their placement in the lumen of the intestine did not alter blood flow (Tables 2 and 3). The hyperemic effect of digested food, therefore, appears to be due to the digested products of food. This conclusion is further supported by the finding that supernatant of digested food has a hyperemic effect similar to digested food while the precipitate has no vascular effect (Tables 2 and 3).

This conclusion is also supported by the findings that the onset of the intestinal hyperemia occurs earlier with digested food than undigested food. Fara et al. (17) found in anesthetized cats that intraduodenal instillation of milk and corn oil did not increase superior mesenteric arterial flow until 7 to 20 minutes after placement. On the other hand, the onset of hyperemia after amino acids placement was much shorter (1 to 5 minutes). Chou et al. (12) also found that blood flow through the superior mesenteric artery did not increase until 30 minutes after intragastric placement of undigested food. However, mesenteric blood flow increased within 5 minutes after the intraduodenal instillation of digested food. These studies indicate that the time of the onset of the hyperemia occurs more rapidly with digested food than undigested food. This present study shows that the digestion of food plays a vital role in postprandial hyperemia and provides an explanation for the delay of the onset of intestinal hyperemia following a meal.

This present study also shows that addition of bile into the digested food markedly increases the hyperemic effect of the food (Tables 2 and 3). The increase is not due to the vascular effect of bile since bile itself in the lumen of the intestine does not alter local blood flow (Tables 2 and 3). The potentiation of the hyperemia appears to be due to the digestive actions of bile on the food.

Gallbladder bile contains bile salts which facilitate digestion of lipids (8,15,49,50). Kvietys et al. (37) have shown that the greater the concentration of the digestive products of food in the gut lumen, the greater was the increase in venous outflow of the intestine. Therefore, one effect of bile in increasing the hyperemic effect of digested food appears to result from an increase in the concentration of digestive products of fat. Another effect of bile may be due to its effect in facilitating the absorption of fatty acids (8,15,49,50), proteins and sugars (1).

The magnitude of hyperemia induced by the intraluminal placement of digested food in the present study was lower than previously reported (12). After the addition of bile, however, digested food increased blood flow by 107 to 230% of control, which was comparable to those values observed previously in both conscious and anesthetized dogs (6,12,22, 56,57,58). The digestive actions of bile, therefore, play an important role in the postprandial intestinal hyperemia.

The second objective of the present study was to examine whether intraluminal placement of the digestive products, glucose and amino acids, as a mixture, have a cumulative effect on blood flow in the small intestine. The vascular effects of the isotonic glucose solution and the glucose-amino acids mixture were determined and compared. Intraluminal placement of the glucose-amino acids

mixture produced a greater hyperemic effect than did the placement of the glucose solution. While the isotonic glucose solution increased blood flow by only 6.4%, the glucose-amino acids mixture raised it by 16.7% above control (Table 4).

The magnitude of the hyperemia produced by the isotonic glucose solution was comparable to that observed in previous studies (10,55). The effects of luminal placement of the 16 amino acids used in this study have been examined recently in our laboratory (unpublished observation). Placement of the 16 amino acids in the jejunal lumen produced an increase of 12.0% above the precontrol flow values. Therefore, the hyperemic effect of the glucose-amino acids mixture appears to be the sum of the vascular effects of glucose and amino acids in combination.

A recent study from our laboratory also showed that a fatty acid and bile salt solution of oleic acid (40 mM), monoolein (20 mM) and taurocholate (10 mM) increased venous outflow when placed into the lumen of the jejunum. Since the critical micellar concentration for taurocholate is 2.5 mM (49), the fatty acids used were in micellar form and, therefore, were well digested. Thus, various digestive products of carbohydrates, proteins and fat are able to increase jejunal blood flow when placed into the lumen of the intestine. The magnitude of the hyperemia, however,

appears to depend not only on the concentration of the digestive products (37) but also on the type of food ingested. It has been suggested that different hyperemic effects may be expected from carbohydrates, protein or fat feedings (43). Many investigators have also shown that protein-rich meals increased splanchnic blood flow (5,18,31) as well as oxygen consumption (5,14,28) more than carbohydrate-rich meals.

This present study shows that the constituents of chyme responsible for postprandial hyperemia are suspended in the supernatant of the digested food and are likely to be the digestive products of food. This study as well as recent studies in our laboratory further show that glucose, amino acids, fatty acids and monoglycerides are vasodilators when placed into the lumen of the upper small intestine. Postprandial intestinal hyperemia, therefore, appears to be triggered by the exposure of these elementary digestive products to the intestinal mucosa. It has been shown that the increase in intestinal blood flow is confined only to the mucosal layer of the intestine which is exposed to food (12). The mucosal layer is the major site for transmembrane transport of water, electrolytes and nutrients in the intestine (13,15,49,50). Thus, it is quite possible that the hyperemia is related to the mucosal absorption of these elementary digestive products. However, mucosal neural reflexes and vasodilating hormones released from the

intestinal tissue may also participste in the hyperemia. These elementary digestive products have been shown to be capable of releasing local hormones (34) and stimulate local mucosal nerves (48,62). Finally, it is possible that during the process of food digestion vasoactive compounds are formed that act directly on the intestinal vasculature to cause vasodilation.

CHAPTER VI

SUMMARY AND CONCLUSION

In order to identify the constituents of chyme that are responsible for the postprandial hyperemia in the intestine, the vascular effects of luminal placement of various food solutions were compared. An in situ double jejunal segment preparation was used and the venous outflow from the segments was measured before, during and after luminal placement of these solutions. The results indicate that:

1) Luminal placement of digested food, its supernatant and the digested food plus bile solution increased local blood flow and decreased vascular resistance.

2) Undigested food, precipitate of the digested food, the pancreatic enzyme preparation and gallbladder bile did not have any vascular effect.

3) The hyperemic effect of digested food and its supernatant was quantitatively similar.

4) The addition of gallbladder bile to the digested food markedly enhanced the hyperemic effect of food.

5) Intraluminal placement of either the glucose or the glucose-amino acids mixture increased venous outflow

and decreased vascular resistance. However, the glucose-amino acids mixture had greater hyperemic effect than did glucose alone.

6) None of the solutions studied had any effect on either luminal or aortic pressure upon luminal placement.

It is concluded that the pancreatic enzyme preparation and gallbladder bile in 1:2 dilution are not vasoactive when placed in the lumen of the jejunum. Postprandial hyperemia in the intestine, however, requires the digestive action of the pancreatic enzyme and is markedly increased by gall-bladder bile. The substances responsible for the hyperemia are suspended in the supernatant of the digested food and likely to be the digestive products of food. The digestive products of carbohydrates and proteins, i.e., glucose and amino acids, both contribute to the hyperemia and their effects are additive.

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