COMPARISON OF VASCULAR EFFECTS OF GASTROINTESTINAL HORMONES ON VARIOUS ORGANS

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Major professor

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ABSTRACT

COMPARISON OF VASCULAR EFFECTS OF GASTROINTESTINAL HORMONES ON VARIOUS ORGANS

By

Chih-Peng Hsieh

The blood flow through the small intestine is increased during digestion and the gastrointestinal hormones, secretin, cholecystokinin and gastrin are released into the circulation during this period. Administrations of these hormones have been shown to increase blood flow in some digestive organs. These hormones, therefore, may contribute in the mesenteric hyperemia during digestion. The purpose of this study was to examine this possibility. The vascular effects of the three hormones on the duodenum, jejunum, heart, kidney, spleen, forelimb, and skin and muscle of the forelimb were compared and the minimum infusion rate at which each hormone significantly decreased the vascular resistance of each organ was estimated. The concentration requirement of each hormone to produce vasodilation in each organ was then calculated from the minimum infusion rate and blood flow.

Chih-Peng Hsieh

The study was performed in an *in situ* constantly perfused duodenum, jejunum, heart, kidney, spleen or forelimb, and naturally perfused forelimb of anesthetized dogs. While continuously recording the perfusion pressure or blood flow, solutions of the three hormones were infused into the local artery. Other measurements in particular organs were: the contractile force of the heart, intestinal motility, and splenic weight. In the naturally perfused forelimb, blood flows from the brachial and cephalic veins, which represent skin and muscle flow respectively were measured. The solvents of the hormones were also infused as a volume control.

The systemic arterial pressure was not significantly altered during local intra-arterial infusion of these hormones to any vascular bed, except to the heart and kidney, in which high doses of cholecystokinin or secretin caused a significant fall in systemic arterial pressure. Secretin produced vasodilation in all eight organs studied. Cholecystokinin produced vasodilation in all organs except the forelimb, skin and muscle. Pentagastrin produced vasodilation only in the duodenum and jejunum. The minimum increments in the calculated local blood concentration which significantly produced vasodilation in these organs were between 7.1 and 32.3 mU/ml for secretin; 2.5 and 32.8 mU/ml for cholecystokinin; and 25 and 50 ng/ml for pentagastrin.

The contractile force of the left ventricle or splenic weight was not significantly altered by any of the hormones studied. Cholecystokinin and pentagastrin regularly increased intestinal motility but secretin did not.

The concentration requirements for vasodilation by secretin and pentagastrin were much greater than their postprandial serum concentrations reported by other investigators with the radioimmunoassay method. However, the concentration requirement for vasodilation by cholecystokinin in the duodenum and jejunum was within the ranges of measured concentration in postprandial serum. Furthermore, within this range, cholecystokinin produced a marked decrease in vascular resistance in the duodenum and jejunum, but did not effect the vascular resistance of non-digestive organs. The cardiovascular response to digestion is a selective hyperemia in the small intestine with no change in heart rate, arterial pressure and blood flow through the heart and kidney, and slight decrease or no change in flow through the limbs.

Comparison of results from this study with the reported cardiovascular adjustments and blood concentration of gastrointestinal hormones following a meal indicates that only cholecystokinin may contribute to postprandial intestinal hyperemia.

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By

Chih-Peng Hsieh

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CHAPTER I

INTRODUCTION

Some of the cardiovascular response to digestion is a selective hyperemia in the small intestine with no changes in heart rate, arterial pressure, and blood flow through the heart and kidney, and slight decrease or no change in flow through the limbs (10,27,28,75,76,77). The mechanism of the increased blood flow in the small intestine, however, is not clear. The gastrointestinal hormones, secretin, cholecystokinin (CCK) and gastrin are released into circulation during digestion. If these hormones produce these responses within the blood concentration ranges attained following a meal, they could be implicated in playing a role in the postprandial cardiovascular adjustment.

Administration of these hormones have been shown to increase blood flow in some digestive organs (10,14,18,24,25,26,31,33,43,45,49,51,69,74). The studies on the vascular effect of the three hormones used a variety of methods, dosages, and routes of administration, and in most studies all three hormones were not studied in a given experiment. It is, therefore, difficult to make quantitative comparisons

of vascular actions of the three hormones on any given organ, or to compare the responses of different organs to the same hormone. In addition, the vascular actions of one or all of these hormones on the coronary, renal, forelimb, splenic, skin and muscle vascular beds have not been studied. Furthermore, it is not known whether the doses of hormones given in these studies are physiologically equivalent or identical to the amount of hormone release in response to a meal.

The purpose of this investigation was twofold: 1) to compare the vascular effects of pentagastrin, secretin and CCK on the duodenum, jejunum, heart, kidney, forelimb, spleen, and skin and muscle of the forelimb; and 2) to estimate the concentration requirements of these hormones in producing vascular effects in each organ.

CHAPTER II

SURVEY OF LITERATURE

Gastrointestinal hormones, gastrin, cholecystokinin (CCK) and secretin are polypeptides produced by the mucosa of the distal portion of the stomach and proximal small intestine. These hormones are well-known for their role in the regulation of the secretory and motor activities of the stomach, small intestine, pancreas, liver and biliary tract. The modern era of the gastrointestinal endocrinology began in 1964, when the structure of gastrin was determined.

Gastrin was first discovered by Edkins in 1905 (19). He found that extracts of gastric pyloric mucosa stimulated gastric secretion when injected intravenously into anesthetized cats. Nearly sixty years later in 1964, gastrin was isolated from hog antrum, and its chemical structure determined by Gregory and Tracy (34,35). Gastrin is a linear peptide consisting of 17 amino acid residues. It has been isolated from the antral mucosa of six species, and the structures of these species differ only by one or two amino acid substitutions.

Two types of gastrin having an identical amino acid composition have been isolated. They differ only in the

presence (gastrin II) and absence (gastrin I) of a sulphate group of the tyrosyl residue at position 6 from the C-terminal. The actions of the gastrin are produced by one small fragment, the C-terminal tetrapeptide amide (-Trp-Met-Asp-Phe-NH_2), which can be called the active fragment of gastrin. Pentagastrin is a synthetic peptide that contains the active fragment of gastrin. It is commercially available and is the form most commonly used to study the actions of gastrin in men and animals (37).

The hormone CCK is the principal stimulus for contraction of the gallbladder and for secretion of pancreatic enzymes. In 1928, Ivy and Oldberg (48) discovered an extract from the mucosa of the small intestine that produced contraction of the gallbladder. In 1943, Harper and Raper (42) found another active principle, which stimulated pancreatic enzyme secretion. These two independent discoveries led to the concept of two separate hormones, which were designated respectively as cholecystokinin (CCK) and pancreozymin. It is now agreed that the two are one, the hormone has been isolated and purified, and its amino acid composition determined by Jorpes and Mutt in 1968 (53,61). Since the CCK activity of the hormone was the earlier discovery, Grossman (38) has proposed the CCK be used exclusively for the hormone.

CCK is a linear peptide consisting of 33 amino acids, of which the five C-terminal residues are identical with those of gastrin. Therefore, CCK and gastrin share the same spectrum of biological activity (39).

Secretin was first discovered by Bayliss and Starling in 1902 (3). They found that placement of weak HCl into the lumen of the denervated jejunum increased pancreatic secretion. After many years of effort devoted to isolation and purification, Mutt and Jorpes identified the full amino acid sequence of secretin in 1966 (62). Secretin is a peptide consisting of 27 amino acids and is strongly basic because of four arginine units. The amino acid sequence of porcine secretin, unlike gastrin and CCK, contains no active fragment. All 27 amino acids are required for activity; substitution for any one of them renders the molecule inactive.

After their release from the mucosa of the upper gastrointestinal tract, these hormones appear to disappear from the circulation very rapidly since their half-life in the circulation is short. The half-life values are about 2.0-6.0 min (59,67,70), 2.8-3.2 min (8,56), and 2.4-2.6 min (66,68) for gastrin, secretin and CCK, respectively. However, it is not known whether the doses of hormones given in these studies on the half-life are physiologically equivalent or identical to the amount of hormone released in response to a meal. Nevertheless, the short half-life of

these hormones in the circulation indicates that the contribution of these hormones to the digestive functions depend primarily on the rate and duration of their release during digestion.

The availability of pure forms of these hormones provides the gastrointestinal investigator a tool to study their specific actions on gastrointestinal functions and their roles in gastrointestinal diseases (40,52). Recent studies suggest that the gastrointestinal hormones may affect the cardiovascular function.

Gastrin

In conscious dogs, while measuring the superior mesenteric arterial flow with an electormagnetic flowmeter, Burns and Schenk (10) found that after subcutaneous injection of gastrin (2 units/kg) superior mesenteric blood flow began to rise within five minutes, reached a mean peak (45% above the fasting level) in one to two hours and remained elevated for up to three hours. In anesthetized dogs, Chou et al. (14) have also demonstrated that local intra-arterial infusions of gastrin (0.2 mg/ml, 0.19-7.75 ml/min) decrease vascular resistance (12%) of the superior mesenteric vascular bed during constant flow perfusion. A similar study by the same authors on gastric circulation, intra-arterial infusion of gastrin (0.2 mg/ml, 0.123-4.94 ml/min) also decreased the vascular resistance (20%) of gastric

circulation (54). In Heidenhain pouches of conscious dogs, infusions of pentagastrin (12.5 to 200 µg/hr) increased gastric mucosal flow (aminopyrine method) and gastric secretion (74). The secretion was positively related to gastric mucosal blood flow, but the total blood flow to the pouches, measured by electromagnetic flowmeter was not significantly altered. Fasth et al. (25) studied the vascular effect of pentagastrin in the in situ small intestinal segment in cats. A local intra-arterial infusion of pentagastrin, 3 µg/kg/min, produced a 50% increase in flow.

In an isolated canine pancreas, Hermon-Taylor (43) has found that administration of gastrin II (0.08 µg/min, i.a.) produces vasodilation which precedes the onset of secretion. Also, the fall in pancreatic vascular resistance caused by gastrin II was associated with a rise in the metabolic activity of the preparation. The vasodilator effect of gastrin on the pancreas has also been shown by an indicator fractionation technique (^{86}Rb) in dogs (33). In this study, intravenous infusion of pentagastrin (0.2 µg/kg/min for approximately two minutes) produced an increase in pancreatic blood flow and no change in cardiac output. In a human subject, using plethysmographs to measure blood flow of hand and forearm (which represent the blood flow to skin and muscle respectively), Adrill et al. (2) found that an intravenous infusion of gastrin II (0.244 µg/kg/min; 50 µg total

in 28 min) or local intra-arterial infusion of gastrin II (2 and 4 μg/min), did not affect skin and skeletal muscle blood flow or arterial blood pressure.

Secretin

The vasodilatory effect of secretin on the superior mesenteric vascular bed has been shown by Burns and Schenk in conscious dogs (10). After a bolus intravenous injection of secretin (1.5 U/kg) (U: Ivy dog units), mesenteric blood flow began to rise within five minutes, reached a maximum (38% above control level) in the second hour, and the increased flow lasted for three hours. In anesthetized dogs, Gerber et al. (31) found that a brief increase in superior mesenteric flow (electromagnetic flowmeter) occurred after a single injection of secretin, one unit per kilogram body weight. Similar findings were made in anesthetized cats by Ross (69), who found that rapid injections of secretin, 1-10 U, into the mesenteric artery increased mesenteric arterial flow (electromagnetic flowmeter) and decreased its vascular resistance 28-48% below control. The vasodilator effect of secretin on the superior mesenteric vascular bed has also been shown by Fara et al. (24) in anesthetized cats. Intravenous infusion of secretin (0.4-10.3 U/kg/hr) produced a 36% increase in mesenteric arterial blood flow.

Secretin has also been shown to increase pancreatic blood flow. With an indicator fractionation technique,

Goodhead et al. (33) found that flow through the pancreas of the anesthetized dog increases from 15.6 ml/min of control to 45.8 ml/min after intravenous injection of 5 U/kg of secretin. In the study by Fara et al. (24), intravenous infusion of secretin (0.4-10.3 U/kg/hr) produced about a 20% increase in pancreatic blood flow. Gerber et al. (31) in their experiments also have demonstrated that pancreatic blood flow was raised 100% above control after a single injection of 1 U/kg of secretin. In anesthetized dogs, Dorigotti and Glasser (18) reported that secretin increases arterial blood flow to the pancreas about 23-30% above control level by reducing local vascular resistance. In their experiments, secretin (0.08-0.8 U), administered intravenously by rapid injection, caused a dose-related increase in blood flow through the pancreatico-duodenal artery, as measured by electromagnetic flowmeter. Frogge et al. (26) measured the venous outflow from an innervated segment of canine pancreas and found that pancreatic blood flow increased to 40% above control after intravenous injection of 75 units of secretin in a two-minute period.

In the canine duodenum, Goodhead et al. (33) have shown that the duodenal blood flow, as measured by the ^{86}Rb fractionation technique, was increased after intravenous injection of secretin (5 U/kg). However, the jejunal and ileal blood flow was only marginally increased.

In anesthetized cats, the study of Fara et al. (24) showed that intravenous infusion of secretin (0.4-10.3 U/kg/hr) produced a 20% increase in jejunal blood flow. In a study performed in the in situ jejunal segment of anesthetized cats, Biber et al. (5) also found that the venous outflow was increased after intra-arterial injection of secretin (1.0-2.5 U) into a branch of the superior mesenteric artery.

In the studies by Fara et al. (24) and Goodhead et al. (33) secretin produced no effect on colonic and gastric blood flow. The lack of vasoactive effect in the stomach has also been demonstrated by the studies of Laureta et al. (54), who found that intra-arterial infusions of secretin (0.133 mg/ml, 0.123-4.94 ml/min) does not significantly alter the vascular resistance of a constantly pump-perfused canine stomach. Gerber et al. (31) have also found that an injection of secretin (1 U/kg) did not alter gastric blood flow as measured by an electromagnetic flowmeter. Jacobson et al. (50) have shown that intravenous infusion of secretin (80 U/15 min) decreases blood flow to the mucosa of a denervated gastric pouch and simultaneously inhibits the gastric secretion which has been stimulated by gastrin.

Intravenous infusions of secretin (0.4-10.3 U/kg/hr) in anesthetized cats, produced no vasodilation in renal or femoral circulation (24). Rapid intravenous injections of secretin (0.08-0.8 U) also produced no change in the femoral

arterial flow in anesthetized dogs (18). However, in anesthetized cats, Ross (69) reported that rapid intra-arterial injections of secretin (1-10 U), increases femoral flow and reduces femoral vascular resistance (2-19%). Rapid intra-arterial injections of secretin, 3 or 10 U, reduced hepatic arterial flow, and increased its vascular resistance, 21 to 35% above control (69).

Secretin, at dosages which increase superior mesenteric, small intestinal and pancreatic blood flow, does not alter cardiac output (24,31) arterial blood pressure (18,26,69) or heart rate (18). However, large doses of secretin increases cardiac output in cats (33) and dogs (69). Goodhead et al. (33) have studied the effect of secretin on the distribution of cardiac output with an indicator fractionation technique (^{86}Rb) in dogs. An intravenous infusion of secretin (5 U/kg in approximately two minutes) produced an increase in cardiac output, and duodenal and pancreatic blood flow. Blood flow to the remainder of the gastrointestinal organs, i.e., stomach, jejunum, ileum, colon, and gallbladder, however, was only marginally increased (33).

In anesthetized cats, a rapid intravenous injection (10 U) or a rapid intra-arterial injection into the mesenteric, femoral, or hepatic vascular beds produces a biphasic effect on systemic arterial pressure, i.e., an initial transient fall lasting for less than a minute, followed by

a rise lasting for three to seven minutes. During the hypotensive phase, there was no change in heart rate, stroke volume, cardiac output, femoral and hepatic vascular resistances, but there was a decline in superior mesenteric resistance; during the hypertensive phase, cardiac output, heart rate, stroke volume and total peripheral resistance increased. Hepatic vascular resistance was also increased, but mesenteric resistance was reduced (69).

Cholecystokinin (CCK)

Fara et al. (24) have shown that intravenous infusions of CCK (0.5-11.3 U/kg/hr) produces about a 38% increase in superior mesenteric flow in anesthetized cats. Ross (69) has also found a similar increase in superior mesenteric flow after an intravenous infusion of CCK (0.6 U/kg/min). In dogs, intra-arterial infusions of CCK (1 U/ml at a sequentially increasing rate of 0.19-7.75 ml/min) produces a 29% decrease in vascular resistance of the superior mesenteric vascular bed (14). Laureta et al. (54) also have found that CCK is a vasodilator in the gastric bed; CCK (0.045 mg/ml at a sequentially increasing rate of 0.123-4.94 ml/min) caused a 7% decrease in gastric vascular resistance. However, Fara et al. (24) found that intravenous infusion of CCK (0.5-11.3 U/kg/hr) have no effect on the gastric blood flow. In the same study (24), however, intravenous infusions of CCK (0.5-11.3 U/kg/hr) caused a 28% increase in

jejunal blood flow. In the in situ small intestinal segment of anesthetized cats, Fasth et al. (25) have shown that infusion of 4.3 U/kg/min of CCK into the superior mesenteric artery produces a maximum response, about a 150% increase in small intestinal arterial flow. A similar study in the in situ jejunal segment by Biber et al. (5) also demonstrated that CCK (1.0-2.5 U) caused vasodilation in the jejunum.

In the pancreas, Goodhead et al. (33) using the radioactive rubidium fractionation technique showed that an intravenous injection of CCK (2 U/kg) increases pancreatic blood flow from 15.6 ml/min of control to 46.4 ml/min. Dorigotti and Glasser (18) also have reported that CCK (0.1-1.5 U by rapid intravenous injection) causes an increase in blood flow through the pancreatico-duodenal artery (electromagnetic flowmeter). Frogge et al. (26) have measured the venous outflow of an intact innervated segment of canine pancreas and found that pancreatic vascular resistance is decreased to 52% below the control level after intravenous infusion of CCK (100 U in approximately two minutes) In anesthetized cats, Hilton and Jones (45) measured the pancreatic venous outflow of pancreas with a photo cell amplifier and recording equipment. An intravenous injection of CCK (5 U) caused a 3-4-fold increase in pancreatic venous flow.

According to the study of Dorigotti and Glasser (18) in anesthetized dogs, rapid intravenous injections of CCK (0.1-1.5 U) did not alter the femoral arterial blood flow. Fara et al. (24) also found that intravenous infusions of CCK (0.5-11.3 U/kg/hr) have no effect on the femoral or renal blood flow in anesthetized cats.

In all these studies, CCK at dosages which increase superior mesenteric, small intestinal and pancreatic blood flow does not alter cardiac output (24,33) arterial blood pressure (18,24,26,45,69) and heart rate (18).

From the foregoing review, it appears that the gastrointestinal hormones gastrin, secretin, and CCK have several cardiovascular actions in common. They increase blood flow or decrease vascular resistance of superior mesenteric vascular bed (10,14,24,31,54,69), small intestine (5,24,25, 33) and pancreas (18,24,26,31,33,43,45), and are without effect on cardiac output (24,31,33), arterial pressure (2,18, 24,26,45,69) and heart rate (18). Cardiac output is increased only by secretin when administered in large doses (33,69). In regard to other regional blood flow, gastrin decreases gastric vascular resistance (54), increases gastric mucosal blood flow but does not effect its total gastric blood flow (74), and does not alter skin and skeletal muscle blood flow (2). Secretin decreases hepatic arterial flow (69) and gastric mucosal blood blow (50), and is without

effect on gastric, colonic and renal blood flow (24,31,33, 54). Secretin increases (69) or does not alter (18,24) femoral arterial flow. CCK does not alter renal or femoral arterial flow (18,24), but decreases gastric vascular resistance (54) and does not effect gastric arterial flow (24).

It has been shown that blood flow to the superior mesenteric vascular bed is increased following meals in man and conscious dogs (9,10,27,28,44,75,76,77). In addition, the effects of digestion on cardiac output and blood flow to various non-digestive organs have been observed. Studies performed prior to 1965 showed that increase in mesenteric blood flow is accompanied by increases in cardiac output (17,36,64) and blood flow to the limbs, kidney, heart and carotid artery (1,20,44). These studies thus appear to indicate that the increased mesenteric blood flow is a part of a generalized cardiovascular response to digestion.

More recent studies, using either an electromagnetic or ultrasonic flowmeter, have yielded different results. These recent studies indicate that the cardiovascular system responds to feeding in two distinctly different phases. During presentation and ingestion of food, cardiac output, heart rate and aortic pressure increase, while superior mesenteric vascular resistance either increases (75,76,77) or does not change (27,28). Renal resistance rises and

coronary resistance falls (76,77). Resistance in limbs either increases (28) or decreases (75,76,77). The changes that occur during the presentation-ingestion phase are transient (10-30 minutes) and can be inhibited by sympathetic blockade (75). Five to 15 minutes following ingestion of food, superior mesenteric blood flow starts to rise and reaches a maximum (15-300% above control) within 30-90 minutes and gradually returns to control levels within three to seven hours. The increase in superior mesenteric blood flow during this digestive phase is not accompanied by significant changes in cardiac output (10,27,28,75,76), aortic pressure (27,28,75,76,77), heart rate (28,75,76,77) or blood flow to the heart and kidney (27,76,77). However, blood flow through the brachio-cephalic and iliac arteries in animals at rest is slightly decreased (28,76) or unchanged (27). Thus a part of the increased superior mesenteric blood flow may result from diversion of blood flow from limbs to digestive organs (27,28,76,77). Mild ambulation or exercise in these animals, however, increases the limb flow, but the increased superior mesenteric blood flow remains elevated (27,76,77). These recent studies thus appear to indicate that while anticipation and ingestion of food elicit a generalized cardiovascular response, the cardiovascular effect of digestion are confined to the digestive organs.

After a meal, the gastrointestinal hormones gastrin, CCK and secretin are released into general circulation from the mucosa of the upper gastrointestinal tract as the mucosa is exposed to the chyme. As described in the previous section, these hormones produce an increase in blood flow through various organs, especially those concerned with digestive functions. Therefore, it is possible that these hormones may be involved in postprandial mesenteric hyperemia. Fara et al. (24) have shown that intraduodenal instillation of small volumes of corn oil, L-phenylalanine, or acid produced an increase in superior mesenteric blood flow was accompanied by increases in gallbladder and duodenal motility and pancreatic enzyme and volume output. Since intravenous infusion of CCK and secretin produced similar vascular, duodenal, pancreatic and biliary responses, they proposed that mesenteric hyperemia is mediated by CCK and secretin. To prove their hypothesis, they performed cross-perfusion experiments (24). The superior mesenteric vascular bed of a recipient cat was perfused by aortic blood of a donor cat. Intraduodenal instillation of oil to the donor cat produced an increased flow through the superior mesenteric artery of the recipient cat. Thus, this study further supports the hypothesis that humoral substances may be involved in postprandial mesenteric hyperemia. The study, however, does not provide information in regard to the site

of origin of the substances, since the investigators studied the vasoactivity of aortic blood. The chemical nature of the substances is also unknown.

As described above, the gastrointestinal hormones gastrin, CCK and secretin have a vasodilating effect on various organs. Therefore, the three hormones may play a role in the cardiovascular response that occurs following a meal. The cardiovascular response to digestion is a selective hyperemia in the small intestine with no changes in heart rate, or arterial pressure and blood flow through the heart, and kidney, and slight decrease or no change in flow through the limbs. If these hormones produce these responses within the blood concentration ranges attained following a meal, they could be implicated in playing a role in the postprandial cardiovascular adjustment. The studies on the vascular effect of the three hormones, as described above, used a variety of methods, dosages, and routes of administration, and in most studies all three hormones were not studied in any given experiment. It is, therefore, difficult to compare the responses of different organs to the same hormone. Furthermore, the vascular actions of one or all of these hormones on the coronary, renal, forelimb, splenic, skin and muscle vascular beds have not been studied.

The purpose of this investigation was twofold: 1) to compare the vascular effects of pentagastrin, secretin and

CCK on the duodenum, jejunum, heart, kidney, forelimb, spleen, and skin and muscle of the forelimb; and 2) to estimate the concentration requirements of these hormones in producing vascular effects in each organ.

CHAPTER III

METHODS AND MATERIALS

Healthy mongrel dogs of either sex, weighing 15-26 kg., and fasted for 24 hours, were used in all studies. They were anesthetized with an intravenous injection of sodium pentobarbital (30 mg/kg). All of the animals were artificially ventilated with a positive pressure respiration pump (Model 607, Harvard Apparatus Co., Inc., Dover, Massachusetts) through a endotracheal tube to maintain a normal blood pH. Both femoral arteries were isolated and cleared of fascia for cannulation. Heparin sodium (6 mg/kg, 120 units/mg) (Wolins Pharmaceutical Corp., Melville, New York) was administered intravenously as an anticoagulant.

The effect of gastrin, CCK and secretin on vascular resistance to blood flow of the heart, kidney, spleen, forelimb, jejunum and duodenum were studied utilizing the constant flow preparation (Figure 1). The artery that perfused the organ was dissected free from the adjacent tissue, and care was taken to minimize damage to periarterial nerves. The artery was cannulated with a steel or polyethylene tubing cannula that was connected to an

Figure 1. Schematic diagram illustrating the preparation for perfusing the organs at a constant flow rate. Arrows indicate the direction of blood flow.

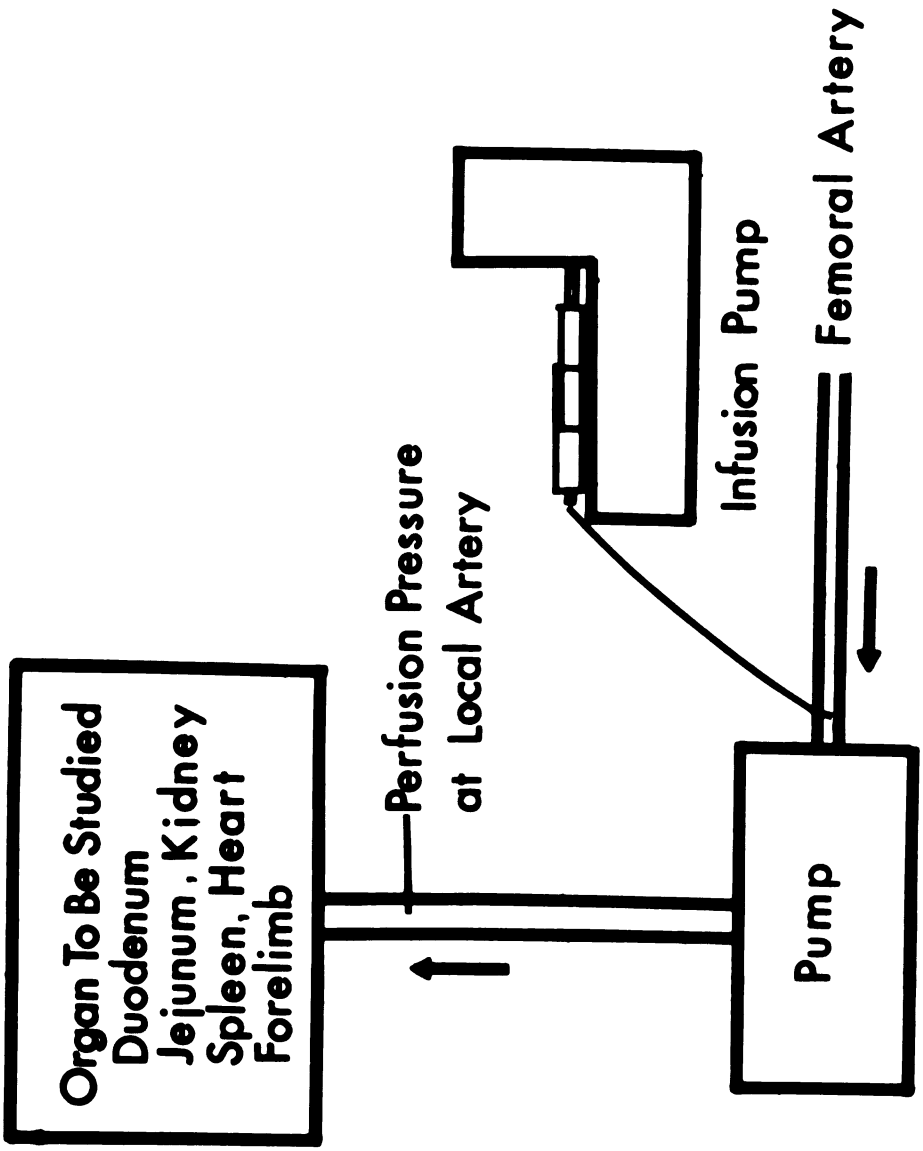
Organ To Be Studied
Duodenum
Jejunum, Kidney
Spleen, Heart
Forelimb
Perfusion Pressure
at Local Artery
Infusion Pump
Femoral Artery
Pump
Resistance = Perfusion Pressure / Pump Flow

Figure 1

extracorporeal pump circuit consisting of a Sigmamotor pump (Model T6SH or Model TM10), polyethylene tubings (PE 280) and two short rubber tubings. One rubber tubing was placed in the pump for conducting blood from a femoral artery to the organs and the other was placed just next to the cannula for the measurement of perfusion pressure by inserting a small catheter into it (Figure 1). Systemic arterial pressure was measured through a catheter (PE 280) inserted via a femoral artery into the aorta. Perfusion pressure and systemic arterial pressure were measured through pressure transducers (Statham, Model P23Gb, Hato Rey, Puerto Rico) and continuously recorded on a direct writing oscillograph (Sanborn, Model 7714A, Waltham, Massachusetts). Pump blood flow was adjusted initially to a rate which provided a perfusion pressure equal to or about 10 mm Hg below the aortic pressure. Blood flow was then maintained constant throughout the experiment. The organs under study were covered with a plastic sheet to retard evaporative water loss and body temperature was maintained near 38°C with a heat lamp.

Pure natural secretin and partially pure natural CCK (17%), with potencies of about 4000 U/mg and 500 U/mg respectively, were obtained from the Gastrointestinal Research Unit, Karolinska Institute, Stockholm. The biological activities of the two hormones are expressed in Ivy dog units (IDU). The IDU (U) for secretin is defined as

that amount of dry material dissolved in normal saline solution which, when injected intravenously in 10-15 seconds to an anesthetized dog weighing about 15 kg, will cause a 10 drops (0.4 ml) increase in the rate of flow of pancreatic juice from the cannulated duct during a period of 10 min, the control flow being not more than one drop in 2 min. The IDU (U) for CCK is defined as that amount of dry material dissolved in normal saline solution which, when injected intravenously in 10-15 seconds to an anesthetized dog weighing about 15 kg, results in a rise in intra-gallbladder pressure of 1 cm of bile during a period of 1-3 min, the basal bile pressure being 7-10 cm. Pentagastrin was obtained from Ayerst Laboratories, New York. Secretin and CCK were dissolved in normal saline, while pentagastrin solution was made as follows: To 10 mg of pentagastrin, 0.3 ml of 0.1 N ammonium hydroxide was added and the mixture was stirred. Twenty milliliters of water were then added and the mixture was stirred again. To this mixture, 0.1 N ammonium hydroxide (approximately 0.3 ml) was added until the pH was between 9.4 and 9.7. Sodium chloride (0.34 gm) was then added to the solution and stirred until the sodium chloride was completely dissolved. The pH of the final solution was adjusted to the range between 7.5 and 8 with 0.1 N HCl (approximately 0.3 ml), and the final volume was brought to 40 ml by the addition of water (0.25 mg pentagastrin per ml). The pentagastrin solution used in the

experiment was made from this stock solution by dilution with normal saline.

The three hormone solutions and their solvents were infused upstream from the pump in random sequence in each experiment. The solvents served as volume controls for the hormone solutions. Each hormone or solvent was infused in sequentially higher infusion rates over a range 0.01 to 7.8 ml/min with an infusion pump (Model 940, Harvard Apparatus Co., Dover, Massachusetts). Each infusion rate lasted two minutes, by which time perfusion pressure usually had reached a new steady level. The concentrations of secretin, CCK and pentagastrin used were 3 U/ml, 3 U/ml, and 20 µg/ml respectively in the experiments on the coronary, renal and forelimb circulations. In the spleen, duodenum and jejunum the concentrations of secretin and CCK used were both 1 U/ml. The concentration of pentagastrin used in the duodenum and jejunum was 10 µg/ml and in the spleen 20 µg/ml.

Surgical Preparation of the Organs

Heart (N = 9). The heart was exposed through the third left intercostal space and a suture was passed around the left common coronary artery at the junction of the artery with the aorta. The animal was heparinized and the input tubing of the Sigmamotor pump (Model T6SH, Sigmamotor Inc., Middleport, N. Y.) was inserted into the aorta via a femoral artery. The extracorporeal pump circuit was filled

with aortic blood. A curved metal cannula having approximately the same diameter as the left common coronary artery and connected to the output tubing of the pump was inserted into the left subclavian artery. With the pump delivering blood at 76 ml/min, the cannula tip was manipulated down the ascending aorta into the mouth of the left common coronary artery and tied in place with the previously placed suture (41). Left ventricular contractile force was measured with 120 ohm calibrated strain gauge arch (P. O. Box 412, Charleston, S. C.) sutured to the surface of the left ventricle.

Kidney (N = 6). The left kidney was exposed retroperitoneally through a flank incision and retracted medially for visualization of the renal artery. Following intravenous injection of heparin, the extracorporeal pump circuit was interposed between the right femoral and left renal artery (41).

Spleen (N = 6). After an abdominal midline incision, the spleen was exteriorized and made free of collateral flow by ligation and section of those vessels lying within the gastrosplenic and gastrocolic ligaments; the pancreatic arterial vessels originating from the splenic artery; and the collaterals joining the spleen and greater omentum. The splenic artery and vein were then isolated and cleared of surrounding tissue (6). In addition to the measurement

of perfusion pressure, changes in splenic volume were also measured by measuring changes in splenic weight. The splenic vein was cannulated (PE 320) to prevent mechanical occlusion of the venous outflow and the spleen was placed on a wire mesh platform suspended on one arm of a strain gauge weighing device. The weighing device was connected to a direct writing oscillograph (Sanborn, Model 7714A, Waltham, Massachusetts). The splenic venous outflow was directed to a blood reservoir filled initially with 250 ml 6% dextran in normal saline. The blood in the reservoir was pumped (Sigmamotor pump, Model T6SH, Sigmamotor, Inc., Middleport, N. Y.) back to the animal via a femoral vein at a rate equal to the venous outflow. The splenic artery was cannulated (PE 280) and perfused at a constant rate by a Sigmamotor pump (Model T6SH) with blood from the right femoral artery.

Duodenum (N = 5). Through a midline incision, a segment of duodenum about 10-13 cm in length and 5-10 cm oral to the ligament of Treitz was exteriorized. After intravenous injection of heparin, the artery that perfused the duodenal segment was cannulated with a steel cannula, which was connected to a polyethylene perfusion tubing of the extracorporeal pump circuit. The duodenal segment was pump-perfused at a constant rate (Sigmamotor pump, Model TM 10, Sigmamotor Inc., Middleport, N. Y.) with blood from a femoral artery. A gastric tube, with an outer diameter of

0.5 cm, was inserted into the duodenal lumen and both ends of the segment were tied. The duodenal lumen was then filled with 10 ml of normal saline. The gastric tube was connected to a Statham pressure transducer (P23 Gb) via a three-way stopcock to monitor intraluminal pressure. The mesentery was also cut completely to exclude collateral flow to the segment.

Jejunum (N = 9). The surgical preparation of the jejunum was the same as that of the duodenum. Through a midline incision a segment of jejunum about 20 cm aboral to the ligament of Treitz and about 15 cm in length was exteriorized. After intravenous injection of heparin, the artery that perfused the jejunal segment was cannulated with a steel cannula that was connected to a polyethylene perfusion tubing of the extracorporeal pump circuit (16). The jejunal segment was pump-perfused at a constant rate (Sigmamotor pump, Model TM 10, Sigmamotor Inc., Middleport, N. Y.) with blood from a femoral artery. A gastric tube, with an outer diameter of 0.5 cm, was inserted into the jejunal lumen and both ends of the segment were tied. The jejunal lumen was then filled with 5 ml of normal saline. The gastric tube was connected to Statham pressure transducer (P23 Gb) via a three-way stopcock to monitor intraluminal pressure. The mesentery was cut to exclude collateral flow.

Forelimb (N = 6). The brachial artery, forelimb nerves, and brachial and cephalic veins were exposed at 3-5 cm above the elbow and dissected free. The remaining connective tissues were tied and cut. The bone was sectioned and the ends filled with bone wax to prevent bleeding. Consequently, all blood entered the limb through the brachial artery and left by the brachial and cephalic veins (41). The brachial artery was cannulated with the catheter connected to the extracorporeal pump circuit. The cephalic and brachial veins and forelimb nerves were left intact.

Skin and Muscle of the Forelimb (N = 6). The total forelimb vascular bed consists of two parallel vascular beds, i.e., skin and muscle. Since the effect of a hormone could differ in these areas it was deemed important to separate their responses. This was done by measuring individual flows from the brachial and cephalic veins. Collateral flow to the forelimb was excluded as described above. With the brachial artery and limb nerves intact, the brachial and cephalic veins were cannulated. The median cubital vein, which represents the major anastomotic channel between the brachial and cephalic veins, was ligated so that the brachial venous flow was predominantly from muscle, while cephalic flow was predominantly from skin (78). Flows from these two veins were periodically measured with graduated cylinders and a stopwatch in

one-minute samples. The outflows were directed into a reservoir maintained at a constant volume by pumping blood back to the animal via a jugular vein at rates equal to venous outflows. A side branch of the brachial artery was cannulated with a catheter (PE 50) for the infusion of hormones.

Analysis of Data

In the constant flow preparation, the hormone or solvent was infused locally after a steady state of perfusion pressure had been established. During the infusion, each infusion rate was maintained for at least 2 minutes, at which time the perfusion pressure was in a new steady level. The perfusion pressure at the steady level before and during the infusion was used for the calculation of the vascular resistance. The vascular resistance was calculated by dividing the perfusion pressure by pump blood flow. All data were expressed in mean $\pm$ standard error. The significance of changes in vascular resistance produced by infusions of hormones or solvents were examined by comparing the resistances during control and infusion periods in each dog by Student's t-test modified for paired comparison between two sample means (73). In the natural flow preparation, the venous outflow values of a steady level before and after infusion of hormones were used for the calculation of the vascular resistance. The same statistical analysis

of Student's t-test modified for paired comparison was used to evaluate the significance of changes in vascular resistance from the control value (73). Furthermore, the changes in vascular resistance produced during the infusion of the hormone solutions were compared to those produced during the infusion of their solvents at the same volume infusion rates. The Student's t-test modified for unpaired comparison between two sample means was used for this analysis (73). A p value equal to or less than 0.05 was considered statistically significant.

CHAPTER IV

RESULTS

Heart

The control systemic arterial pressure (101 ± 2.7 mm Hg) was not significantly altered during local intra-arterial infusion of any of the three hormones or their solvents, except when CCK was infused at and above 2 ml (6U)/min or secretin above 3.9 ml (11.7 U)/min. At the infusion rate of 6 U/min, CCK significantly lowered the systemic arterial pressure from the control level of 101 ± 2.7 mm Hg to a level of 96 ± 2.9 mm Hg ($p < 0.05$, Student's t-test, paired comparison). At an infusion rate of 11.7 U/min, CCK further decreased systemic arterial pressure to 90 ± 2.8 mm Hg ($p < 0.05$, Student's t-test, paired comparison). Secretin also lowered the systemic arterial pressure during infusion rate of 11.7 U/min; the control pressure of 101 ± 5.1 mm Hg fell to 95 ± 5.0 mm Hg ($p < 0.05$, Student's t-test, paired comparison).

The effects of secretin, CCK and pentagastrin on coronary vascular resistance are shown in Table 1. Secretin caused a significant decrease in coronary vascular resistance

Table 1. Coronary vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in pump-perfused canine hearts. (N = 9)

Solutions	Control	Infusion rates (ml/min) 0.2	0.39	1.0	2.0	3.9	Changes in Contractile Force[a]
Secretin (3 U/ml)	1.09±0.11	1.07±0.11	1.01±0.11	0.95±0.10*	0.89±0.09*	0.84±0.08*	+(2), -(2), 0(5)
CCK (3 U/ml)	1.16±0.12	1.14±0.12	1.13±0.12	1.10±0.11*	1.00±0.10*	0.92±0.11*	-(5), 0(4)
Normal saline	1.11±0.14	1.08±0.12	1.08±0.12	1.08±0.12	1.06±0.11	1.00±0.10*	0(9)
Pentagastrin (20 µg/ml)	1.18±0.16	1.18±0.16	1.17±0.16	1.16±0.17	1.18±0.18	1.19±0.18	0(9)
Pentagastrin solvent	1.31±0.16	1.31±0.16	1.25±0.14	1.22±0.13	1.15±0.11	1.08±0.11*	0(9)

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

[a]Direction of changes in contractile force of the left ventricle: + = increase, - = decrease, 0 = no change; numbers in parentheses = numbers of the hearts responding.

Pump blood flow = 92.9±5.98 ml/min.

when the infusion rate was increased to 1 ml (3 U)/min. Further increases in the infusion rate produced further decreases in resistance. The effects of CCK on coronary resistance were similar to those observed with secretin. At and above the infusion rate 1 ml (3 U)/min, CCK significantly decreased resistance. Normal saline, the solvent for secretin and CCK, significantly decreased resistance only when the infusion rate was raised to 3.9 ml/min. Even at this infusion rate, the decrease in resistance produced by normal saline (-10% of control) was statistically smaller than that produced by secretin (-23% of control) and CCK (-21% of control) at the same infusion rate. The decreased resistance caused by local infusions of secretin or CCK, therefore, was not due to hemodilution. Pentagastrin and its solvent did not significantly alter coronary vascular resistance except the solvent at the infusion rate 3.9 ml/min significantly lowered coronary resistance (Table 1).

The change in the contractile force of the left ventricle was determined by the change in the height of the excursion on the recording paper in millimeters. The total excursion during infusion of hormones was divided by that during control period (average value was 23 mm) and expressed in percentage. The contractile force of the left ventricle was decreased only by CCK at and above the infusion rate of 3 U/min, in five out of nine experiments

(Table 1). In these five dogs, the average decrease in the contractile force was 11.6 ± 4.5% below the control level. In the remaining four experiments, the contractile force of the left ventricle was unchanged during the local intra-arterial infusion of CCK at all infusion rates. The effect of secretin on the contractile force was irregular; the contractile force increased in two of the nine animals studied and decreased in another two. The average increase or decrease in the force in these dogs was 13 ± 1.0% and 13 ± 4.5% above or below the control level, respectively, at an infusion rate of 3.9 ml (11.7 U)/min. In the remaining five animals, contractile force was unchanged at all infusion rates. Pentagastrin or its solvents did not alter the contractile force.

Kidney

Control systemic arterial pressure (128.8 ± 2.6 mm Hg) was not significantly altered during local intra-arterial infusion of secretin, pentagastrin or their solvents. CCK at an infusion rate of 3.9 ml (11.7 U)/min, however, significantly lowered the systemic arterial pressure from a control of 128.8 ± 2.6 mm Hg to 123 ± 1.7 mm Hg ($p < 0.05$, Student's t-test, paired comparison).

The effects of secretin, CCK and pentagastrin on renal vascular resistance are shown in Table 2. Secretin caused a significant decrease in renal vascular resistance at and

Table 2. Renal vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in pump-perfused canine kidneys. (N = 6)

Solutions	Control	Infusion rates (ml/min) 0.2	0.39	1.0	2.0	3.9
Secretin (3 U/ml)	0.57±0.06	0.54±0.05	0.52±0.05*	0.49±0.04*	0.48±0.04*	0.47±0.04*
CCK (3 U/ml)	0.57±0.05	0.57±0.06	0.56±0.06	0.55±0.05*	0.53±0.05*	0.52±0.05*
Normal saline	0.59±0.06	0.59±0.06	0.58±0.05	0.58±0.05	0.57±0.05	0.56±0.05
Pentagastrin (20 µg/ml)	0.60±0.07	0.56±0.06	0.57±0.06	0.58±0.07	0.60±0.06	0.60±0.06
Pentagastrin solvent	0.61±0.07	0.61±0.07	0.62±0.07	0.61±0.07	0.60±0.07	0.60±0.07

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

Pump blood flow = 135.33 ± 7.71 ml/min.

above the infusion rate of 0.39 ml (1.17 U)/min. The effect of secretin appeared to reach its maximum at the infusion rate of 1.0 ml (3 U)/min, since further increases (i.e., two-and four-fold) in infusion rate did not produce a further decrease in resistance. CCK significantly decreased renal vascular resistance at and above infusion rate of 1.0 ml (3 U)/min. Neither pentagastrin nor its solvent produced a significant change in resistance.

Spleen

Systemic arterial pressure was not significantly changed during local intra-arterial infusion of any of the three hormones or their solvents. The average control arterial pressure was 116 $\pm$ 10.4 mm Hg.

As shown in Table 3, splenic vascular resistance decreased progressively in response to secretin. The fall in resistance was statistically significant at and above the infusion rate 1.0 ml (1 U)/min. CCK produced a similar vascular effect and the minimum infusion rate at which CCK produced a significant decrease in splenic vascular resistance was also 1.0 ml (1 U)/min. Infusion of normal saline had no significant effect on resistance. Infusion of pentagastrin caused a significant decrease in splenic vascular resistance at and above the infusion rate of 2.0 ml (40 µg)/min. Infusion of pentagastrin solvent also significantly decreased the splenic vascular resistance at and above the

Table 3. Splenic vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in pump-perfused canine spleens. (N = 6)

Solutions	Control	Infusion rates (ml/min) 0.2	0.39	1.0	2.0	3.9
Secretin (1 U/ml)	2.23±0.11	2.18±0.12	2.15±0.11	1.98±0.10*	1.82±0.08*	1.63±0.07*
CCK (1 U/ml)	2.20±0.10	2.18±0.13	2.15±0.10	1.96±0.11*	1.84±0.11*	1.57±0.11*
Normal saline	2.25±0.12	2.25±0.12	2.24±0.12	2.19±0.12	2.15±0.12	2.07±0.12
Pentagastrin (20 µg/ml)	2.25±0.11	2.25±0.11	2.25±0.11	2.20±0.11	2.13±0.10*	2.01±0.09*
Pentagastrin solvent	2.24±0.09	2.24±0.09	2.21±0.09	2.14±0.08	2.10±0.09*	1.97±0.08*

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

Pump blood flow = 63.3 ± 7.50 ml/min.

infusion rate of 2.0 ml/min. The decrease in resistance produced by pentagastrin was statistically the same as that produced by its solvent. Therefore, the effect of pentagastrin appeared to be due to pentagastrin solvent.

In no case did local infusion of any hormone or solvent significantly alter splenic weight, an indicator of splenic volume. The effect of secretin and CCK on splenic weight was irregular. Infusion of secretin increased splenic weight (1-5 gm) in two of the six animals studied; decreased the weight (1-3 gm) in one; and did not change the weight in the remaining three. Similarly, infusion of CCK increased splenic weight (1-3 gm) in two of the six animals studied; decreased the weight (1-5 gm) in two, and did not change in the remaining two. Infusion of pentagastrin decreased splenic weight (1-5 gm) in two of the six animals studied. In the remaining four animals, splenic weight remained unchanged. Solvents of hormones did not alter splenic weight in any of the dogs studied.

Forelimb

Systemic arterial pressure was not significantly altered during local infusion of any hormone or solvent. The average control arterial pressure was 126 $\pm$ 10.0 mm Hg. The average effects of secretin, CCK and pentagastrin on forelimb vascular resistance are shown in Table 4. Only secretin caused a significant decrease in forelimb vascular

Table 4. Forelimb vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in pump-perfused canine forelimbs. (N = 6)

Solutions	Control	Infusion rates (ml/min) 0.2	0.5	1.0	2.0	3.9
Secretin (3 U/ml)	1.42±0.06	1.27±0.08*	1.13±0.11*	1.01±0.12*	0.93±0.13*	0.88±0.15*
CCK (3 U/ml)	1.81±0.27	1.77±0.27	1.71±0.26	1.63±0.23	1.53±0.21	1.41±0.21
Normal saline	1.65±0.04	1.65±0.04	1.64±0.04	1.64±0.04	1.54±0.05	1.45±0.06
Pentagastrin (20 µg/ml)	1.88±0.02	1.91±0.02	1.95±0.03	1.93±0.04	1.88±0.04	1.72±0.02
Pentagastrin solvent	1.73±0.04	1.72±0.03	1.72±0.03	1.68±0.03	1.63±0.03	1.54±0.04

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

Pump blood flow = 80.8 ± 6.42 ml/min.

resistance. The significant decrease in resistance occurred at and above the infusion rate 0.2 ml (0.6 U)/min. Further increases in the infusion rate progressively decreased resistance. Infusion of CCK did not significantly alter resistance. Although the resistance tended to fall as the infusion rate was increased, the decreases were not statistically significant because of a large variation in responses. Infusion of normal saline also tended to lower resistance as the infusion rate was increased. The magnitude of the decrease in resistance produced by CCK was statistically not different from that produced by normal saline. However, the decreased resistance produced by secretin was significantly greater than that produced by normal saline, indicating that the effect of secretin was not due to hemodilution. Neither pentagastrin nor its solvent significantly altered vascular resistance.

Skin and Muscle of Forelimb

Systemic arterial pressure was also not significantly altered during local infusions of secretin or CCK; the average control arterial pressure was 124 $\pm$ 6.6 mm Hg. The average effects of secretin and CCK on the forelimb and its skin and muscle vascular resistance are shown in Table 5. Only secretin significantly lowered the vascular resistance. Secretin at and above the infusion rate of 0.5 ml (1.5 U)/min significantly decreased the resistance of the forelimb

Table 5. Forelimb and its skin and muscle vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin and CCK in the naturally perfused canine forelimb. (N = 6)

	Solutions	Control	Infusion rates (ml/min) 0.2	0.5	1.0	2.0
Skin	Secretin (3 U/ml)	2.35±0.30	2.21±0.27	2.06±0.25*	1.85±0.22*	1.69±0.20*
	CCK (3 U/ml)	2.24±0.40	2.27±0.42	2.26±0.43	2.22±0.43	2.12±0.42
	Normal saline	2.36±0.36	2.38±0.39	2.39±0.38	2.35±0.28	2.36±0.40
Muscle	Secretin (3 U/ml)	3.70±0.81	3.47±0.84	3.33±0.83*	3.07±0.81*	2.79±0.71*
	CCK (3 U/ml)	4.07±0.69	4.32±0.77	4.25±0.77	4.13±0.80	3.98±0.68
	Normal saline	3.93±0.77	3.82±0.76	3.85±0.76	3.81±0.76	3.78±0.74
Forelimb	Secretin (3 U/ml)	1.35±0.16	1.26±0.15	1.20±0.15*	1.11±0.16*	1.00±0.14*
	CCK (3 U/ml)	1.47±0.17	1.43±0.18	1.40±0.19	1.38±0.20	1.30±0.19
	Normal saline	1.46±0.18	1.44±0.18	1.44±0.17	1.44±0.18	1.43±0.19

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

and its skin and muscle. Infusion of CCK or normal saline had no effect on these vascular resistances. The vascular resistance of skin and muscle in response to secretin was quantitatively similar. At an infusion rate of 0.5 ml (1.5 U)/min, secretin produced a 12% and 10% decrease from control levels in the resistance of muscle and skin, respectively. This indicated that secretin equally affects the vasculature of the skin and muscle of the forelimb.

Duodenum and Jejunum

Systemic arterial pressure was not significantly altered during local infusion of any hormone or solvent. The average control arterial pressures were 112 $\pm$ 8.2 mm Hg and 115 $\pm$ 9.5 mm Hg in the studies of the duodenum and jejunum, respectively.

Table 6 shows the response of duodenal vascular resistance to infusion of secretin, CCK or pentagastrin. Secretin at and above an infusion rate 0.2 ml (0.2 U)/min, CCK at and above 0.05 ml (0.05 U)/min, and pentagastrin at and above 0.1 ml (1 µg)/min significantly decreased duodenal vascular resistance. Further increases in the dosage of these hormones produced further decreases in resistance. The solvents for the hormones did not significantly affect resistance.

The response of jejunal vascular resistance to secretin, CCK or pentagastrin is shown in Table 7. The patterns

Table 6. Duodenal vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in the pump-perfused canine duodenum. (N = 5)

Solutions	Control	Infusion rates (ml/min) 0.05	0.1	0.2	0.5	1.0	2.0
Secretin (1 U/ml)	5.42±0.39	5.42±0.39	5.30±0.40	5.06±0.41*	4.62±0.41*	3.88±0.26*	3.38±0.21*
CCK (1 U/ml)	6.75±0.51	6.27±0.52*	5.63±0.46*	4.86±0.41*	4.35±0.39*	4.05±0.40*	3.75±0.40*
Normal saline	5.58±0.57	5.58±0.57	5.57±0.57	5.66±0.57	5.63±0.62	5.48±0.61	5.41±0.65
Pentagastrin (10 µg/ml)	6.10±0.61	5.68±0.53	5.30±0.52*	4.90±0.43*	4.74±0.43*	4.70±0.47*	4.42±0.38*
Pentagastrin solvent	6.50±0.55	6.50±0.55	6.48±0.55	6.57±0.57	6.54±0.58	6.42±0.60	6.25±0.64

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denoted that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

Pumped blood flow = 20.0 ± 2.83 ml/min.

Table 7. Jejunal vascular resistance (mmHg/ml/min) during local intra-arterial infusions of secretin, CCK and pentagastrin in the pump-perfused canine jejunum. (N = 9)

Solutions	Control	Infusion rates (ml/min) 0.05	0.1	0.2	0.5	1.0	2.0
Secretin (1 U/ml)	7.69±0.56	7.53±0.56	7.42±0.55*	7.01±0.57*	6.06±0.56*	4.93±0.52*	4.12±0.40*
CCK (1 U/ml)	7.81±0.86	7.45±0.82*	6.36±0.79*	5.36±0.71*	4.79±0.68*	4.22±0.53*	3.91±0.50*
Normal saline	7.78±0.97	7.76±0.98	7.76±0.98	7.74±0.97	7.59±0.97	7.24±0.92*	6.74±0.86*
Pentagastrin (10 µg/ml)	6.43±0.67	5.72±0.62*	5.19±0.60*	5.02±0.56*	5.02±0.52*	4.74±0.51*	4.37±0.55*
Pentagastrin solvent	5.46±0.97	5.46±0.97	5.46±0.97	5.43±0.96	5.37±0.97	5.04±0.86*	4.46±0.65*

All values are mean ± S.E. The S.E. indicates the variation among animals.

*Denotes that the value is significantly different from the control value at $p < 0.05$, Student's t-test, paired comparison.

Pump blood flow = 15.60 ± 1.68 ml/min.

of jejunal vascular response to secretin, CCK and pentagastrin were very similar to those observed in the duodenum. Secretin at and above an infusion rate of 0.1 ml (0.1 U)/min, CCK at and above 0.05 ml (0.05 U)/min, and pentagastrin at and above 0.05 ml (0.5 μg)/min significantly lowered jejunal vascular resistance. Further increases in the dosage of these hormones resulted in further decreases in resistance. The solvents of these hormones did not significantly affect resistance until infusion rates were above 1.0 ml/min. However, at these infusion rates, the decrease in resistance caused by the solvents was significantly smaller than that produced by the hormones ($p < 0.05$, Student's t-test, unpaired comparison), indicating that the decreased resistance caused by local infusion of hormones was not due to hemodilution.

In addition to the vasodilator action, local intra-arterial infusion of CCK and pentagastrin regularly produced phasic contractions of the duodenum and jejunum in all dogs studied. Secretin, however, did not alter jejunal lumen pressure, and its effect on duodenal lumen pressure was not uniform. Of 10 experiments, duodenal luminal pressure was unchanged in four at any dosage. In two experiments, no effect was seen until the infusion rate was raised above 0.5 U/min, at which time pressure was decreased. In the remaining four experiments, the duodenal lumen pressure was

slightly increased over the infusion rate of 0.2 to 1.0 U/min, but with further increases in the infusion rate the pressure fell to zero and phasic contractions ceased.

Comparisons of Responses in Eight Vascular Beds

Figure 2 compares the effects of secretin on vascular resistance of eight vascular beds studied. The percent changes in resistance caused by infusion of secretin are plotted against the increase in the concentration of the hormone in the arterial blood during infusions. The increases in concentration were calculated by dividing infusion rates (ml/min) by pump blood flows (ml/min). Infusion of secretin caused a significant fall in the vascular resistance of all eight vascular beds studied. The slopes of the dose-response curves of secretin in the eight organs appear to be similar. The minimal calculated increments in local arterial concentration of secretin, which produced a significant decrease in vascular resistance of eight vascular beds (concentration requirement) are shown in Table 8. The minimum increase in local secretin concentration required to produce a significant decrease in resistance in the eight organs ranged from 7.1 to 32.3 mU/ml. Also, the concentration requirements for the digestive organs, i.e., duodenum and jejunum were within the range of those for non-digestive organs (7.4-32.3 mU/ml).

Figure 2. Comparison of the effect of secretin in eight vascular beds. The percent changes in resistance caused by infusion of secretin are plotted against the increase in the concentration of the hormone in the arterial blood during infusions. The increases in concentration were calculated by dividing infusion rates (U/min) by pump blood flows (ml/min).

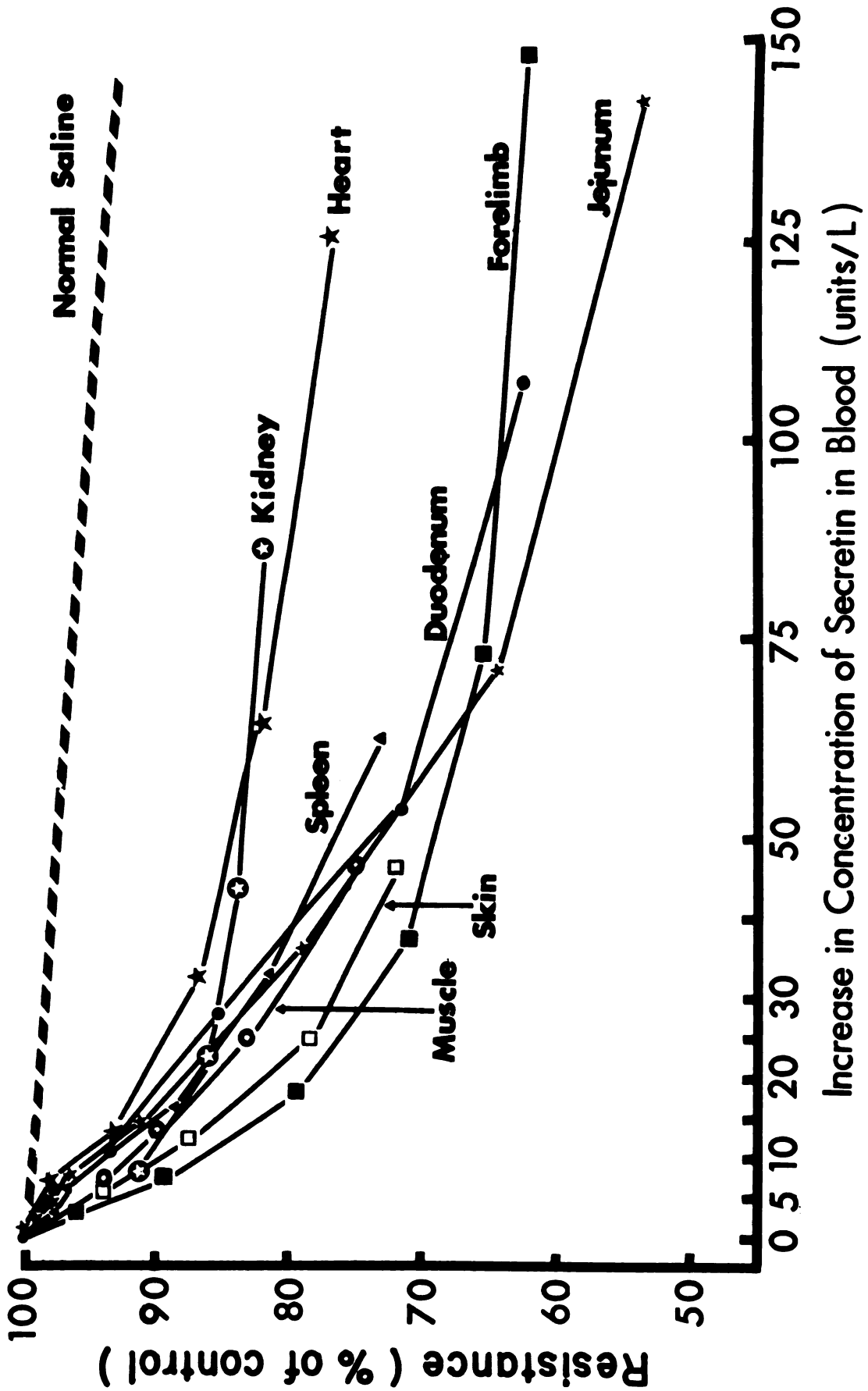
Normal Saline
Heart
Kidney
Spleen
Duodenum
Forelimb
Jejunum
Muscle
Skin
Resistance (% of control)
100
90
80
70
60
50
0 5 10 20 30 50 75 100 125 150
Increase in Concentration of Secretin in Blood (units/L)

Figure 2

Table 8. Minimum increments in local arterial concentration of secretin, CCK and pentagastrin which produce a significant ($p < 0.05$) decrease in local vascular resistance (R) in eight vascular beds.

	Secretin		CCK		Pentagastrin	
	Δ Conc. + mU/ml	ΔR %	Δ Conc. + mU/ml	ΔR %	Δ Conc. + ng/ml	ΔR %
Duodenum	10.7	- 7.0	2.5	- 7.0	50.0	-13.0
Jejunum	7.1	- 4.0	2.6	- 5.0	25.0	-11.0
Heart	32.3	-13.0	32.8	- 5.0	-	0
Kidney	8.6	- 9.0	22.2	- 5.0	-	0
Spleen	15.8	-11.0	20.8	-11.0	-	0
Forelimb	7.4	-10.0	-	0	-	0
Muscle	14.0	-10.0	-	0	-	0
Skin	14.0	-12.0	-	0	-	0

ΔR = Change as percentage of control.

Figure 3 compares the effects of CCK on vascular resistance of the eight vascular beds studied. CCK produced two distinguishable groups of dose-response curves in these eight organs. The duodenum and jejunum were uniquely responsive to CCK over the lower part of the infusion rates used in this study. Their response over the higher infusion rates, however, was similar to that of the other organs studied. A sharp fall in duodenal and jejunal vascular resistance occurred as the local concentration of CCK was increased by 10 mU/ml; thereafter, further increment in local CCK concentration produced small decrease in resistance. The concentration requirements for CCK in mU/ml, i.e., the minimal increments in local concentration which significantly lowered vascular resistance, are shown in Table 8. The small intestine, i.e., duodenum and jejunum, was most sensitive to CCK. The concentration requirement for CCK in the small intestine was 1/8 to 1/13 of that in the other organs affected. CCK did not affect forelimb, skin and muscle vascular resistance.

Figure 4 compares the effects of pentagastrin on vascular resistance of the eight vascular beds studied. Similar to CCK, pentagastrin had significant effect on the duodenal and jejunal vascular resistance. A sharp and rapid fall in duodenal and jejunal vascular resistance occurred as the local concentration of pentagastrin was raised by 50 ng/ml.

Figure 3. Comparison of the effect of CCK in eight vascular beds. The percent changes in resistance caused by infusion of CCK are plotted against the increase in the concentration of the hormone in the arterial blood during infusions. The increases in concentration were calculated by dividing infusion rates (U/min) by pump blood flows (ml/min).

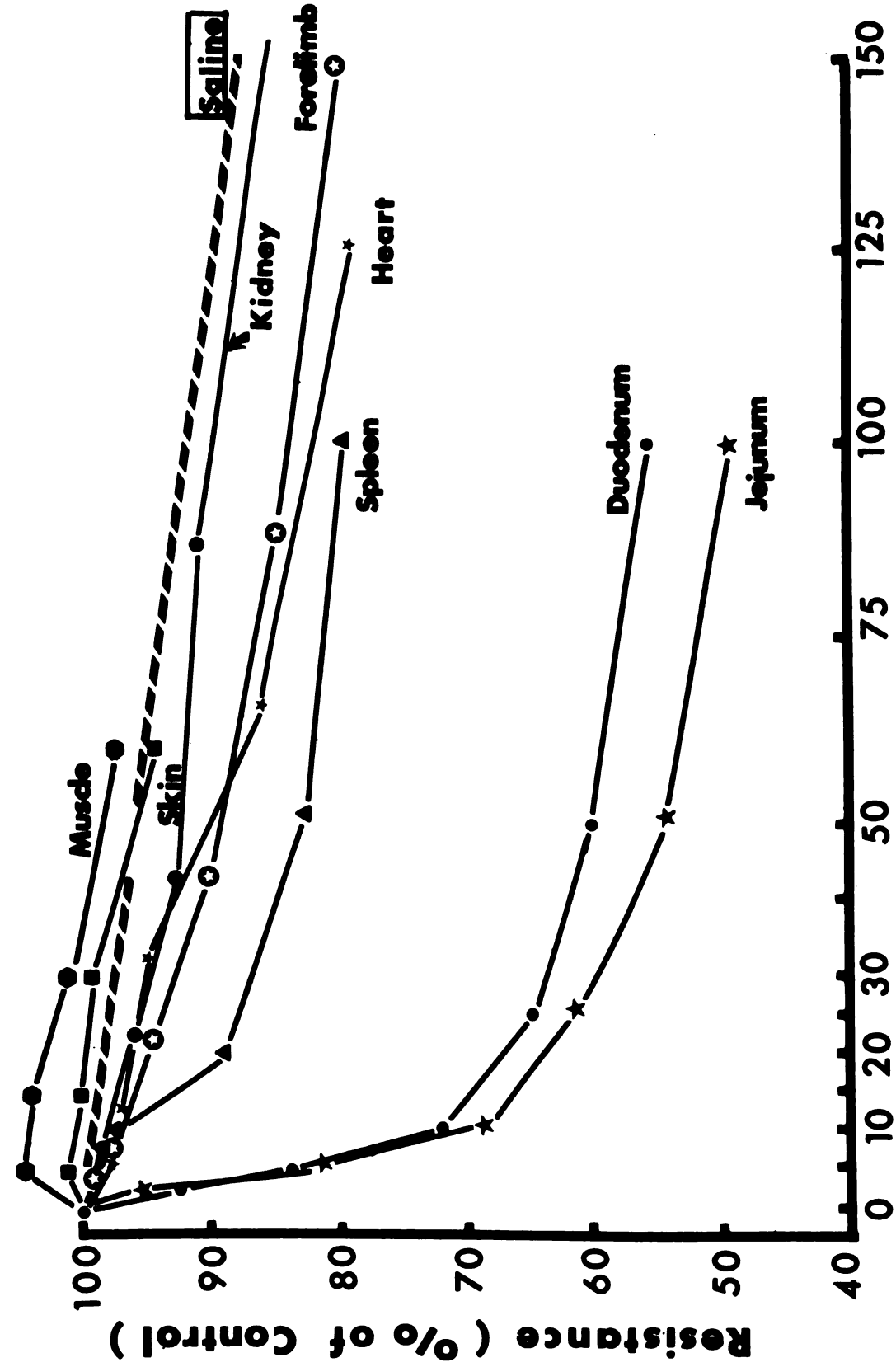
Resistance (% of Control)
100
90
80
70
60
50
40
0
10
20
30
50
75
100
125
150
Increase in Concentration of CCK in Blood (units/L)
Saline
Forelimb
Kidney
Heart
Spleen
Duodenum
Jejunum
Skin
Muscle

Figure 3

Figure 4. Comparison of the effect of pentagastrin in eight vascular beds. The percent changes in resistance caused by infusion of pentagastrin are plotted against the increase in the concentration of the hormone in the arterial blood during infusions. The increases in concentration were calculated by dividing infusion rates (μg/min) by pump blood flows (ml/min).

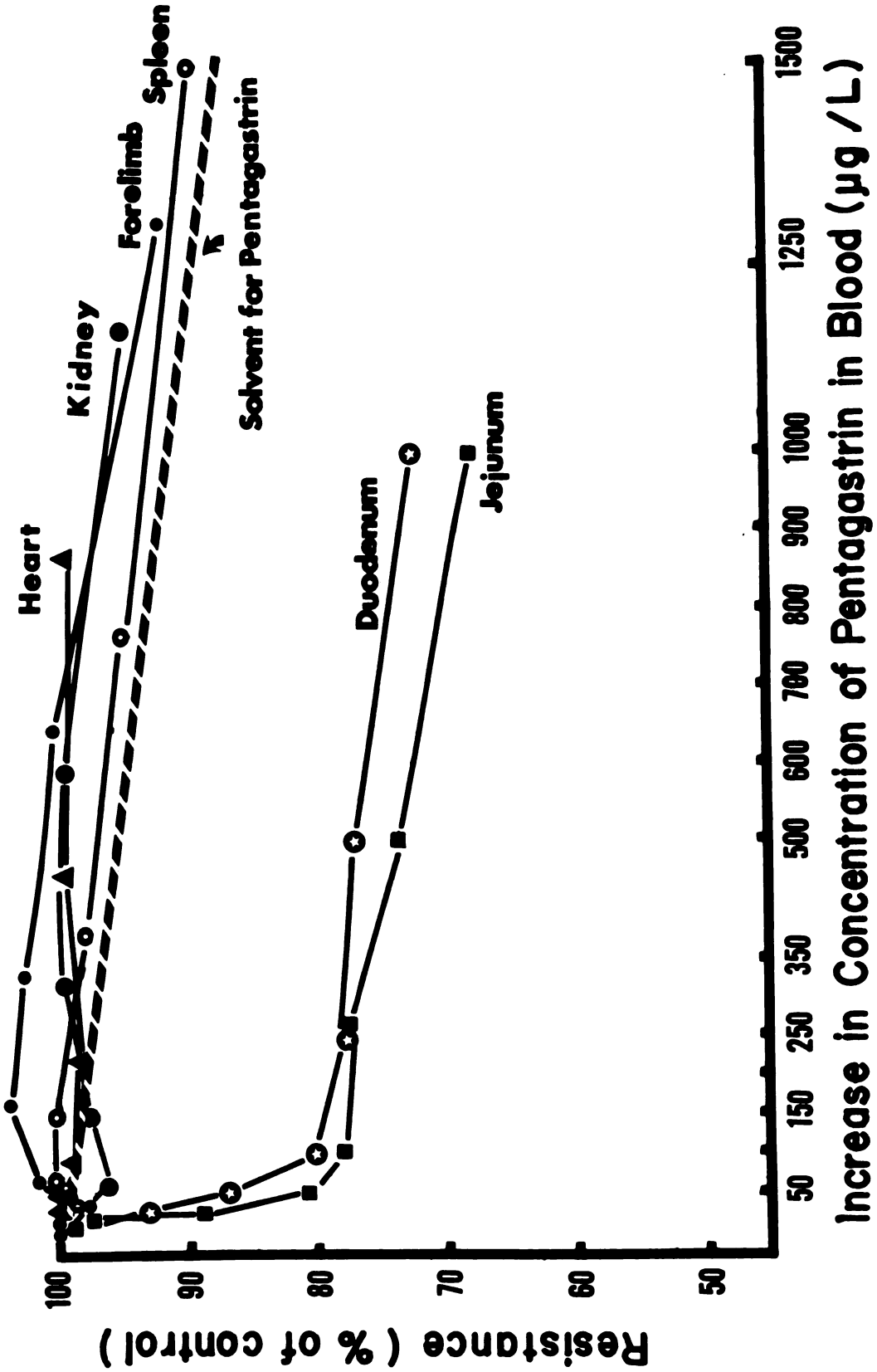
Resistance (% of control)
100
90
80
70
60
50
50
150
250
350
500
600
700
800
900
1000
1250
1500
Increase in Concentration of Pentagastrin in Blood (µg /L)
Heart
Kidney
Forelimb
Spleen
Solvent for Pentagastrin
Duodenum
Jejunum

Figure 4

Further increment in local pentagastrin concentration only caused a slight fall in resistance. The concentration requirement, ng/ml, for pentagastrin in the duodenum and jejunum were 50 and 25, respectively (Table 8). Pentagastrin did not significantly alter the vascular resistance of the heart, kidney, spleen and forelimb.

CHAPTER V

DISCUSSION

The gastrointestinal hormones, gastrin, CCK and secretin are released into the circulation following a meal and play an important role in the regulation of the secretory and motor activities of the digestive organs. In addition to these functions, they may also be involved in postprandial intestinal hyperemia since these hormones have been shown to increase blood flow in the small intestine (5,10, 14,24,25,31,33,70). However, it is still not clear whether the vasodilator effect of the hormones in the small intestine is physiological or pharmacological. The cardiovascular adjustments during digestion is an increased blood flow in the digestive organs with no significant changes in blood flow to the heart, kidney and skeletal muscle. Therefore, if these hormones are involved in postprandial intestinal hyperemia, they should affect only the vasculature of the small intestine within the concentration range achieved following a meal.

The purposes of this study were 1) to compare the vascular effects of pentagastrin, CCK and secretin on the

duodenum, jejunum, heart, kidney, forelimb, spleen, and skin and muscle of the forelimb; and 2) to estimate the concentration requirements of these hormones in producing vasodilation in each organ. The study was performed utilizing the constant flow and natural flow preparations, and the hormones were infused at sequentially higher rates into a local artery.

The study shows that systemic arterial pressure was not significantly altered during local infusion of pentagastrin. This finding is in agreement with that of Jacobson and Chang who found that gastrin has no consistent depressor action on systemic arterial pressure in conscious dogs (49). Ardill et al. also reported that intravenous infusion of gastrin II did not significantly alter systemic arterial pressure in a human subject (2).

In the present study, local infusion of pentagastrin significantly decreased the vascular resistance in the duodenum and jejunum (Tables 6 and 7) but did not affect the resistance of the other organs studied, i.e., heart, kidney, spleen and forelimb (Tables, 1, 2, 3 and 4). It has been reported that local infusion of gastrin had no effect on the skin and muscle blood flow of the human forelimb (2). Burns and Schenk (10) found that subcutaneous injections of gastrin produced a prolonged increase in superior mesenteric flow in conscious dogs. Chou et al. (14,54) also found that

local intra-arterial infusion of gastrin reduced vascular resistance of the superior mesenteric and gastric vascular beds in the dog. In addition, local intra-arterial infusion of gastrin produced intestinal vasodilation in anesthetized cats (25). The present study thus confirms that gastrin or pentagastrin is a vasodilator of the small intestine, but has little or no effect upon the forelimb vasculature.

The literature contains no references to the effects of exogenous administration of gastrin on renal, coronary and splenic blood flow. However, Hjelmquist et al. (46) have shown that irrigation of the isolated innervated antrum with 0.5% solution of acetylcholine increases arterial serum gastrin concentration from the basal level of 47 $\pm$ 6 pg/ml to 165 $\pm$ 14 pg/ml and decreases renal blood flow 13% below the control level. This study, therefore, appears to indicate that gastrin is a vasoconstrictor in the kidney.

In the present study, local infusion of pentagastrin to raise pentagastrin concentration in the arterial blood by as much as 1000 ng/ml did not significantly alter renal vascular resistance (Figure 4, Table 2). The finding, therefore, is in conflict with that of Hjelmquist et al. However, it should be pointed out that irrigation of the gastric antrum with 0.5% acetylcholine in addition to releasing gastrin from the antrum can initiate other responses, such as stimulation of afferent nerves and/or

release of vasoactive substances. Therefore, the decreased renal blood flow observed by Hjelmquist et al. may not have been due to the rise in arterial gastrin concentration.

Gastrin has been shown to dilate the pancreatic vasculature (33,43), but its effect on the total gastric blood flow varies from one report to another (33,54). The present study showed that pentagastrin did not significantly alter the vascular resistance of the forelimb, kidney, spleen and heart but significantly altered the resistance of the small intestine. Gastrin, therefore, did not appear to be a general vasodilator in all tissues and organs of the body. This suggests that the vasodilator effect of gastrin on the gastric mucosa (51,74), pancreas (33,43) and small intestine might not be due to its direct action on the vascular smooth muscle but seemed to be mediated by an indirect mechanism. In the present study, pentagastrin produced vasodilation within a few seconds after intra-arterial infusion, and disappears within 20 seconds after stopping the infusion. The dilation, therefore, appeared to be mediated by a local mechanism.

Gastrin stimulates secretion in the stomach, pancreas and liver, and stimulates smooth muscle contraction in the stomach, small intestine, and gallbladder (37). Jacobson et al. (51,74) provided evidence of a linear relationship between gastric mucosal blood flow and the rate of

gastrin-induced secretion in the Heidenhain pouch. The total blood flow to the pouch, however, was not significantly altered. They therefore suggested that the mucosal vascular response appears to be secondary to the metabolic demands associated with augmented secretion. Recently, a number of reports have appeared to suggest that gastrin inhibits fluid absorption or even stimulates secretion in the small intestine (12,30,32). In hamsters, gastrin inhibited sodium transport in in vitro preparations of jejunal and ileal everted sac (30). In dogs, gastrin inhibited ileal (32) and jejunal (12) net absorption of sodium, potassium and water. This effect seems due either to an inhibition of active absorption of sodium or to a stimulation of sodium secretion. Furthermore, gastrin stimulates protein synthesis in the gastrointestinal tract (52). Thus, the vasodilator effect of gastrin may possibly be coupled to its metabolic effect.

Intra-arterial infusion of CCK, in the present study, significantly decreased the vascular resistance of the heart, kidney, spleen, jejunum and duodenum, but did not change the resistance of the forelimb and its skin and muscle (Tables, 1, 2, 3, 4, 5, 6, and 7). These findings agree with the reports of Ross (69), Fara et al. (24) and Dorigotti and Glasser (18), who found that intravenous infusions or bolus injection of CCK produced an increase in

jejunal and superior mesenteric artery flow but had no effect on femoral flow. On the other hand, Fara et al. (24) found that intravenous infusion of CCK caused small and insignificant blood flow changes in the kidney in chloralose-anesthetized cats. The most likely explanation of this discrepancy appears to be in the differences in anesthesia, species, modes and dosages of administration, and preparation of the studies. The literature contains no reference to the effect of CCK on splenic and coronary blood flow.

Several mechanisms have been proposed to explain the vasodilator action of CCK. In this present study, the vasodilator effect of CCK occurs within a few seconds after infusion of effective dose of CCK. This appears to indicate that the vasodilator effect of CCK is mediated by a local mechanism. Fara (21) has found that CCK relaxes the rat portal vein in vitro and the action is not mediated by α and β adrenergic or cholinergic receptors. In his earlier study (24), CCK however did not relax the cat mesenteric artery segment which was exposed to the Krebs-bicarbonate solution containing norepinephrine. The segment was able to respond to isoproterenol with a relaxation. Fara attributed the difference in CCK action in these two studies to differences in species used, tissues tested, i.e., veins versus arteries, the level of tension at which CCK was tested and the length of time the tissue was exposed to CCK (21).

Biber et al. have found that CCK caused vasodilation in the intestinal segment in which nerve conductivity had been blocked by administration of tetradotoxin (5). Thus, the vasodilator action of CCK appears not to be neurogenic in origin.

Fara et al. (24) suggested that the vasodilation could be secondary to a metabolic effect of CCK in intestinal tissue, since there is a linear relationship between the increase in jejunal and pancreatic blood flows and their oxygen consumption. The increased metabolism may be due to stimulatory effect of CCK on secretion and absorption. CCK stimulates secretion by the glands of Brunner in the duodenum (71). In hamsters, CCK inhibits the net transfer of sodium, chloride, and fluid across the everted gut sac (30). In dogs, CCK inhibits absorption of fluid, sodium, potassium and chloride from isolated loops of jejunum and ileum in situ, and increases the absorption of glucose in the jejunal loop (11). The inhibition of net absorption of electrolytes and water might result from an increase in secretion (exsorption) because net absorption is an algebraic sum of bidirectional fluxes of fluid, i.e., insorption and exsorption. Thus the intestinal vasodilating effect of CCK, like gastrin, may possibly be coupled to the intestinal secretion or absorption.

The vasodilator action of CCK may be mediated by local vasodilator substances which are not products of metabolism. Hilton and Jones (45) have shown that kallikrein, a potent vasodilator, is released from the pancreas after administration of CCK and suggested that local vasodilator substances mediate the increase in blood flow. This hypothesis is further substantiated by Frogge et al. (26), who found in dogs that administration of CCK to the pancreatic artery increases blood flow to the pancreas and decreases the vascular resistance of an isolated limb which was perfused by the pancreatic venous effluent. The decrease in vascular resistance of the assay limb occurs simultaneously with the beginning of pancreatic secretion. Furthermore, the maximal decrease in limb resistance occurs at the time of peak blood flow in the intact pancreas. Biber et al. (5) have demonstrated in cats that CCK does not produce vasodilation in in situ jejunal segments after administration of a serotonin blocking agent, dihydroergotamine. They, therefore, suggested that CCK-induced intestinal vasodilation seems to act through a vascular smooth muscle control mechanism which is dependent upon an intact serotonin receptor function. Serotonin increases motility and decreases the vascular resistance of the small intestine; the effects are similar to those of CCK. The intestinal vasodilation caused by CCK, therefore, may result from release of local vasoactive substances, such as kinins and serotonin.

Intra-arterial infusion of secretin caused a fall in vascular resistance of all eight organs studied in this present work (Figure 2). Utilizing an indicator fractionation technique (^{86}Rb), Goodhead et al. (33) found that an intravenous injection of secretin produced a significant increase in blood flow in the duodenum and pancreas. Blood flow to the remainder of the gastrointestinal tract, i.e., stomach, jejunum, ileum, colon, and gallbladder is only marginally increased. With a single injection of secretin, Gerber et al. (31) found that blood flow in the pancreaticoduodenal and superior mesenteric arteries increased, but hepatic or gastric blood flow was not significantly changed. Fara et al. (24) found that intravenous infusion of secretin increased blood flow in the superior mesenteric, pancreatic and jejunal arteries, and produced no significant increase in flow to the gastric, large intestinal, femoral and renal circulation. Ross (69), however, has shown that intra-arterial injection of secretin increases flow through both the superior mesenteric and femoral artery. Dorigotti and Glasser (18) and Chou et al. (14) found that secretin did not alter vascular resistance of the forelimb and superior mesenteric vascular beds. The results obtained from various investigators, therefore, are not the same.

The vasodilator action of secretin appears to be mediated by a local mechanism since it occurred within a few

seconds after intra-arterial infusion in this present study. Ross (69) has reported similar observations in the superior mesenteric and femoral vascular beds after local denervation or ganglionic blockade. That secretin-induced intestinal vasodilation is not mediated via nervous pathways has also been shown by Biber et al. (5). They used tetrodotoxin to block nerve conductivity in the cat jejunal segment in situ and did not block the vasodilator action of secretin. Fara et al. (24) also have reported that the action of intestinal vasodilation induced by secretin, like CCK, was not mediated through the β-adrenergic receptor in the intestinal vessels.

Fara et al. (24) have suggested that the vasodilator action of secretin is secondary to its metabolic effect since there is a linear relationship between the increased flow and oxygen consumption. Secretin stimulates bicarbonate secretion from the Brunner's gland (71), liver and pancreas. It inhibits sodium transport in the jejunal and ileal everted sacs of hamsters (30) but has no effect on intestinal transport in dogs (12). Intestinal motility is not affected or decreased by secretin. Thus, there is little correlation between the vasodilator effect of secretin and its effect in increasing the activity of intestinal parenchymal cells. Furthermore, secretin is a strong stimulator of bile secretion from the liver but intra-arterial injection of secretin increased hepatic arterial

vascular resistance (69). The hepatic vasoconstriction, occurs more than 20 seconds after injection and is not neurally mediated, nor is it due to catecholamine release from the adrenal medulla. Ross (69) has suggested that secretin may initiate changes in the liver parenchyma, which indirectly lead to hepatic vascular constriction. This present study shows that secretin equally dilates the vasculature of all organs studied. Since the action of secretin is mainly on digestive secretion, the finding appears to indicate that vasodilator action of secretin is a direct one on the vascular smooth muscle. Secretin has been shown to relax rat portal vein in vitro (21).

In addition to their effects on vascular resistance, CCK and gastrin increase and secretin appears to decrease duodenal and jejunal motility. The results are in agreement with current consensus (39). The contractile force of the left ventricle of the heart is decreased by CCK infused into the coronary artery at high infusion rates which increase local blood CCK concentration by more than 32.8 mU/ml. Gastrin had no effect and secretin had irregular effects on the contractile force.

The cardiac effects of CCK and gastrin have not been studied but secretin has been shown to increase heart rate, stroke volume and cardiac output following a rapid intravenous injection of 10 units or 5 U/kg of secretin (33,69).

This present study shows that systemic arterial pressure is decreased following infusion of CCK or secretin into the coronary and renal artery at high infusion rates. In most studies reported by other investigators, local or systemic administration of secretin or CCK, in doses which increase pancreatic, small intestinal and superior mesenteric arterial blood flow, did not modify arterial blood pressure and heart rate (18,24,26,45,69). Ross (69) has shown that an intravenous or intra-arterial injection (to superior mesenteric or femoral artery) of secretin produces a biphasic effect on systemic arterial pressure, an initial fall for less than one minute, followed by a rise for three to seven minutes. The doses given are pharmacologic in his study. The mechanism by which a large dose of CCK or secretin alters systemic arterial pressure, heart rate or cardiac output has not been studied. It is possible that these hormones may have inotropic and chronotropic effects on the heart at high doses in addition to their vasodilator effect. This present study shows that high doses of CCK decreases the contractile force of the left ventricle which may contribute in decreasing arterial pressure. The decreased resistance in the small intestine may also contribute to the decrease in arterial pressure. The systemic arterial depressor responses caused by high doses of CCK was seen also when it was infused into the renal artery in this present study. Thus CCK, in addition to its vasodilator effect on renal vessels, may have

an action in the kidney to lower systemic arterial pressure. The mechanism probably is mediated by a nerve reflex.

As described in Chapter II (Survey of Literature), a variety of methods have been used in the studies of vascular actions of gastrin, secretin and CCK. It is, therefore, difficult to make quantitative comparisons of vascular actions of the three hormones on any given organ, or to compare the responses of different organs to the same hormone. By utilizing the same method, i.e., constant flow technique, this study compared quantitatively the effects of raising local arterial concentration of CCK, secretin and pentagastrin on the vascular resistance of the duodenum, jejunum, heart, kidney, forelimb, spleen and the skin and muscle of the forelimb. The study specifically asked 1) do the three hormones produce similar effects in a given organ, 2) are the responses of the organs to a given hormone similar, and 3) what is the minimal increment in local hormone concentration (concentration requirement) which decreases resistance? Whether the action of these hormones in an organ is physiologic or pharmacologic might then be deduced by comparing the concentration requirements with postprandial increments in serum concentrations of these hormones determined by others. Vascular resistance is determined by blood viscosity and geometry of the vessel. Control infusions of solvents established that changes in resistance

produced by the hormones are not due to alterations in viscosity. Therefore, the observed fall in resistance indicates vasodilation.

Quantitatively the vascular effects of CCK, secretin and gastrin on any organ are not the same. In the duodenum, a 28% decrease in duodenal resistance was associated with a rise of 10 mU (0.86 picomoles*)/ml in CCK concentration in duodenal blood; whereas, a similar decrease in resistance with secretin required 35.7 mU (4.39 picomoles)/ml., and with pentagastrin 1 μg (1.53×10^3 picomoles)/ml. Thus in the duodenum the vasodilating action of CCK is about 3.6 times more potent than that of secretin on a unit basis. On a molar basis, CCK is about five times more potent than secretin and 1780 times more potent than pentagastrin in dilating the vasculature. Secretin is about 350 times more potent than pentagastrin on molar basis.

In the jejunum, a 20% fall in vascular resistance was associated with a rise of 5.2 mU (0.45 picomoles)/ml in local blood CCK concentration. To produce a similar decrease in resistance with secretin required 35.5 mU (2.91 picomoles)/ml; and with pentagastrin, 100 ng (0.16×10^3 picomole)/ml. On a unit basis, the jejunal vasodilator

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*Picomoles of these hormones were calculated from the molecular weights of CCK (3883), secretin (3565), and pentagastrin (653) and IDU/mg of pure CCK (3000 IDU/mg) and secretin (4000 IDU/mg).

action of CCK is about seven times more potent than that of secretin. On a molar basis, CCK is about six times more potent than secretin and 355 times more potent than pentagastrin in dilating the vasculature. Secretin is about 55 times more potent than pentagastrin on molar basis.

In the spleen, infusion of CCK at a rate which produced an 11% decrease in resistance was associated with a rise of 6.3 mU (0.54 picomoles)/ml in local blood concentration of CCK. Secretin produced a similar decrease in resistance when its local blood concentration was increased by 15.8 mU (1.3 picomoles)/ml. Thus, on a unit or a molar basis, CCK is about twice as potent as secretin in producing splenic vasodilation.

In the heart, secretin produced a 13% decrease in coronary resistance when local secretin concentrations was raised by 32.3 mU (2.64 picomoles)/ml. A similar decrease in resistance with CCK required 65.7 mU (5.65 picomoles)/ml. Thus the vasodilator action of secretin is about two times that of CCK on a unit or molar basis.

In the kidney, a 9% decrease in renal vascular resistance occurred when local blood secretin concentration was increased by 8.6 mU (0.71 picomoles)/ml. A similar decrease in resistance with CCK required an increment of 86.5 mU (7.44 picomoles)/ml. Thus in the kidney, secretin is about 10 times more potent than CCK in producing vasodilation on a unit or molar basis.

Thus, in the duodenum and jejunum, all three hormones produce vasodilation but the potency of CCK is about 5-6 and 350-1700 times more potent than secretin and pentagastrin, respectively, on molar basis. In the heart, kidney, and spleen, only secretin and CCK produce vasodilation. CCK is twice as potent as secretin in the spleen but only 1/2 and 1/10 as potent as secretin in the heart and kidney, respectively. In the forelimb, skin and muscle, only secretin produces vasodilation.

Of the three hormones, only secretin significantly decreases the vascular resistance of all the eight organs studied. The slopes of concentration-response curves of secretin in the eight organs appear to be similar (Figure 2) and the concentration requirements for vasodilation in the eight organs are between 7 and 32 mU/ml (Table 8). Secretin, therefore, appears to uniformly decrease the vascular resistance of the small intestine and non-digestive organs over the same concentration range. In contrast, CCK causes a large decrease in vascular resistance of the duodenum and jejunum and slight decrease in resistance of the heart, kidney and spleen and has no effect on the resistance of the forelimb or its skin and muscle (Figure 3, Tables 4 and 5). The concentration requirements for CCK, in mU/ml, are duodenum 2.5; jejunum 2.6; heart 32.8; kidney 22.2; and spleen 20.8 (Table 8). The dilating effect of CCK, therefore, is most potent in the small intestine, about 8 to 13

times that in the heart, kidney, or spleen. Of the three hormones, pentagastrin is the weakest vasodilator. It has no effect on the vascular resistance of the heart, kidney, spleen, and forelimb even when the local pentagastrin concentration is increased by 850-1500 ng/ml (1.11-1.95 nanomoles/ml). Furthermore, significant decrease in duodenal and jejunal vascular resistance occurs only when local blood pentagastrin concentration is increased by 25-50 ng/ml. These findings indicate that while secretin uniformly dilates the vasculature of all organs studied, CCK and pentagastrin do not.

Some of the cardiovascular changes that occur during digestion are vasodilation in the small intestine with no change in the coronary and renal blood flow and no change or slight decrease in blood flow to the limbs (10,27,28,75, 76,77). The increased flow in the intestine has been shown to be mainly due to an increased flow through the mucosa (15). If CCK, secretin and/or pentagastrin are involved in the postprandial hemodynamic change, these hormones must be able to dilate the intestinal vasculatures, particularly the mucosal vasculatures, while exerting no vascular effect on the heart, kidney and limbs within the concentration ranges attained after a meal. As discussed above, secretin uniformly decreases the vascular resistance of the small intestine and non-digestive organs over the same concentration

range. Furthermore, secretin has been shown to redistribute the blood flow away from the mucosa (23), an effect opposite to the response seen during digestion (15). Therefore, secretin does not appear to play a role in postprandial intestinal hyperemia. In contrast, pentagastrin and CCK have prominent vasodilator effect on the duodenum and jejunum but not on non-digestive organs (Figures 3 and 4). Since vasodilation occurs only in the small intestine during digestion, these two hormones may play a role in the post-prandial hemodynamic adjustment.

Recent development of sensitive and specific radio-immunoassay methods have made it possible to determine gastrointestinal hormone concentrations in blood. Table 9 summarizes the concentration of these three hormones in the blood before and following a meal, placement of food into the gastric pouch or intraduodenal instillation of HCl, amino acids, fatty acids or sugar as measured with radio-immunoassay methods. As shown in Table 9, following a meal, gastrin concentration in the peripheral venous blood was increased by 35 to 173 pg/ml (equivalent to 0.017-0.082 picomoles/ml, based on G-17 with a molecular weight of 2100). The minimal increment in local blood pentagastrin concentration to produce vasodilation in the duodenum and jejunum, was 50 and 25 ng/ml (equivalent to 76.6 and 38.5 picomoles/ml) respectively (Table 8), which was 470 to 4500

Table 9. Effects of feeding on serum concentration of gastrin, secretin and CCK.

	Species	Fasting	Feeding*	Change	Type of experiment and food	Reference
Gastrin pg/ml	Man	35	70-175	35-140	Lunch: protein 60g, fat 40g, CHO 160g.	58
	Man	30	66	36	Standard breakfast	4
	Man	105	180-220	75-115	Grilled steak	29
	Monkey	86	259	173	Banana, cookies	60
	Dog	58	200	142	Pavlov pouch. Liver 250g, water 400 ml.	63
	Dog	43	274	231	Heidenhein pouch. Liver 250g, water 250g.	70
Secretin mU/ml	Man	0.02	0.38	0.36	HCl infused intraduodenally	13
	Dog	0.25	0.61	0.36	HCl infused intraduodenally	7
	Dog	0.22	0.57	0.35	HCl infused intraduodenally	8
	Dog	0.11	0.21	0.10[a]	Amino acids infused intraduodenally	7
	Dog	0.32	0.18	-0.14[a]	Fatty acids infused intraduodenally	7
	Dog	0.24	0.28	0.04[a]	Fructose infused intraduodenally	7
CCK mU/ml	Man	2.4	4.6	2.2	Fatty meal	66
	Man	0.2	11.0	10.8	Fatty meal	57
	Dog	9.3	17.5	8.2	Placement of amino acids in duodenum	66

*Values are mean peak concentration after feeding.

[a]The change is not statistically significant.

times greater than postprandial increment in gastrin concentration. Although gastrin concentration at the sites of release is expected to be higher than that in the peripheral blood, it seems unreasonable to expect the local tissue concentration being 470-4500 times greater than blood concentration. Furthermore, high concentration of gastrin is in the gastric antrum and not in the small intestinal mucosa. Therefore, it is likely that the amount of gastrin released following a meal is insufficient to produce a vasodilation in the small intestine. The vasodilator action of pentagastrin observed in this study appears to be pharmacologic and therefore gastrin does not seem to contribute in postprandial intestinal hyperemia.

Peripheral venous secretin concentration is not significantly increased following a meal (55) and following intraduodenal instillation of nutrients in dogs (7,8). Even during intraduodenal instillation of acid, the strongest stimulator of secretin release, the increments in secretin concentration are 0.87-0.99 mU/ml in the portal venous blood (7,8) and 0.35-0.36 mU/ml in the peripheral blood (Table 9). As shown in Table 8, the minimal increment in local blood secretin concentration to produce vasodilation in the small intestine was 7.1-10.7 mU/ml, which was about 10 and 20-30 times greater than the increased secretin concentration in the portal and peripheral

blood during intraduodenal instillation of acid. The comparison, therefore, appears to suggest that the vasodilator effect of secretin may be pharmacologic and secretin may not contribute in postprandial intestinal hyperemia. Other findings which support this thesis are as follows. Secretin uniformly decreases the vascular resistance of the small intestine as well as non-digestive organs over the same concentration range (Figure 2). Secretin decreases mucosal blood flow of the small intestine (23) and its concentration is not significantly increased following a meal (7,8,55). Although the local tissue concentration of secretin during duodenal acidification may be high enough to produce local vasodilation, physiologically the only area in the intestinal tract in which lumen pH is low enough for secretin release is confined to the first few centimeters of the duodenum.

The range of mean fasting blood concentration of CCK is between 0.2 and 9.3 mU/ml, and following a meal the concentration increases by 2.2-10.8 mU/ml (Table 9). In this present study, CCK significantly decreased the vascular resistance of the duodenum and jejunum when local arterial blood concentration of CCK was raised by 2.5-2.6 mU/ml (Table 8) and the marked decrease in duodenal and jejunal vascular resistance occurred when local CCK concentration was raised by about 10 mU/ml (Figure 3). Furthermore, the

vascular resistance of the heart and kidney was not affected until the concentration was raised by 20 mU/ml and that of the forelimb was not affected at all at any dosage (Table 8). These findings, therefore, suggest that over the concentration range achieved following meals, i.e., 2.2-10.8 mU/ml, as reported by others, CCK markedly dilates the duodenal and jejunal vasculature but does not affect the vasculature of the non-digestive organs. The effect is similar to the responses seen following a meal (76,77).

Other findings also support the possibility that CCK may be a determinant of intestinal blood flow following a meal. CCK has been shown to increase musocal blood flow in the jejunum, an effect similar to the response seen during digestion (15,22). Furthermore, the venous blood from a duodenum containing a fat and protein meal decreases the vascular resistance of a bioassay jejunum and also increases its motility (47). In the present study CCK was found to simultaneously increase jejunal motility and decrease its vascular resistance.

Fara et al. (24) have previously proposed that CCK and secretin may play a role in the hyperemia occurring in the small intestine following a meal. As discussed above, there is good evidence to support the contention that CCK contributes to the postprandial intestinal hyperemia. Fara et al., in a recent study (22), also reached the same

conclusion. They found that CCK and intraduodenal instillation of fat, both redistribute jejunal blood flow in favor of the mucosal layer while secretin redistribute the flow away from the mucosa (22,23).

CHAPTER VI

SUMMARY AND CONCLUSION

The vascular effect of raising local arterial concentration of secretin (0.2-150 mU/ml), CCK (0.2-150 mU/ml) and pentagastrin (2-1500 ng/ml) in the constantly perfused heart, kidney, spleen, duodenum, jejunum, forelimb and naturally perfused forelimb were studied in anesthetized dogs. Perfusion pressure was measured in all organs studied at constant blood flow. Other measurements in particular organs were: the contractile force of the heart, intestinal motility, and splenic weight. The results are summarized as follows:

1. Systemic arterial pressure was not significantly altered during local intra-arterial infusion of any of the three hormones to any vascular beds, except to the heart and kidney; raising coronary blood concentration of CCK above 65 mU/ml, or secretin above 128 mU/ml; or raising renal blood concentration of CCK above 87 mU/ml caused a significant fall in systemic arterial pressure.

2. Local infusion of secretin produced vasodilation in all eight organs, with similar dose-response curves. The minimum increments in local blood secretin concentration

required for vasodilation (concentration requirement) in these organs were between 7.1 and 32.3 mU/ml.

3. CCK produced vasodilation in all organs studied except the forelimb, skin and muscle. The concentration requirements of CCK, in mU/ml, were duodenum 2.5; jejunum, 2.6; heart, 32.8; kidney, 22.2; and spleen, 20.8. The vasodilating effect of CCK in the duodenum and jejunum was about eight to 13 times more potent than that in the heart, kidney and spleen.

4. Pentagastrin produced vasodilation only in the duodenum and jejunum, and the concentration requirements were 50 and 25 ng/ml respectively.

5. The dose-response curves of CCK and pentagastrin in the duodenum and jejunum were L-shaped, with a steep slope over the low concentration range.

6. In the duodenum and jejunum, the vascular dilating potency of CCK was about five to six times that of secretin on a unit basis. On a molar basis, the vasodilating potency of CCK was about five times and 350-1700 times that of secretin and pentagastrin respectively. Secretin, on a molar basis, was about 55-350 times more potent than pentagastrin.

7. On a unit or molar basis, the vasodilating effect of CCK was twice as potent as secretin in the spleen but only 1/2 and 1/10 as potent as secretin in the heart and kidney respectively.

8. The left ventricular contractile force and splenic weight were not significantly altered by secretin, CCK or pentagastrin. However, CCK at high infusion rates decreased the contractile force in 5 of the 9 experiments. Intestinal motility was regularly increased by CCK and pentagastrin. Secretin, however, did not consistently alter motility.

9. The concentration requirements for vasodilation by secretin and pentagastrin are much greater than postprandial serum concentrations as measured by others with radioimmunoassay. However, the concentration requirement for CCK in the duodenum and jejunum is within the range of measured concentration of postprandial serum. Furthermore, within this range, CCK produced the greatest decrease in resistance in the duodenum and jejunum but had no effect on the vascular resistance of non-digestive organs.

Comparison of these results with the reported cardiovascular adjustments and blood concentration of gastrointestinal hormones following a meal indicates that only cholecystokinin may contribute to postprandial intestinal hyperemia.

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