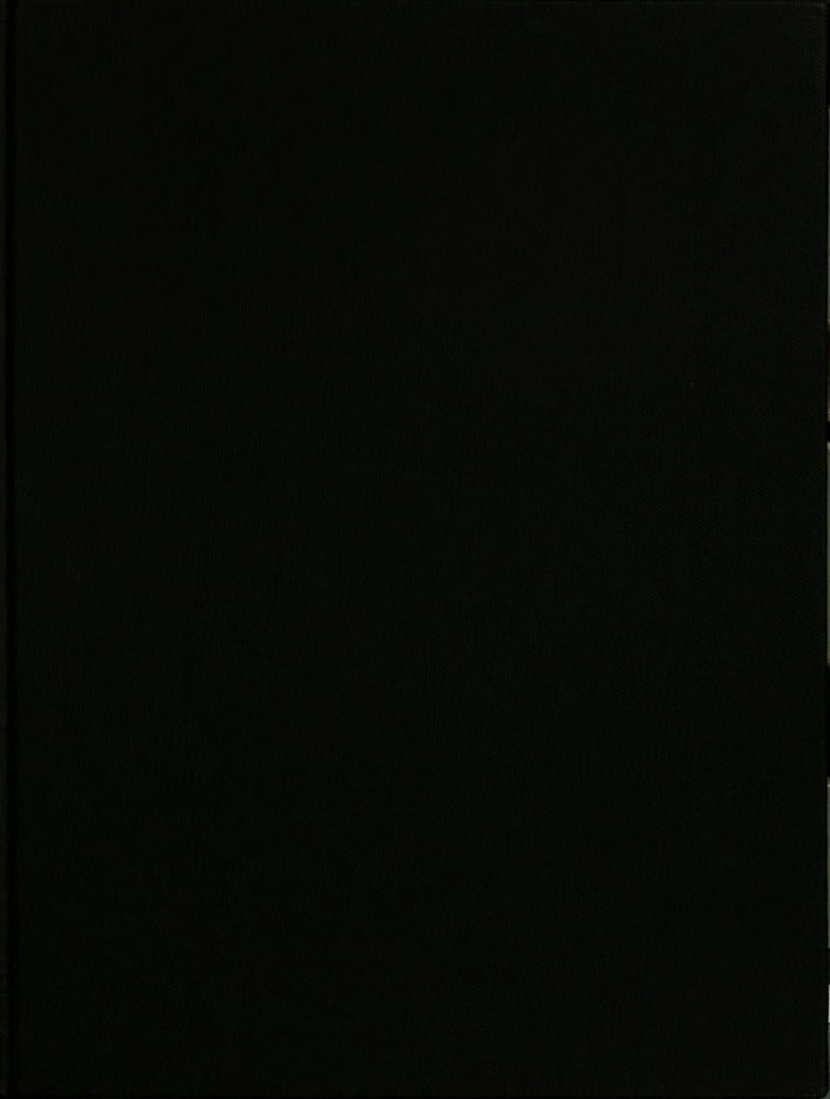




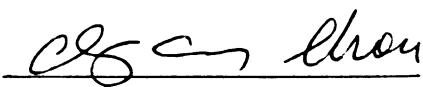
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CYCLOOXYGENASE INHIBITORS AND
THE POSTPRANDIAL INTESTINAL HYPEREMIA

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ROBERT HENRY GALLAVAN, JR.

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CYCLOOXYGENASE INHIBITORS
AND THE POSTPRANDIAL
INTESTINAL HYPEREMIA

By

ROBERT HENRY GALLAVAN, JR.

A DISSERTATION

Submitted to
Michigan State University
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ABSTRACT

CYCLOOXYGENASE INHIBITORS AND THE POSTPRANDIAL INTESTINAL HYPEREMIA

By

ROBERT HENRY GALLAVAN, JR.

Intestinal blood flow increases following a meal in those portions of the intestine exposed to chyme. Neural, metabolic and hormonal factors have been proposed as mediators of this response but there is no conclusive evidence to indicate one as the sole or primary regulator. Prostaglandins are synthesized throughout the gastrointestinal tract and appear to play a role in regulating resting intestinal blood flow and motility. The purpose of this study was to determine if prostaglandins also play a role in the regulation of the postprandial intestinal hyperemia in the dog. Therefore, The effects of intraluminal placement of food on jejunal metabolism and blood flow were studied before and after infusion of either the cyclooxygenase inhibitors indomethacin and mefenamic acid or their carrier solutions. The jejunal response to food was also tested before and during angiotensin II infusion as a control for the effects of decreased resting blood flow.

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When food was placed in the lumen of the small intestine, there was a significant increase in both blood flow and oxygen consumption. In addition, there was an increase in aerobic glucose metabolism with an accompanying increase in lactic acid production. Following either intravenous or intraarterial infusion of the cyclooxygenase inhibitors, there was a significant decrease in resting blood flow and an enhancement of the food-induced intestinal hyperemia. Furthermore, the intravenous infusion of mefenamic acid resulted in an enhancement of the food-induced increase in oxygen consumption, glucose absorption and lactic acid production as well. All three factors may have contributed to the enhancement of the food-induced hyperemia.

Both intravenous and intraarterial infusion of the cyclooxygenase inhibitors significantly increased the mean peak pressure of intestinal contractions but did not alter their frequency or mean basal lumen pressure. The presence of food in the lumen did not further alter intestinal motility so that enhanced intestinal motor activity is not a likely explanation for the increase in the food-induced increase in oxygen consumption after cyclooxygenase inhibition. However, the increase in motility may have improved mixing of chyme in the lumen, and enhanced nutrient absorption thereby indirectly increasing oxygen consumption.

Control studies using either the intraarterial infusion of angiotensin II or the intravenous or intraarterial infusion of the drug carrier solutions indicate that the enhancement of the food-induced intestinal hyperemia was not due to the decrease in resting blood flow associated with cyclooxygenase inhibitor infusion, the carrier

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solutions themselves or the effects of time. Although the cyclooxygenase inhibitors were infused at a rate which has been shown to inhibit prostaglandin synthesis in other organs, there is no direct evidence that prostaglandin synthesis was inhibited in this study; nor is it certain that the effects of these drugs on the intestinal response to food were mediated by this route of action alone.

This study confirms the observations of other authors that the cyclooxygenase inhibitors reduce resting blood flow and stimulate motility in the small intestine. In addition, they enhance the jejunal vascular response to food, possibly by metabolic mechanisms. It is suggested that prostaglandins may serve to limit the postprandial intestinal hyperemia as part of a negative feedback loop.

To my wife, Ellen, and our children,
Robbie, Theresa, Stephanie and any
others that pop up along the way.

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INTRODUCTION

Following a meal, there is a significant increase in blood flow to the small intestine (28, 37, 76, 78, 137, 178, 179, 180). This increase in blood flow appears to occur only in those areas of the intestine that are exposed to chyme (42, 43, 45, 78, 109, 113). Although there is some question as to whether or not there is a redistribution of blood flow within the intestinal wall of those areas, it is clear that the major portion of the increase in blood flow is directed through the mucosal layer. The stimulus for this response has been shown to be the end products of food digestion, however, their mechanism of action is unclear (45, 113).

One possible mechanism which has been suggested by recent studies is that the presence of food induces the release of intestinal hormones. Investigators have proposed a role for both cholecystokinin (44, 61, 62) and histamine (162). There is, however, another large class of compounds which have been shown to have pronounced vascular and metabolic effects in the small intestine - the prostaglandins. Various prostaglandins have been shown to inhibit blood flow and secretory activity in the stomach (11, 41, 103, 149, 165, 167) and pancreas (107), and it appears that prostaglandins play a role in regulating resting intestinal blood flow (25, 77, 103, 138, 153) and motility (153).

The purpose of this study was to examine the effects of prostaglandin synthesis inhibition on the food-induced jejunal hyperemia.

In addition, the contribution of metabolic factors to the intestinal hyperemia both before and after prostaglandin synthesis inhibition was determined.

LITERATURE REVIEW

Postprandial Intestinal Hyperemia

Evidence in support of the hypothesis that blood flow to the gastrointestinal tract increases following a meal was first provided by Brodie et al (33) in 1910. The authors used a modification of the plethysmographic method to demonstrate that placement of a nutrient solution in the lumen of the canine intestine results in an increase in blood flow to that organ. Subsequent studies have examined the nature of the cardiovascular response to feeding in dogs (28, 36, 37, 76, 97, 178, 179), subhuman primates (180), and man (31, 39, 121, 137). The most recent evidence indicates that there is a brief, generalized cardiovascular response prior to and during ingestion (36, 76, 178, 179, 180) and that, subsequently, blood flow returns to control levels in all organs except the stomach, liver, pancreas, and small intestine (28, 31, 36, 39, 76, 78, 97, 121, 137, 178, 179, 180).

Within the gastrointestinal tract, the postprandial hyperemia appears to be limited to that portion which is exposed to chyme. Chou et al (43) found that placement of a food solution in the stomach of an anesthetized dog resulted in a rapid increase in celiac artery blood flow which lasted less than one hour. Blood flow through the superior mesenteric artery increased approximately 30 minutes after the placement of food in the stomach, and remained elevated for over three hours. On the other hand, when predigested food was infused directly into the

duodenum, celiac artery blood flow did not change, while superior mesenteric artery blood flow increased rapidly and remained elevated for several hours.

The authors concluded that the increase in blood flow through the celiac artery, which perfuses the stomach, liver, pancreas, spleen, and proximal duodenum, was due to an increase in gastric blood flow as it did not occur when food was infused directly into the duodenum. They also concluded that the delay in onset of the superior mesenteric artery hyperemia following gastric placement of food represented the time necessary to move a sufficient amount of food into the small intestine during the course of gastric emptying. Within the small intestine, they found that superior mesenteric artery blood flow increased when food was perfused into the duodenum, as before, but that the venous outflow of an isolated loop of the jejunum that contained only saline did not change. Conversely, placement of food in the lumen of the jejunal loop increased venous outflow but did not alter superior mesenteric artery blood flow.

These findings are supported by a number of studies in which the venous outflows of two isolated jejunal loops were measured during intraluminal perfusion or placement of a variety of solutions (42, 45, 109, 113). In all cases, the presence of nutrient solutions in the lumen of one segment increased flow to that segment with no effect on blood flow to the adjacent segment. In conscious dogs, the postprandial hyperemia has been shown to be limited to the duodenum and proximal jejunum 30 minutes following ingestion of a meal (78), and to extend to the entire small intestine at 45 minutes (28) and 90 minutes (78) after feeding. These changes in blood flow correlate well with the movement

of chyme along the small intestine (121).

Studies performed in the laboratory of Dr. C. C. Chou, utilizing the radioactive microsphere technique for the measurement of blood flow, indicate that in dogs the postprandial intestinal hyperemia is confined to the mucosal-submucosal layer with no significant change in flow to the muscularis (43, 78, 197). However, a similar study by Bond et al (28) as well as studies of intestinal vascular diameter in rats by Bohlen (26, 27) indicate a uniform increase in blood flow to all three layers of the small intestine when food is in the lumen. In either case, the mucosal-submucosal layer receives approximately eighty percent of total intestinal wall blood flow so that the contribution of the muscularis layer to the postprandial intestinal hyperemia is minor.

Although the hemodynamics of the gastrointestinal response to food are well documented, the regulatory mechanisms appear to be complex and are poorly defined. Chou et al (45) have shown that food homogenates must be treated with pancreatic enzymes to induce an intestinal hyperemia. Furthermore, of the major products of food digestion, only glucose and micellar solutions of fatty acids are capable of increasing intestinal blood flow. A variety of amino acid solutions were tested, but none were found to be vasoactive.

Kvietys et al (113) demonstrated that the addition of gallbladder bile to the various nutrient solutions significantly enhanced the hyperemic effect of glucose and produced a pronounced hyperemia when mixed with a number of fatty acids. Bile itself was not found to be vasoactive at the concentrations used in these studies (10%).

The action of bile on the intestinal vascular response to fatty acid

solutions appears to be due to its detergent properties. That is, the vasoactivity of an aqueous fatty acid solution can be enhanced just as well by increasing the pH of the solution to 9.4 (112). At this pH, fatty acids are readily dissolved in an aqueous solution. However, the mechanism by which bile enhances the hyperemic effect of glucose is unclear as it neither increases glucose absorption nor enhances the glucose-induced increase in oxygen consumption.

As in other vascular beds, metabolic, myogenic, hormonal, and neural mechanisms have been proposed to account for local regulation of blood flow. Of these, the myogenic hypothesis is least likely to account for the postprandial intestinal hyperemia. It has been shown that an increase in intestinal venous pressure results in an increase in pre-capillary resistance. This phenomenon is called the venous-arteriolar response and is considered to be a myogenic response. Yet, Granger and Norris (82) have shown that during a food-induced intestinal hyperemia the sensitivity of the intestinal vasculature to elevated venous pressure decreases. This would imply that non-myogenic factors are operating to maintain the hyperemia.

According to the metabolic theory of local regulation of blood flow, an increase in cellular metabolism would result in an increase in cellular and, subsequently, interstitial fluid levels of certain vasoactive metabolic by-products. As their concentration in the interstitial fluid rose, these metabolites would induce a decrease in vascular tone. This in turn would increase blood flow to the metabolically active region until a new steady state was achieved. As cell metabolism decreased so would the concentration of vasodilator

metabolites resulting in an increase in vascular tone and a decrease in local blood flow (89).

The most common measure of metabolic activity under normal conditions is oxygen consumption. Intestinal oxygen consumption has been shown to increase when a variety of absorbable solutes are placed in the lumen. Valteau et al (175) and Brodie et al (32) have shown that the absorption of a salt solution from the lumen of intestinal loops is associated with an increase in blood flow and oxygen consumption. Similar results with isotonic glucose have been reported by Sit et al (163), Varro et al (177), Valteau et al (175), Pawlik et al (144), and Nyhof (140). Intestinal blood flow and oxygen consumption also increase when the intraluminal stimulus is oleic acid (46, 140), a peptone solution (33), or digested food and bile (46, 140, 162, 164).

In two studies, the authors reported a significant correlation between the change in blood flow and oxygen consumption (163, 164). However, most of the data reported represent steady state responses and, at least in the case of intraluminal glucose, Fondacaro and Jacobson (72) have reported that early in the hyperemic response, there is a substantial temporal dissociation (1-10 minutes) between the increase in intestinal blood flow and the subsequent increase in oxygen consumption. Furthermore, although Bohlen (26) demonstrated that superfusion of the rat intestinal mucosa with glucose produced a decrease in villus pO_2 and an increase in mucosal blood flow; the same study showed an increase in muscularis blood flow despite an increase in muscularis pO_2 .

It may be that other factors initiate the food-induced intestinal hyperemia, with the metabolic effect dominating in the later stages. It is also possible that both the vascular and metabolic responses are secondary to hormonal release and that any correlation between the two may not be causative. At present, no specific vasodilator metabolite has been proposed as a mediator of the postprandial intestinal hyperemia.

The role of extrinsic and intrinsic nerves in the food-induced intestinal hyperemia has been examined in both intact and isolated intestinal preparations with results which appear to depend on the nature of the preparation. Fara et al (61) reported that disruption of vagal activity reduced or abolished the mesenteric vascular response to the placement of fat or L-phenylalanine in the duodenum of anesthetized cats. Vatner et al (179) however, reported that chronic vagotomy had no effect on the postprandial intestinal hyperemia in conscious dogs. Tibbleu et al (174) reported only a transient effect of acute vagotomy and no effect of chronic vagotomy on the cardiovascular response to feeding in dogs. Both Fara et al (61) and Vatner et al (179) reported that neither α - nor β -adrenergic blockade altered the nutrient-induced mesenteric hyperemia. Finally, Nyhof (140) has reported that denervation of the isolated intestinal loop did not significantly alter the intestinal vascular response to food.

Atropine has been reported to block the hyperemic effect of nutrients on the intact gastrointestinal tract of anesthetized cats (61, 62) and conscious dogs (179). However, a number of studies in isolated intestinal segments contradict this finding. Kviety et al (111) have shown that atropine enhances the initial hyperemic effect of

oleic acid in the intestine, although it does not significantly alter the steady state response. Bohlen (26, 27) used atropine to minimize motility in the rat intestine and still reported significant increases in intestinal blood flow in response to mucosal superfusion with isotonic glucose. Nyhof (140) found that atropine actually enhanced the hyperemic effect of food in isolated intestinal loops while hexamethonium, tetrodotoxin, and methysergide had no effect on either the vascular or metabolic response.

The reasons for the discrepancies in the atropine data are not clear, although it may be related to an atropine-induced decrease in intestinal motility. This may decrease the mixing of chyme and increase transit time in the intact intestine. This may, in turn, decrease the intensity of the stimulus as well as the amount of intestine exposed to the chyme at a particular time relative to control experiments. These factors would be less critical in isolated segments.

Although the gastrointestinal tract contains a wide variety of hormones, many of which are potent vasoactive agents, there have been few studies on the effects of intraluminal food placement on intestinal hormone release. This is in part due to a lack of specific assays for many of the hormones. Fara et al (61, 62) reported that intraduodenal placement of fat in anesthetized cats resulted in an increase in superior mesenteric blood flow, gall bladder and duodenal motility, and the enzyme content of pancreatic secretions. Furthermore, when blood from the experimental animal was cross-circulated to another animal, mesenteric blood flow increased in the recipient. All these actions were mimicked by intravenous infusion of cholecystokinin (CCK) in the

experimental animal.

Both Bown et al (30) and Fara et al (61, 62) have shown that CCK increases both intestinal blood flow and oxygen consumption, although Biber et al (24) have reported that the vascular effect may be mediated by serotonin. Chou et al (44) studied the effects of intraarterial infusions of CCK in a variety of organs and found that it significantly increased duodenal and jejunal blood flow at physiological concentrations, but was ineffective in other organs. Fara and Madden (63) have also shown that the hyperemia induced by CCK is distributed mainly to the mucosal layer of the intestinal wall. It would appear, then, that CCK may play a role in the regulation of the postprandial intestinal hyperemia. However, recent studies indicate that at least one other endogenous substance may play a role in regulating the hyperemia. Siregar (162) has shown that histamine H-1 receptor blockade significantly reduces both the vascular and metabolic response of the intestine to food.

Thus, of the four major regulatory mechanisms, the current evidence seems to favor either a metabolically or hormonally mediated intestinal vascular response to food. It is also possible that both mechanisms are involved. One class of compounds which have been shown to have a variety of actions in the gastrointestinal tract and which have not been studied in relation to the postprandial intestinal hyperemia are the prostaglandins. Numerous papers on prostaglandins and gastrointestinal function have been published; however, this review will be limited to those studies involving the small intestine.

Prostaglandins

Prostaglandins were first discovered by Goldblatt (80) and von Euler (59) in 1934; and their chemical structures were determined by Bergstrom (21) in 1963. Prostaglandin synthesis occurs to some extent in all three layers of the intestinal wall (16, 116, 148) and throughout the length of the small intestine (4, 23, 29, 68, 106, 114, 116, 117, 153, 181, 182, 189, 196), both at rest (16, 29, 68, 106, 116, 117, 153, 171, 182) and in response to a variety of stimuli (23, 29, 106, 114, 153). The synthetic pathways and chemical structures of the major prostaglandin and thromboxane compounds are shown in Figure 1.

The prostaglandins and thromboxanes are derived from essential fatty acids and their exact chemical structures are determined by the available substrate. The most common prostaglandins are bisenoic (PGE_2 , $\text{PGF}_{2\alpha}$, PGD_2 , PGI_2 , TxA_2 , and TxB_2) and are derived either directly from arachadonic acid or from linoleic acid after elongation of the carbon chain from 18 to 20 carbon units. The monoenoic forms (PGE_1 , etc.) are derived from dihomio- γ -linolenic acid while eicosapentaenoic acid is the substrate for the trienoic prostaglandins (PGE_3 , etc.) (176). With the exception of prostaglandin I_2 (9, 93, 183, 192), the prostaglandin and thromboxane compounds are inactivated in the lungs (15, 67, 192). Prostaglandins released in the gastrointestinal tract may be metabolized by the liver as well (67). Prostaglandin I_2 is apparently inactivated by the liver and kidneys (172, 193).

Of the various prostaglandins, most studies have been devoted to the

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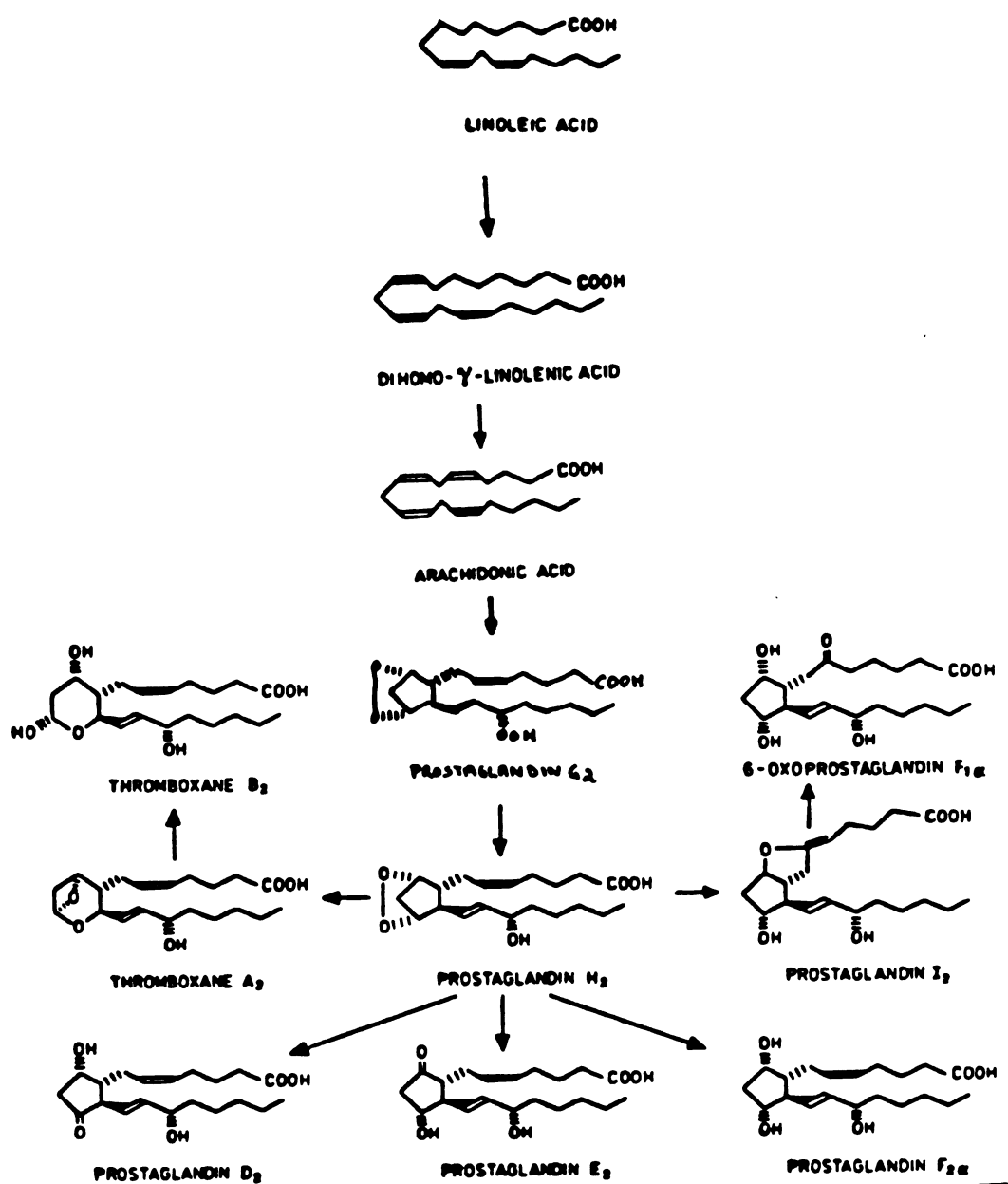


Fig. 1. Biosynthetic pathways of the major prostaglandins

E and F series. This is in part due to the fact that they were the first to be indentified and also to the lack of adequate assays for the remaining prostaglandins. Recent work by Le Duc and Needleman (116) indicates that microsomal preparations of the canine intestinal mucosal and muscularis layers are capable of synthesizing the prostaglandins E_2 , F_{2a} , D_2 and I_2 as well as thromboxane A_2 . Other studies using rat intestinal homogenates (196) and minced jejunal segments (106) have shown that these tissues can synthesize the prostaglandins D_2 , E_2 , and F_{2a} . The current studies of prostaglandin release in vivo indicate that the E and F prostaglandins are released from the intestinal tract at rest (182), and in response to acetylcholine (153) and mechanical stimulation (23). There have been no in vivo studies in which assays were conducted for the remaining prostaglandin compounds, therefore, it is not certain if they are released under physiological conditions.

Much of the work on prostaglandins and the intestinal tract has been concerned with the effects the various prostaglandins have on motility, both directly and as modulators of other agents. In 1959, Bergstrom (20) reported that both the E and F prostaglandins caused the contraction of intestinal segments in vitro. They found that the E series were more potent than the F series in the rat and chicken jejunum and the guinea pig ileum, while the opposite was true in the rabbit jejunum.

A number of authors have reported similar findings in other regions of the small intestine in a variety of species. Anggard and Bergstrom (8) found that prostaglandin F_{2a} contracts rabbit and rat duodenal

segments while Stracykowski reported that prostaglandin A_2 produces an initial spike contraction in the isolated guinea pig ileum followed by an increase in resting tension (170). Prostaglandin D_2 has been shown to contract the rabbit jejunum (100), but it apparently has no effect on the guinea pig ileum (19).

Prostaglandin E_1 has been reported to either contract (99) or relax (104) the isolated rat duodenum and to decrease motility in the canine jejunum (156) and ileum (102). Fountain et al (75) reported that both prostaglandin E_1 and prostaglandin E_2 made contractions of the isolated guinea pig ileum more regular, while Shehadeh et al (156) have shown that prostaglandin F_{2a} stimulates motility, as measured by intraluminal pressure recordings, in the intact canine jejunum.

With the exception of the studies by Shehadeh et al (156), all of the studies listed above were conducted on isolated intestinal segments suspended intact in an organ bath. The tension developed in these preparations is considered to be due primarily to longitudinal muscle activity.

Bennett et al (14, 15) reported that prostaglandin E_1 and prostaglandin E_2 contracted longitudinal muscle strips of the human jejunum and ileum and the guinea pig and rat ileum. These same prostaglandins either relaxed circular smooth muscle strips or inhibited acetylcholine-induced contractions of circular smooth muscle strips from the same intestinal regions. In contrast, Sanger and Watt (154) reported that prostaglandin E_1 stimulated rhythmic contractions of circular smooth muscle from the guinea pig ileum.

Dejani et al (53) reported that prostaglandin F_{2a} stimulates

norepinephrine on ileal motility. The author concluded that the prostaglandins acted postjunctionally. The author's findings are supported by those of Sanger and Watt (154). However, Abdel-Aziz (1) found that although prostaglandin E_1 and prostaglandin F_1 inhibited the effects of nerve stimulation, they had no effect on exogenous norepinephrine.

Bartho (13) also reported that indomethacin inhibited cholinergically initiated ileal contractions in a dose-dependent manner. Additional studies by Bennett et al (17), Sokunbi (166), and Stockley (169) indicate that while prostaglandin synthesis is necessary for normal cholinergic transmission and acetylcholine release in the guinea pig ileum, prostaglandins do not alter the direct effects of acetylcholine on intestinal smooth muscle. In addition, Ferriera et al (68) and Botting et al (29) reported that acetylcholine does not induce prostaglandin release in the guinea pig ileum. These studies would indicate that prostaglandins alter cholinergic activity prejunctionally. However, it should be noted that Laekeman and Herman (114) did report on acetylcholine-induced prostaglandin release and Grbovic and Radnanovic (81) found that low concentrations of prostaglandin E_2 and prostaglandin F_{2a} potentiated the effects of acetylcholine on ileal motility.

Regardless of the site of action, it appears that in the guinea pig prostaglandins are capable of modulating the effects of the autonomic nervous system on ileal motility. In addition, indomethacin has been shown to inhibit serotonin (60) and cholecystokinin (198) induced contractions of the guinea pig ileum. This would imply that

prostaglandins play a role in the response to these agents as well.

In other species, prostaglandin E_1 and prostaglandin E_2 have been shown to inhibit acetylcholine-induced contractions in human jejunal and ileal circular smooth muscle (14). Although indomethacin and aspirin apparently have no effect on acetylcholine-induced motility in the rat ileum (51), they do inhibit bradykinin-induced contractions in the rat ileum (51, 104, 186, 187, 188) and bradykinin-induced relaxation in the rat duodenum (104, 186). The data suggest, then, that prostaglandins play a role in the regulation of motility in a number of species under a variety of conditions.

Prostaglandins have also been proposed to play a role in the control of intestinal secretion and absorption. The techniques used range from simple measurements of volume secretion/absorption to radioisotope studies of transmucosal ion movement to measurements of transmucosal or transmural potential and short circuit current (I_{sc}). The latter technique involves measuring the current which must be passed across a membrane to negate the current developed by mucosal ion transport. As such, these experiments provide only evidence of changes in net ion transport, but do not indicate the ion(s) involved.

In 1971, Matuchansky and Bernier (127) reported that the intraluminal infusion of prostaglandin E_1 produced an increase in the secretion of Na^+ , Cl^- , K^+ , HCO_3^- , and water in the human jejunum. Furthermore, they found that the increase in Na^+ and water secretion was due to a large increase in the blood to lumen flux with no change in the lumen to blood flux. These findings are supported by those of Meij et al (133) in conscious humans and Rask-Madsen and

Bukhave (34, 148) in isolated human jejunal mucosa. Matuchansky and Bernier (128, 129) also reported that prostaglandin E_1 decreased glucose absorption in the human jejunum by 25%, but that its effects on ion movement were independent of this activity.

Prostaglandin E_1 has also been shown to increase the I_{sc} in rabbit ileal mucosa (3, 88). However, Al-awqati and Greenough (3) found that in this species the mechanism of action involved an inhibition of the lumen to blood Na^+ flux rather than the blood to lumen flux as seen in humans. In other species, prostaglandin E_1 and prostaglandin E_2 increased the I_{sc} in the guinea pig ileum (105) and either inhibited absorption or stimulated secretion in the dog (88, 145) and cat (81). Furthermore, both of these prostaglandins inhibited glucose absorption when placed in the lumen of the dog jejunum (105). Prostaglandin E_2 has been shown to decrease the I_{sc} in the rat jejunum by means of a decrease in the lumen to blood flux of Na^+ and Cl^- (54).

Rask-Madsen and Bukhave (148) have reported that prostaglandin F_{2a} has no effect on human jejunal mucosa I_{sc} or ion fluxes. Cummings et al (52) did find that prostaglandin F_{2a} increased water, Na^+ and Cl^- secretion in humans, but only after 30 minutes of continuous intravenous infusion. Prostaglandin F_{2a} has been shown to increase the net secretion of water, protein, and electrolytes (145) and to inhibit glucose absorption (10) in the dog. In addition, prostaglandin F_{2a} produces an increase in the rabbit intestine I_{sc} due to a decrease in the lumen to blood flux of Na^+ and Cl^- (3). Prostaglandin A_2 has been shown to increase the net water and

electrolyte secretion in the canine jejunum, but neither prostaglandin A_1 nor prostaglandin F_{2a} altered the I_{sc} in the guinea pig ileum (145).

These studies indicate that prostaglandin E_1 is a more potent intestinal secretory agent than prostaglandin F_{2a} and that prostaglandin A_1 also stimulates secretion. Furthermore, both prostaglandin E_1 and prostaglandin F_{2a} have been shown to inhibit intestinal glucose absorption. However, there is no evidence to date that any of these prostaglandins regulate intestinal secretion or absorption.

Inhibition of prostaglandin synthesis results in a decrease in blood flow to the small intestine in the dog (77), rabbit (25), and cat (153). The magnitude of the response ranges from a 34% decrease in blood flow in conscious rabbits (77) to a 71% decrease in blood flow in anesthetized cats (153). In addition, Nowak and Wennmalen (138) have shown that indomethacin produces a decrease in splanchnic blood flow in man. Inhibition of prostaglandin synthesis in mesenteric artery strips inhibits the response to norepinephrine in the rat (122, 1230), but it either potentiates (122) or has no effect on the response in the rabbit (159).

Stimulation of prostaglandin synthesis by infusion of arachadonic acid causes intestinal vasodilation (7, 40). The effects of intra-arterial infusion of the individual prostaglandins into the small intestine have been studied by a number of investigators. Prostaglandin E_1 is an intestinal vasodilator in man (47, 138), dogs (40, 55, 66), and cats (81). In dogs, the increase in flow is associated with an

increase in oxygen consumption of similar magnitude (143). Prostaglandin F_{2a} has been shown to be an intestinal vasoconstrictor (40, 64, 142, 156) and Pawlik et al (142) have shown that the decrease in canine intestinal blood flow during infusion of prostaglandin F_{2a} is associated with a decrease in oxygen consumption. The thromboxanes A_1 , A_2 , and B_2 appear to initially dilate and then constrict the mesenteric vasculature (64, 90).

The effect of prostaglandin D_2 on the intestinal circulation appears to depend on the method of administration. Chapnick and Feigen (40, 65) reported that bolus injections of prostaglandin D_2 into the superior mesenteric artery resulted in a decrease in intestinal blood flow. However, Fondacaro et al (73) found that the response was biphasic when the prostaglandin was infused continuously at a rate of $0.5 \mu\text{g/kg-min}$. Blood flow initially decreased, but then returned to control and rapidly increased to a level nearly twice that of control. This increase in blood flow was distributed exclusively to the muscularis layer of the small intestine, while blood flow to the mucosal-submucosal layer actually decreased. Infusion of prostaglandin D_2 at this dose also increased intestinal oxygen consumption.

Prostaglandin I_2 is also a potent vasodilator in the intestinal circulation (35, 40, 57, 66, 73). Both Fondacaro et al (73) and Pawlik et al (142) have reported that the increase in flow following infusion of prostaglandin I_2 into the superior mesenteric artery is directed mainly to the mucosal-submucosal layer. In addition, there is a significant increase in intestinal oxygen consumption during infusion of the prostaglandin.

It would appear that prostaglandins have a marked effect on intestinal blood flow and motility and that they are capable of altering the secretion or absorption of water, electrolytes and glucose. The mechanisms by which prostaglandins exert these effects are not clear.

It is possible that prostaglandins act intracellularly as they are lipid soluble. Coceani and Wolfe (49) have reported that this is not true of PGE_1 in rat intestinal smooth muscle as glycerinated muscle strips, i.e. those in which the cell membrane has been destroyed with glycerine, showed no response to the prostaglandin but were still activated by calcium and ATP. In vascular smooth muscle, the prostaglandins interact with sulfhydryl groups on or in the membrane of the muscle cell (87). The various prostaglandins appear to have individual receptors (65, 92, 125, 132) which are distinct from the α - and β -adrenergic receptors and the muscarinic cholinergic receptors of the autonomic nervous system (1, 65, 102, 104, 126, 132, 136).

Lochette et al (120) have reported that the prostaglandins A_1 , E_2 , and F_{2a} enhanced K^+ -induced relaxation of rat vascular smooth muscle and that the action of PGE_2 was blocked with ouabain. The authors concluded that the prostaglandins were acting to stimulate the Na-K-ATPase system, but they did not relate this to their physiological activity. Mujazaki et al (134) found that the ability of prostaglandin E_1 to contract longitudinal smooth muscle was dependent upon the presence of Na^+ , and sensitive to the concentrations of Mg^+ and K^+ in the muscle bath. The authors concluded that the action of prostaglandin E_1 in this tissue was dependent on the electrical activity of the membrane.

Greenberg et al (85) attempted to correlate the physiological activity of the prostaglandins E_1 , E_2 , and F_{2a} and the thromboxanes A_2 and B_2 with their effect on calcium uptake. The thromboxanes were found to cause contraction of the mesenteric vascular strips and an increase in intracellular calcium release. However, the E prostaglandins produced relaxation of the strips with no change in calcium activity, while prostaglandin F_{2a} had no effect upon the strips but increased the membrane permeability to calcium. Although the latter observation provides a mechanism for the ability of prostaglandin F_{2a} to sensitize smooth muscle to various stimuli such as norepinephrine and KCl (86), the study in general speaks against changes in calcium activity as the sole mechanism of prostaglandin activity in vascular smooth muscle.

It has also been suggested that prostaglandins act to stimulate the adenylyl-cyclase enzyme and thereby increase intracellular levels of cAMP. Indeed, prostaglandins have been shown to stimulate adenylyl-cyclase activity in the small intestine of the rat (105, 125, 161), rabbit (105), guinea pig (105), and human (160). It should be noted that Roemer et al (150) found that prostaglandin E_1 can also activate duodenal guanylate cyclase activity, an enzyme system which has been proposed as the mediator of cholinergic activity (12).

Simon et al (161) reported that prostaglandin E_2 stimulated both adenylyl-cyclase activity and intestinal secretion in the rat, while prostaglandin I_2 had no effect on either. Furthermore, Kimberg et al (105), have found that the E prostaglandins stimulate both adenylyl-cyclase activity and ion transport in the guinea pig, rat and rabbit,

but that prostaglandin F_{2a} did not stimulate either. In addition, Field et al (69) have reported that cAMP stimulates Cl^- and HCO_3^- transport in rabbit ileal mucosa.

On the other hand, Coupar and Meoll (50) found that the E and F prostaglandins inhibited glucose absorption, but that dibutyl 3', 5' c-AMP, a more diffusible analogue of cAMP, slightly enhanced glucose absorption. In addition, Manku et al (125) reported that although the prostaglandins E_1 , E_2 , and I_2 increased rat mesenteric artery cAMP levels, each had a different effect on the response of the vessels to norepinephrine, angiotensin II and K^+ . It would seem, therefore, that none of the mechanisms suggested in these studies can be the sole mediator of prostaglandin activity.

From the studies presented in this review, it seems that prostaglandins may play an important role in the regulation of intestinal activity. They are synthesized throughout the gastrointestinal tract, they are released under a variety of conditions, and inhibition of their synthesis dramatically alters intestinal blood flow and motility. Given their potential to alter secretion and absorption as well as blood flow, it is not unlikely that they would also play a role in the postprandial intestinal hyperemia. The purpose of this study, therefore, was to determine the effects of cyclooxygenase inhibitor infusion on the vascular and metabolic response of the jejunum to the luminal presence of food.

MATERIALS AND METHODS

Materials

Heparin was obtained as a sodium salt from Sigma Chemical Co. (St. Louis, MO) and a stock solution was prepared in normal saline at a concentration of 1000 units/ml. Angiotensin II was obtained from Sigma Chemical Co. and was dissolved in ethanol to form a stock solution with a concentration of 1.0 mg/ml. The stock solution was kept at -5°C . Just prior to use, 50 μl of the stock solution was pipetted into 50 ml of normal saline with a micropipette (Cole Parmer, Chicago, IL) to make a solution of 1.0 $\mu\text{g/ml}$. Sodium pentobarbital was obtained in powder form from Abbott Laboratories (Chicago, IL), and prepared fresh each day in normal saline (60 mg/ml).

Indomethacin was obtained in pure form from Sigma Chemical Co., and all indomethacin solutions were prepared within four hours of their infusion. For those experiments in which indomethacin was to be infused intravenously, the indomethacin was prepared in a 5% ethanol solution buffered with sodium bicarbonate ($\text{pH} = 8.8 \pm 0.2$) at a concentration of 5 mg/ml. For those experiments in which the indomethacin was to be infused intraarterially, it was prepared in a saline solution buffered with sodium bicarbonate ($\text{pH} = 8.4 \pm 0.1$, $\text{osm} = 314 \pm 8 \text{ mOsm/kg}$) at a concentration of 3.3 mg/ml. Mefenamic acid was obtained from either the Parke-Davis Co. (Detroit, MI) as Ponstel, or in filler-free form from Warner-Lambert Laboratories (Ann Arbor, MI). In all experiments, mefenamic acid was prepared within two hours of use in a saline solution

buffered with sodium bicarbonate ($\text{pH} = 8.6 \pm 0.1$, $\text{osm} = 321 \pm 8 \text{ mOsm/kg}$). The concentrations of the solutions were the same as those for indomethacin. Carrier solutions were prepared for each experiment and the pH and osmolarity were adjusted to match those of the drug solution being used that day.

The food solution used in these experiments was prepared so as to contain equal parts by weight of fat, carbohydrate, and protein. This was accomplished by adding 30 gm of a high fat test diet, 15 gm of a high protein test diet, and 5 gm of a high carbohydrate test diet (U.S. Biochemical, Cleveland OH) to 400 ml of 0.1N sodium bicarbonate. The nutrients were digested by adding 500 gm of a pancreatic enzyme preparation (Viokase, Viobin Co., Monticello, IL) and gently mixing the solution with a magnetic stirrer for 5 hours at room temperature. The solution was stored in a refrigerator overnight.

Prior to the start of each experiment, nine parts of the digested food solution were mixed with one part of the dog's gallbladder bile. The pH of the solution ($\text{pH} = 7.1 \pm 0.1$) was adjusted using either NaOH or HCL, and the osmolarity ($\text{osm} = 316 \pm 5 \text{ mOsm/kg}$) was adjusted with NaCl. Both the digested food plus bile solution and the normal saline solution were kept at 37°C during the experiments.

Surgical Preparation and Protocol

Fasted mongrel dogs of either sex (15-25 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and ventilated with room air by means of an endotracheal tube and a positive pressure respirator

(Model 607, Harvard Apparatus, Dover, MA). The volume and rate of the respirator were adjusted to achieve a normal arterial blood pH (pH = 7.38 - 7.42). A saline-filled catheter (PE 320, i.d. = 2.69 mm, o.d. = 3.50 mm) was inserted into the femoral artery and connected to a low volume displacement pressure transducer (Statham p23Gb, Hato Rey, Puerto Rico) in order to record systemic pressure on a direct-writing oscillograph (Sanborn Model 7714-04A or Hewlett Packard Model 7796A, Waltham, MA). The abdomen was opened with a midline incision and the contents of the gallbladder were removed with a needle and syringe for preparation of the food solution.

Series 1. (N=8) A segment of the jejunum approximately 40-50 cm long (152 ± 13 gm) beginning in the region of the ligament of Treitz and perfused by four to six jejunal arteries was exteriorized and surgically isolated from the remainder of the jejunum and ileum. The section of the superior mesenteric artery perfusing the distal jejunum and ileum was tied off and those portions of the small intestine were removed. An electromagnetic flow transducer (Biotronex series 5000, Silver Springs, MD) connected to a Biotronex EL-610 flowmeter was placed around the superior mesenteric artery proximal to the first artery perfusing the isolated segment (Figure 2). A hydraulic occluder was placed between the flow transducer and the first jejunal artery in order to obtain zero blood flow recordings during the course of the experiment. The output of the flowmeter was recorded continuously on the direct-writing oscillograph. Ink was injected intraarterially at the end of several experiments to verify that the flow transducer monitored only the flow which perfused the isolated segment. Visual examination of adjacent

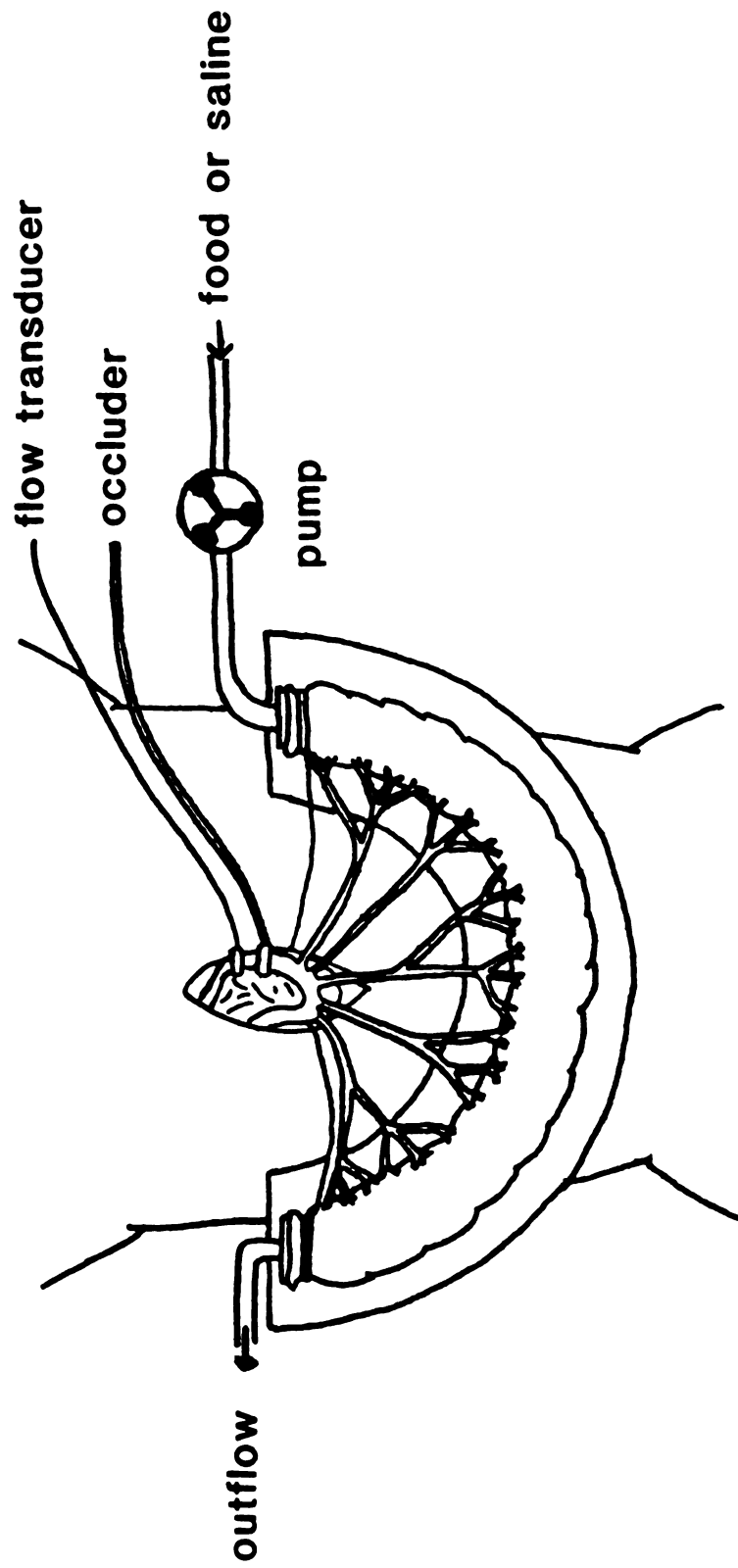


Fig.2. Isolated jejunal loop preparation

jejunal and colonic segments did not indicate the presence of ink in these tissues.

A rubber tube (Levine, 18 FR, American Hospital Supply, McGraw Park, IL) was inserted at each end of the jejunum. The tube in the proximal end was connected to the outflow line of a pump (Masterflex, Model 7553-00 with a 7014 head, Cole Parmer Instr. Co.) for the perfusion of either saline or digested food plus bile at a rate of 4 ml/min. The tube at the distal end of the segment allowed for drainage. Both ends of the segment were tied and cut and the mesentery was cut to exclude collateral flow. The isolated segment was arranged in a semi-circular manner on a platform so as to avoid obstruction of the lumen, moistened with warm saline, and covered with a clear plastic wrap to prevent dessication of the tissue. The femoral vein was cannulated with a saline-filled catheter (PE 280, i.d. = 2.16 mm, o.d. = 3.25 mm) for intravenous infusion of supplemental anesthetic and drugs.

The segment was perfused with normal saline until the blood flow had attained a steady state for twenty minutes. At that time, the perfusate was changed to the food solution. The digested food plus bile was placed on a magnetic stirrer and continuously mixed as it was perfused through the segment. The perfusion of food was maintained until the intestinal hyperemia had reached a plateau for at least twenty minutes. The increase in blood flow due to food was calculated as the difference in blood flow between the two steady state periods, control and experimental.

After the perfusion with food was stopped, the segment was perfused with normal saline until flow had returned to control levels. At that

time, either indomethacin (N=4) or mefenamic acid (N=4) was infused over a period of ten minutes to a total dose of 10 mg/kg. This dose has been shown to effectively inhibit prostaglandin synthesis (71). The segment was perfused with warm saline for one hour following infusion of the cyclooxygenase inhibitor. At that time, the response to food was tested once more.

At the end of the experiment, the superior mesenteric artery was cannulated and the electromagnetic flowmeter was calibrated in situ. The animal was killed with an overdose of anesthetic and the segment was excised, cleared of the mesentery, and weighed. The tissue weight was used to calculate the blood flow per gram of tissue.

Series 2. (N=8) This series was identical to series one, except that the carrier solutions for either indomethacin or mefenamic acid were infused rather than the drugs themselves. This series served as the time control for series one. The experiments in series one and two were conducted in a paired manner; that is, two animals were surgically prepared on the same day and one was selected randomly to receive the cyclooxygenase inhibitor, while the other animal received the carrier solution. The same food solution was used for the preparation of the digested food plus bile for each animal.

Series 3. (N=14) A loop of jejunum approximately 30-40 cm distal to the ligament of Treitz was exteriorized and two segments, each perfused by a single artery and drained by a single vein, were surgically isolated. A side branch of the artery perfusing each segment was cannulated (PE 100, i.d. = 0.86 mm, o.d. = 1.52 mm) to allow the intraarterial infusion of the cyclooxygenase inhibitor or its

carrier solution. The animal was heparinized (10,000 units), each vein was cannulated, and the venous outflows were directed to a reservoir containing 200 ml of 6% Dextran (Dextran 70, Medical Grade Dextran, Sigma Chemical Co.) in normal saline. The volume of the reservoir was maintained at 200 ml by pumping the contents into the femoral vein at a rate equal to the venous outflows (Holterpump, Model RE 161, Extracorporeal Medical Specialties, Inc., King of Prussia, PA).

A rubber tube was placed in the lumen of each segment for the introduction and withdrawal of the saline and food solutions. At all other times, the tubes were connected to a pressure transducer (Statham, P23Gb) in order to record lumen pressure during the experiment. Both ends of each segment were tied and cut, and the mesentery was cut to exclude collateral flow (Figure 3). Each segment was thoroughly rinsed with normal saline after which 10 ml of saline were placed simultaneously in the lumen of each segment for 15 minutes. During that time the venous outflows were collected in graduated cylinders for two minutes at 1 min., 5 min., 9 min., and 13 min. after placement of the saline in the lumen. The blood flow measured during the last two minute collection (13 - 15 min.) represents the steady state response, and as such, was used in the comparison of treatments.

At the end of the 15 minute period, the segments were gently and thoroughly washed with normal saline and the procedure was repeated until the blood flow recorded during the last two minutes of two successive 15 minute periods differed by no more than 2 ml. When both segments had attained a stable resting blood flow, the segments were washed and filled simultaneously with 10 ml of the food solution for

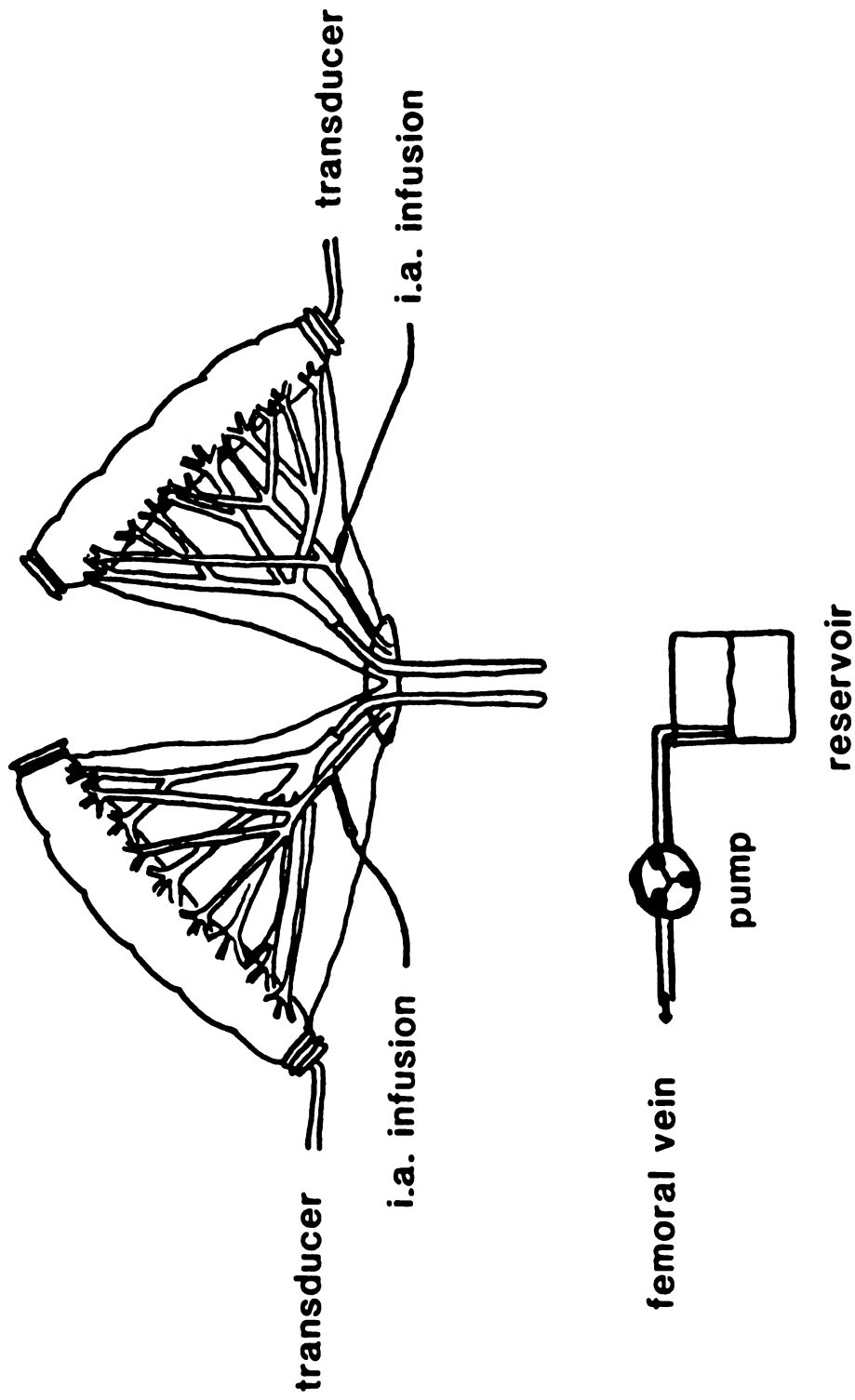


Fig. 3. Double isolated jejunal segment preparation

15 minutes. Blood flow was measured as before and the blood flows during the last two minute collection period were used for comparison of treatments.

After determining the response to food in both segments, one segment was randomly selected for intraarterial infusion of 100 mg of either indomethacin (N=8) or mefenamic acid (N=6) in a buffered saline solution for one hour at a rate of 0.494 ml/min. An equal volume of the appropriate carrier solution was infused intraarterially to the control segment at the same rate. During the infusion period, venous outflow from the treated segment was discarded and replaced with blood from a donor dog in order to prevent the cyclooxygenase inhibitor from reaching the control segment. At the end of the infusion period, the response to food was again determined simultaneously in both segments. The animals were then killed with an overdose of anesthetic and the segments were removed and weighed.

Series 4. (N=8) A loop of jejunum approximately 30-40 cm from the ligament of Treitz was exteriorized and a segment which was drained by a single vein was isolated. The animal was heparinized (10,000 units) and the vein was cannulated. The venous outflow was directed through an electromagnetic flow transducer (Biotronex BLC-2048-EO4 connected to a Biotronex BL-610 flowmeter) to a reservoir containing 200 ml of 6% Dextran in normal saline. The reservoir volume was maintained at 200 ml as in series three. A rubber tube was placed in each end of the segment as in series one and two, and the ends of the segment were cut and tied to eliminate collateral circulation.

The remaining femoral artery of the animal was cannulated with a flow-through arterial loop. The side ports of the loop were used to provide the arterial blood for sample collection and for the measurement of the arterial-venous oxygen content difference. This was determined continuously by perfusing a portion of the jejunal venous outflow and femoral arterial blood (6 ml/min.) through separate cuvettes of a spectrophotometric arteriovenous oxygen content analyzer (A-Vox System, San Antonio, TX) with a Gilson pump (Minipuls 2, Gilson Med Electronics, Middletown, WI). The analyzer was calibrated with a Lex-O₂-Con-TL oxygen content analyzer (Lexington Instruments, Waltham, MA). The outflow from each cuvette was directed to the venous reservoir (Figure 4).

The flowmeter and arteriovenous oxygen content analyzer data were recorded continuously on a direct-writing oscillograph. The flowmeter was calibrated periodically during the course of the experiment by measuring the venous outflow with a graduated cylinder and stopwatch. As the flowmeter recording included that portion of the venous outflow which was directed to the arteriovenous oxygen content analyzer, the flow rate of the pump was added to all blood flow measurements when calibrating the flowmeter. The pump speed was measured at the beginning of each experiment and after any change.

The oxygen consumption of the tissue was calculated as the product of the blood flow and arteriovenous oxygen content difference recordings. In order to compensate for the temporal dissociation of the two recordings due to the distance between monitoring points, a bolus of saline was injected into the venous catheter immediately upstream from

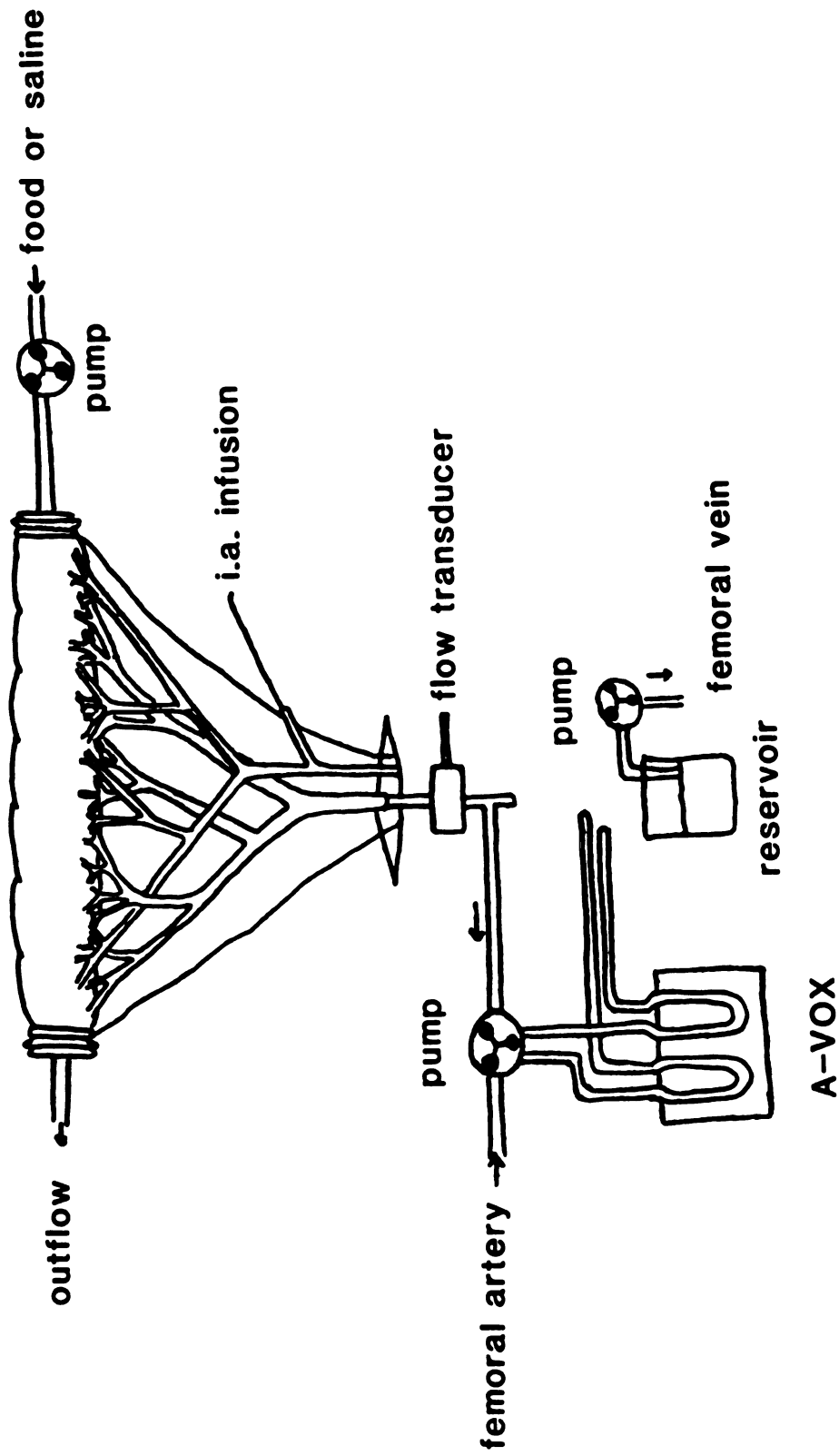


Fig. 4. Single isolated jejunal segment preparation

the flowmeter. The time between the peak flow as indicated on the flowmeter tracing and the decrease in the arteriovenous oxygen content difference was measured and the appropriate corrections made.

Upon completion of the surgical preparation, the segment was perfused with normal saline (4 ml/min.) until both blood flow and the arteriovenous oxygen content difference had reached a steady state for at least twenty minutes. At that time, the venous outflow was measured for one minute with a graduated cylinder and stopwatch. Immediately following the measurement of flow, duplicate samples of arterial and venous blood were collected for the measurement of blood gases, glucose, lactic acid and pyruvic acid. Venous blood was also collected in capillary tubes for the measurement of hematocrit. The exact collection techniques are described in the section on chemical assays.

A second one minute blood flow measurement was taken upon completion of sample collection and the segment was perfused with digested food plus bile. The food solution was mixed continuously on a magnetic stirrer during the perfusion period. The perfusion was maintained until blood flow and the arteriovenous oxygen content difference reached a steady state (10-15 minutes). At that time, a one minute blood flow measurement was taken, followed by sample collection and another blood flow measurement as before.

After the response of the segment to food had been determined, the segment was perfused with saline until blood flow returned to control levels. Mefenamic acid was then infused intravenously for ten minutes to deliver a total dose of 10 mg/kg. The segment was perfused with normal saline for one hour after infusion of the cyclooxygenase

inhibitor, and the response to food was tested as before. The animal was killed at the end of the experiment with an overdose of anesthetic and the segment was excised, trimmed of mesentery, and weighed.

Series 5. (N=6) The surgical preparation for this series was the same as in series four with one addition. A side branch of the artery perfusing the isolated segment was cannulated with a saline-filled catheter (PE 100) for the intraarterial infusion of angiotensin II. The protocol for the experiment was the same as in series four up to and including the initial determination of the response of the segment to food.

After blood flow had returned to control levels, angiotensin II was infused intraarterially at a rate sufficient to reduce resting blood flow approximately 40% ($0.73 \pm 0.18 \mu\text{g/min./100 gm}$). This decrease in blood flow is similar to that seen following cyclooxygenase inhibitor infusion. The response to food was determined during angiotensin II infusion as before. This series served as a control for the effects of a decrease in resting blood flow on the jejunal response to food.

Chemical Assays

Blood Gases. Arterial and venous blood pH, pO_2 and pCO_2 were measured before and during the intraluminal perfusion of food both before and after drug infusion in series 4 and 5. Duplicate samples of arterial and venous blood were drawn in saline-filled syringes at the appropriate time from the femoral arterial loop and the venous outflow line, respectively. The syringes were flushed several times before the

final sample was taken to insure that the sample was not diluted, and care was taken to insure that the sample was not contaminated with air bubbles. The syringes were capped and stored on ice to minimize red blood cell metabolism prior to the determination of pH, pO_2 , and pCO_2 .

The arterial and venous blood gases were measured with the BMS 3 MKII Blood Micro System and Acid Base Analyzer (London Co., Cleveland, OH). Corrections for temperature differences between the blood gas electrodes (37°) and the segment were made using the Severinghaus nomogram (155). The animal's body temperature and that of the segment were monitored during the course of several experiments in series 4 and 5. It was found that body temperature was approximately 36° C and the segment temperature was approximately 34° C.

Glucose, Lactic Acid, Pyruvic Acid. Approximately 5 ml of arterial and venous blood were collected on ice in a Vacutainer containing 30 mg NaF (Fischer Scientific, Pittsburgh, PA). The venous blood was collected from the venous outflow cannula while the arterial sample was collected simultaneously from a side port of the femoral artery loop. One milliliter of each sample was quickly pipetted with an automatic pipette (Cole Parmer) into a test tube containing 2 ml of an 8% perchloric acid solution and agitated on a Vortex mixer (Scientific Industries, Inc., Bohemia, NY) in order to precipitate the blood proteins. This was necessary to prevent degradation of the pyruvic acid in the sample.

The test tubes with the blood-perchloric acid mixture were centrifuged (Model CL, International Equipment Co., Needham, MA), and

the supernatant was pipetted into an empty test tube. The supernatant was stored at 4° C until required for the lactic acid or pyruvic acid assay. These assays were performed in accordance with Sigma Technical Bulletin No. 726-W/826-W(9-74) (Sigma Chemical Co.) and are based on the following reaction:



where: NADH = reduced nicotinamide adenine dinucleotide; NAD = oxidized nicotinamide adenine dinucleotide; LDH = lactic acid dehydrogenase. The reaction is reversible and can be driven in either direction with excess reagent.

Pyruvic acid levels are determined by measuring the decrease in ultraviolet absorption at 340 nm as NADH levels in the solution decrease. The concentration of pyruvic acid in mg/100 ml blood is calculated from the equation:

$$\text{Blood Pyruvic Acid} = \Delta A_{340} \times \frac{3.0 \times 88.1}{6.22 \times 0.667 \times 1 \times 10} = \Delta A_{340} \times 6.37$$

where: ΔA_{340} = initial absorbance at 340 nm - final absorbance at 340 nm; 3 = reaction volume (ml); 6.22 = millimolar extinction coefficient of NADH at 340 nm; 0.667 = volume (ml) of blood sample in the cuvette; 1 = light path (cm); 88.1 = molecular weight of pyruvic acid; 10 = a conversion factor for concentration/100 ml.

Lactic acid levels are determined by measuring the increase in ultraviolet absorbance at 340 nm due to the formation of NADH. The equation for the calculation of lactic acid concentration in mg/100 ml blood is:

$$\text{Blood Lactic Acid} = A_{340} \times \frac{3.0 \times 90.0}{6.22 \times 0.0667 \times 1 \times 10} = A_{340} \times 65.1$$

where: A_{340} = final maximum absorbance at 340 nm; 90.0 = molecular weight of lactic acid; 0.0667 = volume of blood sample in the cuvette. The other factors are the same as listed above.

After the blood for the lactate and pyruvic assays had been withdrawn, the arterial and venous blood samples were gently agitated to insure that the NaF in the tubes dissolved. The NaF served as a metabolic poison to prevent glucose utilization by red blood cells. All sample tubes were stored on ice until required for the glucose assay.

Blood glucose levels were determined by injecting whole blood samples of constant volume into a YSI model 23A glucose analyzer (Yellow Springs, OH). The instrument uses a glucose oxidase method of analysis and indicates the glucose concentration in mg/100 ml. The instrument was calibrated with a standard solution at the start of each assay to ± 1 mg /100 ml, and checked periodically during the run.

Statistical Analysis

All data are presented as the mean $\pm$ S.E.M. The data were analyzed using analysis of variance and the Tukey B test for the comparison of means. Statistical significance was set at $p < 0.05$. Linear regressions were performed using the least squares method and comparison of regression equations was accomplished with analysis of variance. In those cases where it was necessary to know whether the mean was significantly different from zero, confidence intervals were determined and the hypothesis $\mu = 0$ was tested.

RESULTS

Systemic arterial pressure, 118 ± 6 mm Hg (N=44), was not significantly altered by either luminal placement or perfusion of a solution, or by intraarterial infusion of angiotensin II or the cyclooxygenase inhibitors. The intravenous infusion of the cyclooxygenase inhibitors in series 1 and 3 did not alter systemic blood pressure; however, the intravenous infusion of mefenamic acid in series 4 significantly increased arterial blood pressure from 114 ± 6 mm Hg to 127 ± 5 mm Hg. The venous hematocrit in series 4 and 5 did not change when food was placed in the lumen or when either drug was infused.

The luminal placement or perfusion of the digested food plus bile solution significantly increased blood flow in each series of experiments. There were no significant differences in the effects of mefenamic acid and indomethacin on blood flow with either saline or food in the lumen. Therefore, the data has been pooled for presentation here.

In series 1, the effects of systemic cyclooxygenase inhibition on the intestinal hemodynamic response to food was examined. The change in blood flow when food was perfused through the lumen was determined before and after the intravenous infusion of mefenamic acid or indomethacin at a dose believed to block prostaglandin synthesis (10mg/kg).

In series 1, the presence of food in the lumen of the jejunum increased blood flow by 13.7 ± 2.5 ml/min/100 gm, an increase of $23.1 \pm 3.2\%$ (Table 1). This corresponds to a decrease in resistance of 0.31 ± 0.06 PRU (PRU = mm Hg/ml/min/100 gm) or $14.7 \pm 3.0\%$ (Table 2).

Table 2. Mean vascular resistances in jejunal segments perfused with normal saline or food before and after intravenous infusion of a cyclooxygenase inhibitor or its carrier.

Lumen Content	Test Series (N = 8)			Control Series (N = 8)		
	Resistance ¹	Δ Resistance ¹	% Δ Resistance	Resistance ¹	Δ Resistance ¹	% Δ Resistance
Saline	Before infusion of cyclooxygenase inhibitor ² 2.32±0.51	-0.31±0.06*	-14.7±3.0*	Before infusion of drug carrier 2.24±0.40	-0.42±0.10*	-18.1±1.7*
Food	2.01±0.49			1.82±0.31		
Saline	After infusion of inhibitor ² 3.78±0.80†	-1.51±0.37*†	-39.3±3.6*†	After infusion of carrier 2.53±0.46	-0.57±0.19*	-17.8±4.6*
Food	2.27±0.46			1.96±0.30		

¹Values are mean ± SEM in PRU

²N = 4 for indomethacin and N = 4 for mefenamic acid

*p < 0.05

†p < 0.05 relative to the corresponding value before infusion

Following the intravenous infusion of the cyclooxygenase inhibitors, the food-induced jejunal hyperemia increased significantly to $+ 30.2 \pm 6.9$ ml/min/100 gm or $+ 74.3 \pm 10.0\%$. The change in resistance also increased significantly to -1.51 ± 0.37 PRU or $-39.3 \pm 3.6\%$.

In order to control for the possible effects of time on the intestinal vascular response to food, the response was tested before and after intravenous infusion of the appropriate carrier solution in another series of experiments (series 2). As seen in Tables 1 and 2, the vascular response to food did not change after infusion of the carrier solutions. Prior to infusion, blood flow increased 14.1 ± 2.4 ml/min/100 gm when food was placed in the lumen, and resistance decreased 0.42 ± 0.10 PRU. After infusion of the carrier solution, the changes were $+11.7 \pm 2.8$ ml/min/100 gm and $- 0.57 \pm 0.19$ PRU, respectively.

It is possible that the enhancement of the food-induced intestinal hyperemia following the intravenous infusion of the cyclooxygenase inhibitors may have been mediated by changes in some central regulatory pathway. Therefore, the prostaglandin synthesis inhibitors were infused intraarterially in order to determine if they were equally effective when only local prostaglandin synthesis was inhibited.

The food-induced jejunal hyperemia was also enhanced following the intraarterial infusion of the cyclooxygenase inhibitors. As seen in Table 3, the luminal placement of food increased jejunal blood flow 23.1 ± 4.1 ml/min/100 gm, or $72.7 \pm 10.7\%$, after infusion as compared to 10.7 ± 1.8 ml/min/100 gm, or $21.6 \pm 3.3\%$ before infusion. The corresponding changes in resistance were -1.58 ± 0.18 PRU ($-39.1 \pm 3.5\%$) after

Table 3. Mean venous outflows from adjacent jejunal segments containing normal saline or food before and after intra-arterial infusion of a cyclooxygenase inhibitor or its carrier.

Lumen Content	Test Segment			Control Segment		
	Blood Flow ¹	Δ Blood Flow ¹	$\Delta\%$ Blood Flow	Blood Flow ¹	Δ Blood Flow ¹	$\Delta\%$ Blood Flow
	<u>Before infusion of cyclooxygenase inhibitor²</u>			<u>Before infusion of drug carrier</u>		
Saline	50.5 $\pm$ 3.8	+ 10.7 $\pm$ 1.8*	+ 21.6 $\pm$ 3.3*	49.4 $\pm$ 4.5	+ 11.3 $\pm$ 1.6*	+ 24.1 $\pm$ 3.5*
Food	61.2 $\pm$ 4.8			60.8 $\pm$ 5.3		
	<u>After infusion of inhibitor²</u>			<u>After infusion of carrier</u>		
Saline	31.6 $\pm$ 2.7†	+ 23.1 $\pm$ 4.1*† ^a	+ 72.7 $\pm$ 10.7*† ^a	36.0 $\pm$ 3.5†	+ 12.2 $\pm$ 2.1*	+ 34.4 $\pm$ 5.0*†
Food	54.7 $\pm$ 6.0 ^a			48.2 $\pm$ 5.1†		

¹Values are means $\pm$ SE in ml/min/100 gm tissue weight

²N = 8 for indomethacin and N = 6 for mefenamic acid.

*p < 0.05

†p < 0.05 relative to the corresponding values before infusion.

^ap < 0.05 relative to the corresponding values in the control segment.

infusion and -0.42 ± 0.05 PRU ($-17.1 \pm 2\%$ before infusion (Table 4).

The vascular response to food in the control segments was not as clear as that in the test segments. The intraarterial infusion of the carrier solutions did not significantly alter the increase in blood flow when food was placed in the lumen; however, there was a significant change in the food-induced decrease in resistance from -0.50 ± 0.06 PRU to -0.89 ± 0.15 PRU (Table 4). On the other hand, while the percent change in resistance did not change, there was a significant increase in the percent change in blood flow from $+ 24.1 \pm 3.5\%$ before infusion of the carrier solution to $34.4 \pm 5.0\%$ after infusion (Table 3). In both cases, however, the change in the response was significantly less than the corresponding change in the test segment.

In addition to their effect on the jejunal vascular response to food, infusion of the cyclooxygenase inhibitors produced a decrease in resting blood flow and a corresponding increase in vascular resistance. In series 1, there was a significant decrease in blood flow from 59.2 ± 7.9 ml/min/100 gm to 41.3 ± 7.9 ml/min/100 gm following the intravenous infusion of the cyclooxygenase inhibitors (Table 1). In that same series, resistance increased significantly from 2.32 ± 0.51 PRU to 3.78 ± 0.80 PRU (Table 2). Infusion of the carrier solutions in series 2 did not significantly decrease either resting blood flow or increase vascular resistance (Tables 1 and 2).

In series 3, there was a significant decrease in resting blood flow and a significant increase in resistance after intraarterial infusion of both the cyclooxygenase inhibitors and their carrier solutions (Tables 3 and 4). Following infusion, blood flow decreased from 50.5 ± 3.8 ml/

Table 4. Mean vascular resistances in adjacent jejunal segments containing normal saline or food before and after intra-arterial infusion of a cyclooxygenase inhibitor or its carrier.

Lumen Content	Test Segment			Control Segment		
	Resistance ¹	Δ Resistance ¹	% Δ Resistance	Resistance ¹	Δ Resistance ¹	% Δ Resistance
	<u>Before infusion of cyclooxygenase inhibitor²</u>			<u>Before infusion of drug carrier</u>		
Saline	2.52 $\pm$ 0.16	- 0.42 $\pm$ 0.05*	- 17.1 $\pm$ 2.0*	2.63 $\pm$ 0.18	- 0.50 $\pm$ 0.06*	- 18.9 $\pm$ 1.9*
	<u>After infusion of inhibitor²</u>			<u>After infusion of carrier</u>		
Food	2.10 $\pm$ 0.15			2.13 $\pm$ 0.15		
Saline	4.12 $\pm$ 0.38 ^{†a}	- 1.58 $\pm$ 0.18 ^{†a}	- 39.1 $\pm$ 3.5 ^{†a}	3.70 $\pm$ 0.36 [†]	- 0.89 $\pm$ 0.15 [†]	- 23.9 $\pm$ 2.9*
Food	2.55 $\pm$ 0.29			2.81 $\pm$ 0.30 [†]		

¹Values are means $\pm$ SEM in PRU

²N = 8 for indomethacin and N = 6 for mefenamic acid

* p < 0.05

[†] p < 0.05 relative to the corresponding value before infusion

^a p < 0.05 relative to the corresponding value in the control segment

ml/min/100 gm to 31.6 ± 2.7 ml/min/100 gm in the test segments (-18.9 ± 2.2 ml/min/100 gm) and from 49.4 ± 4.5 ml/min/100 gm to 36.0 ± 3.5 ml/min/100 gm in the control segments (-13.4 ± 2.8 ml/min/100 gm). Although there is no significant difference in mean resting blood flow between the segments either before or after infusion, the mean decrease in blood flow in the test segment (-18.9 ± 2.2 ml/min/100 gm) is significantly greater than that in the control segment (-13.4 ± 2.8 ml/min/100 gm). The vascular resistance of the test segment with saline in the lumen after infusion of the cyclooxygenase inhibitors, 4.12 ± 0.38 PRU, was significantly higher than that in the control segment after infusion of the carrier solutions, 3.70 ± 0.38 PRU.

It would appear, then, that both the intravenous and intraarterial infusion of the cyclooxygenase inhibitors indomethacin and mefenamic acid significantly reduced resting blood flow and significantly increased the food-induced jejunal hyperemia. However, Meyers and Honig (131) have suggested that initial resistance plays a significant role in determining the magnitude of the vascular response to a given stimulus. This concept is supported by work by Granger and Norris (82) in the intestinal circulation. Therefore, it is possible that the enhancement of the jejunal hyperemia in these experiments may have been due solely to changes in initial resistance.

This possibility was examined by analyzing the relationships between initial resistance and the change in resistance produced by food in series 1, 2 and 3. For the purposes of analysis, the data in both the intraarterial and intravenous infusion series were divided into two groups, i.e., treated and untreated. The treated group contained only

the data from the segments which had been exposed to the cyclooxygenase inhibitors. The untreated group included the data from the control segments both before and after carrier infusion as well as the data from the test segments before infusion of the cyclooxygenase inhibitors.

For each series, regression analysis was performed using the method of least-squares and comparisons between treatments were made using analysis of variance. In all cases, there is a significant correlation between initial resistance and the magnitude of the vascular response to food ($p \leq 0.05$). However, whether the cyclooxygenase inhibitors are infused intravenously (Figure 5) or intraarterially (Figure 6), the linear regression equation for the treated segments is significantly different from that of the untreated segments. That is to say, for a given initial resistance, the same food solution elicits a significantly greater decrease in resistance after infusion of a cyclooxygenase inhibitor than before.

To further test this relationship, the jejunal vascular response to food was examined before and during the intraarterial infusion of angiotensin II, a potent vasoconstrictor. The infusion of angiotensin II significantly increased the initial vascular resistance of the jejunal segment from 2.60 ± 0.32 PRU to 4.41 ± 0.31 PRU (Table 5). In addition, the food-induced decrease in resistance increased from -0.43 ± 0.10 PRU before infusion to -0.76 ± 0.18 PRU after infusion. As before, there was a significant correlation between initial resistance and the change in resistance due to food in this series (Figure 7). The linear regression equation however is significantly different from those of the segments treated with the cyclooxygenase inhibitors (Figure 7). Thus,

Figure 5. Relationship between initial resistance and the change in resistance due to food in the jejunum. Those segments treated with intravenous indomethacin or mefenamic acid are denoted by the open circles (N=14). Untreated segments are denoted by closed circles (N=32). The regression lines are significantly different ($p < 0.05$).

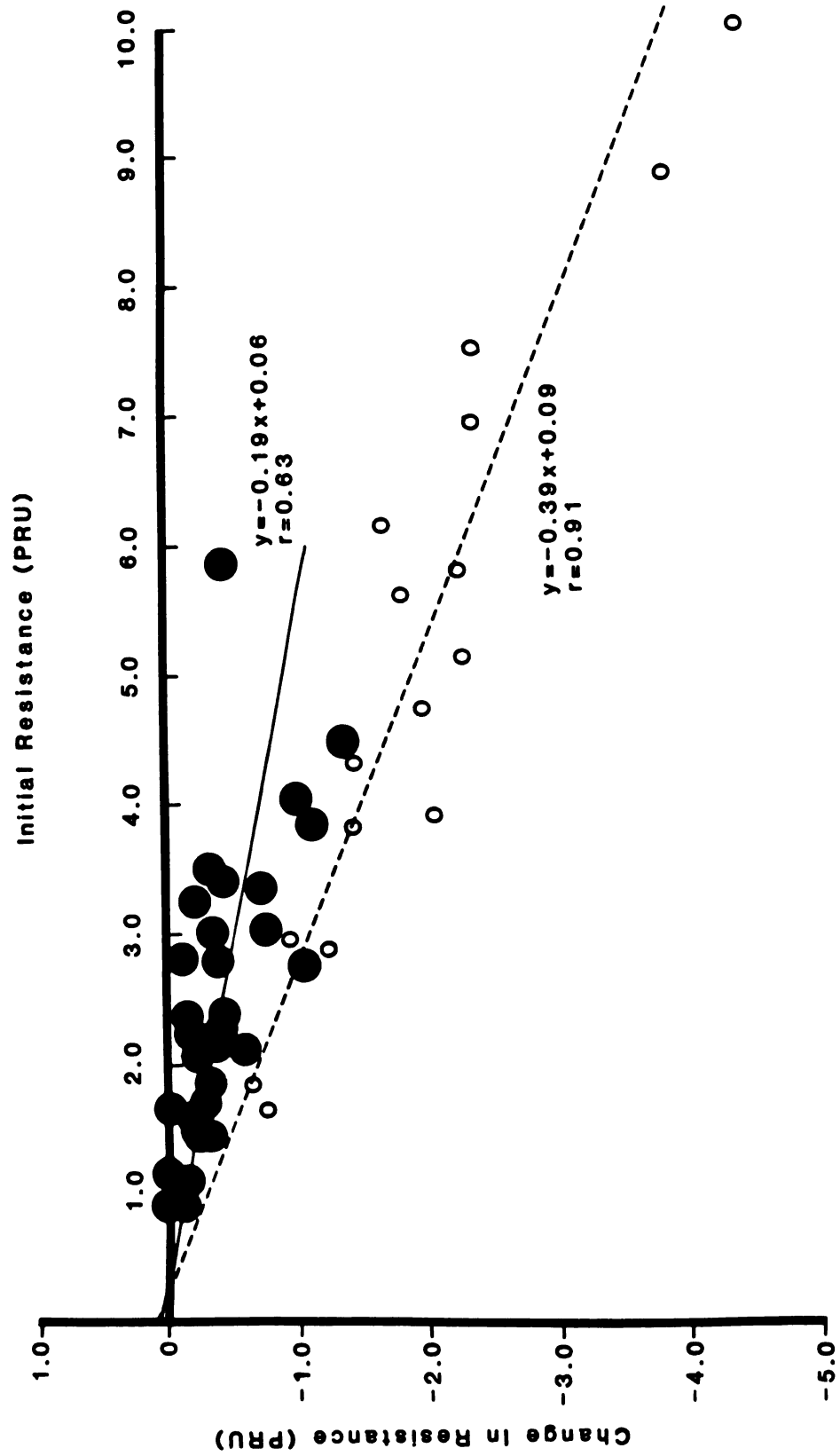


Figure 6. Relationship between initial resistance and the change in resistance due to food in the jejunum. Those segments treated with intraarterial indomethacin or mefenamic acid are denoted by the open circles (N=14). Untreated segments are denoted by the closed circles (N=42). The regression lines are significantly different ($p < 0.05$).

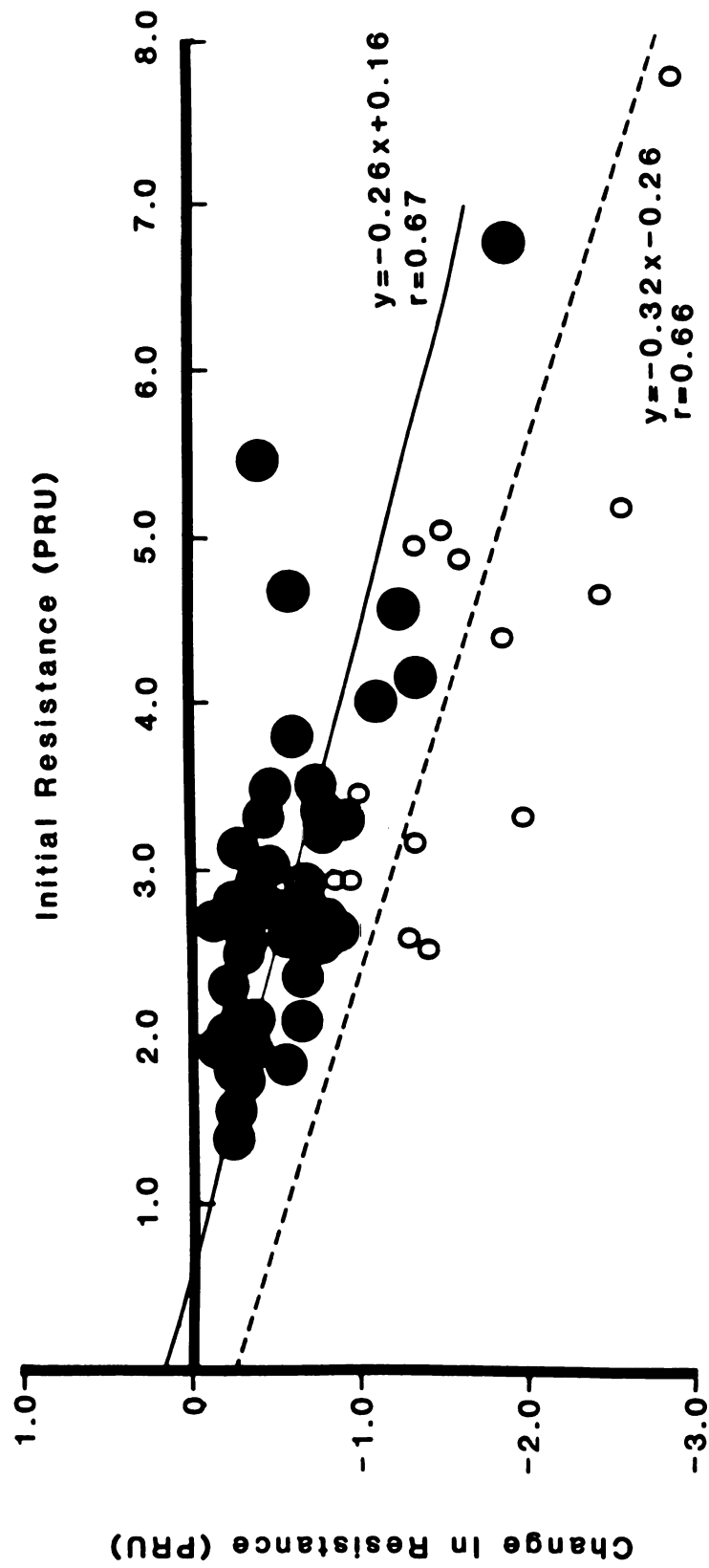


Table 5. Mean venous outflows, vascular resistances, arterial-venous oxygen content difference and oxygen consumption in jejunal segments perfused with normal saline or food before and during intra-arterial infusion of angiotensin II.

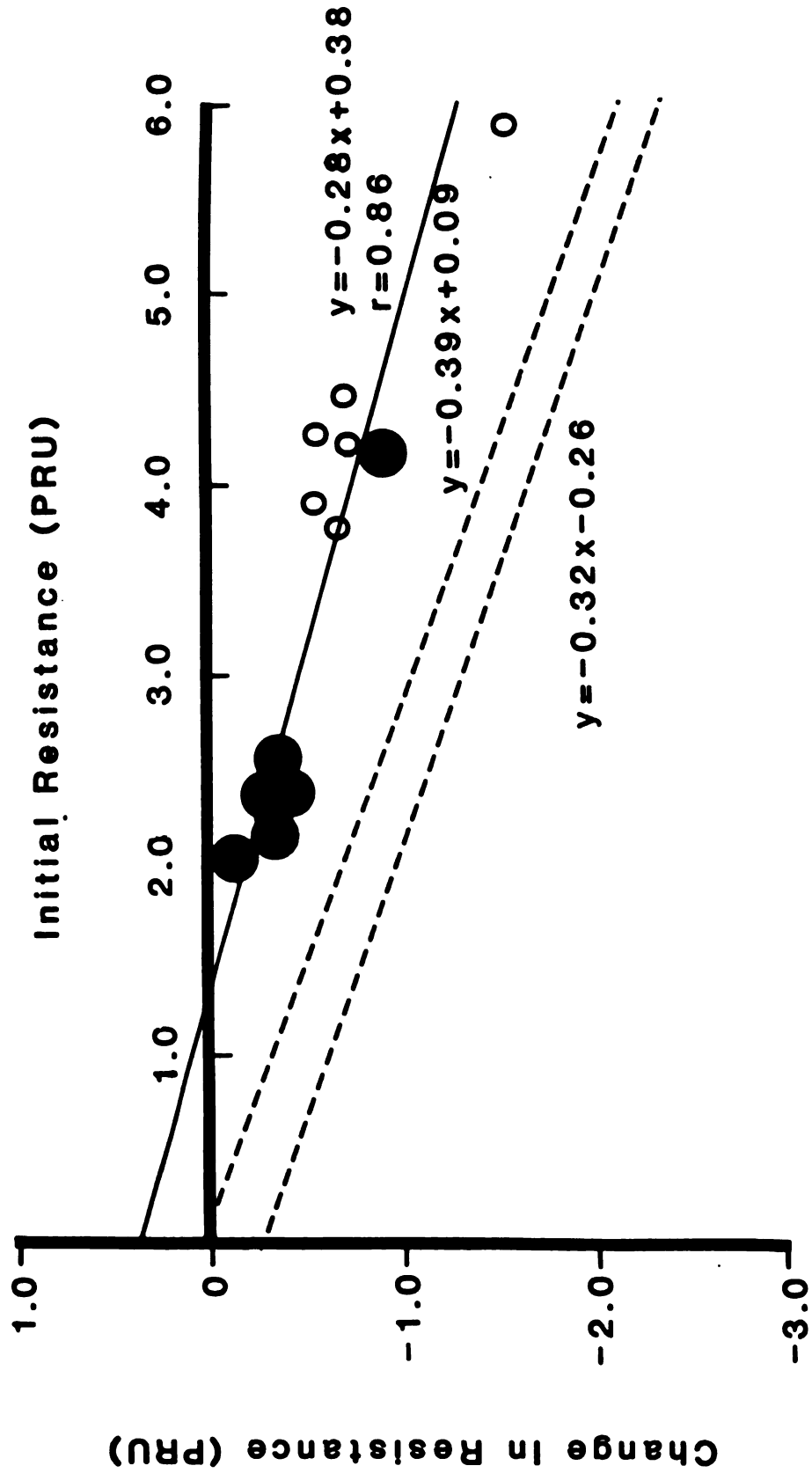
Lumen Content	Saline	Food	Difference	% Difference
<u>Before angiotensin II¹</u>				
Blood Flow	46.8±5.0	56.1±5.6	9.3±1.7*	20.8±3.5*
Resistance	2.60±0.32	2.17±0.22	-0.43±0.10*	-15.5±2.2*
ΔAVO ₂	4.0±0.6	3.8±0.5	-0.2±0.1	
VO ₂	1.77±0.12	2.03±0.17	0.26±0.08*	14.6±3.5*
<u>During angiotensin II¹</u>				
Blood Flow	27.8±1.9†	33.5±1.0†	5.7±0.7*†	20.8±3.0*
Resistance	4.41±0.31†	3.65±0.14†	-0.76±0.18*†	-16.3±2.5*
ΔAVO ₂	5.9±0.6*	5.5±0.6*	-0.4±0.1*	
VO ₂	1.60±0.15	1.81±0.17†	0.21±0.08*	13.2±5.0*

¹ N = 6; Values are mean ± SEM; Blood flow in ml/min/100 gm; Resistance in PRU; ΔAVO₂ in ml O₂/100 ml; VO₂ in ml O₂/min/100 gm

* p < 0.05

† p < 0.05 relative to the corresponding value before infusion

Figure 7. Relationship between initial resistance and the change in resistance due to food in the jejunum. Those segments treated with angiotensin II are denoted by open circles (N=6), untreated segments by closed circles (N=6). The regression line for the angiotensin series (solid line) is significantly different from those from segments treated either intraarterially or intravenously (broken line) with a cyclooxygenase inhibitor ($p < 0.05$). The cyclooxygenase inhibitor data are reproduced from Figures 5 and 6.



although initial resistance does play a role in determining the jejunal vascular response to food, the enhancement of the food-induced hyperemia following prostaglandin synthesis inhibition is independent of the associated increase in vascular resistance.

Although the increase in vascular resistance per se does not appear to account for the enhancement of the food-induced hyperemia by the cyclooxygenase inhibitors, it is possible that the decrease in resting blood flow produces a change in the rate of metabolism or causes a shift from aerobic to anaerobic metabolism. This then may indirectly alter the vascular response to food. Therefore, oxygen consumption and glucose, lactic acid, and pyruvic acid metabolism were measured at rest and with food in the lumen both before and after mefenamic acid infusion in order to determine its effects on oxidative and anaerobic metabolism

As seen in Table 6, the presence of food in the lumen of the jejunum elicits an increase in both oxygen consumption ($+0.23 \pm 0.07$ ml O_2 /min/100 gm) and blood flow (6.4 ± 1.6 ml/min/100 gm) with no change in the arterial-venous oxygen content difference. The intravenous infusion of mefenamic acid significantly reduced resting blood flow from 43.2 ± 4.5 ml/min/100 gm to 20.8 ± 1.7 ml/min/100 gm and increased the arterial-venous oxygen content difference from 3.9 ± 0.4 ml O_2 /100 ml to 7.2 ± 0.4 ml O_2 /100 ml. There was no significant change in oxygen consumption.

The food-induced increase in both blood flow (11.7 ± 1.8 ml/min/100 gm) and oxygen consumption (0.48 ± 0.10 ml O_2 /min/100 gm) after mefenamic acid infusion were significantly greater than before infusion. There was also a significant decrease in the arterial-venous

Table 6. Mean venous outflows, vascular resistances, arterial-venous oxygen content difference and oxygen consumption from jejunal segments perfused with normal saline or food before and after intravenous infusion of mefenamic acid.

<u>Lumen Content</u>	<u>Saline</u>	<u>Food</u>	<u>Difference</u>	<u>% Difference</u>
<u>Before mefenamic acid¹</u>				
Blood Flow	43.2±4.5	49.6±5.4	6.4±1.6*	14.8±3.5*
Resistance	2.78±0.17	2.43±0.18	-0.35±0.07*	-12.7±2.6*
ΔAVO ₂	3.9±0.4	3.9±0.4	0.0±0.1	
VO ₂	1.63±0.14	1.86±0.16	0.23±0.07*	14.2±4.0*
<u>After mefenamic acid¹</u>				
Blood Flow	20.8±1.7†	32.5±3.3†	11.7±1.8*†	55.4±6.1*†
Resistance	6.54±0.64†	4.20±0.41†	-2.34±0.32*†	-35.6±2.8*†
ΔAVO ₂	7.2±0.4†	6.1±0.4†	-1.1±0.2*†	
VO ₂	1.48±0.13	1.95±0.19	0.48±.10*†	31.5±6.0*†

¹ N = 8; values are means ± SEM. Blood flow in ml/min/100 gm; resistance in PRU; ΔAVO₂ in ml O₂/100 ml;

VO₂ in ml O₂/min/100 gm

* p < 0.05

† p < 0.05 relative to the corresponding value before infusion

oxygen content difference (-1.1 ± 0.2 ml/min/100 gm). The changes in blood flow and oxygen consumption were linearly correlated both before and after mefenamic acid infusion. The equation for the regression line determined from all the data points is indicated in Figure 8. The individual regression equations for the response prior to infusion ($y = 18.2X + 2.16$; $r = 0.77$) and after infusion ($y = 16.0X + 4.10$; $r = 0.89$) are not significantly different.

The jejunal metabolic response to food was also tested before and during the intraarterial infusion of angiotensin II. The food-induced increases in jejunal blood flow and oxygen consumption prior to angiotensin II infusion were 9.3 ± 1.7 ml/min/100 gm and 0.26 ± 0.08 ml O_2 /min/100 gm respectively (Table 5). During angiotensin II infusion, resting blood flow decreased from 46.8 ± 5.0 ml/min/100 gm to 27.8 ± 1.9 ml/min/100 gm, but oxygen consumption was not significantly changed. There was a significant increase in the arterial-venous oxygen content difference from 4.0 ± 0.6 ml O_2 /100 ml to 5.9 ± 0.6 ml O_2 /100 ml. In contrast to mefenamic acid, angiotensin II did not enhance the food-induced increase in oxygen consumption. The food-induced change in blood flow during infusion, $+5.7 \pm 0.7$ ml/min/100 gm was significantly smaller than the change in flow before infusion and there was a significant decrease in the arterial-venous oxygen content difference, -0.4 ± 0.1 ml O_2 /100 ml.

The change in glucose metabolism in both the mefenamic acid and angiotensin II series of experiments are presented in tables 7 and 8. Glucose uptake and pyruvic acid and lactic acid production were determined by multiplying the blood flow in ml/min/100 gm, by the

Figure 8. Correlation between changes in jejunal blood flow and oxygen consumption elicited by predigested food in the lumen. Open circles represent measurements before mefenamic acid infusion, closed circles after infusion.

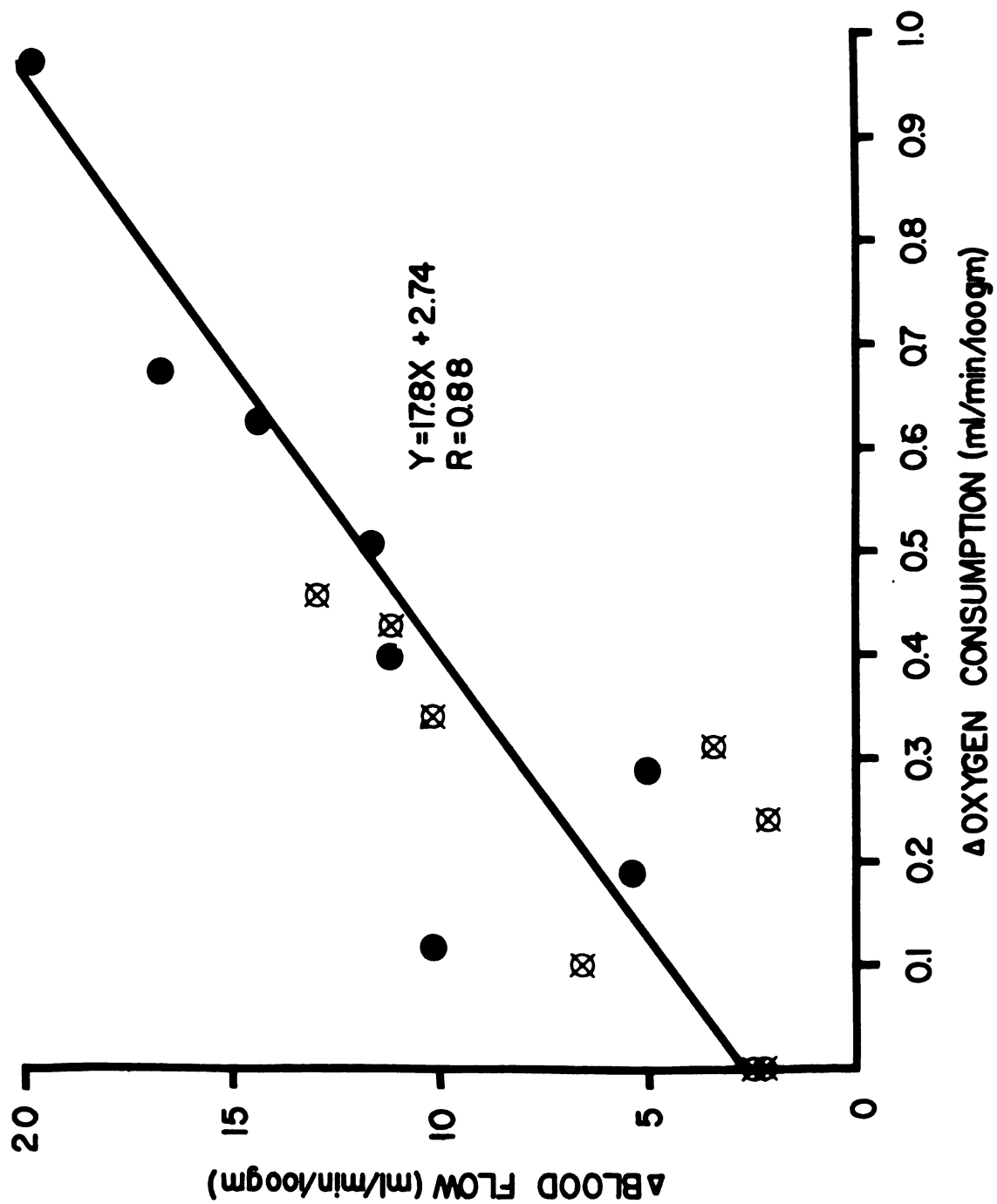


Table 7. Glucose, lactic acid and pyruvic acid metabolism of jejunal segments perfused with normal saline or food before and after intravenous mefenamic acid infusion.

Lumen Content	Before Mefenamic Acid			After Mefenamic Acid		
	Saline	Food	Difference	Saline	Food	Difference
Glucose ¹	1.82±0.34 ^a	-0.71±0.76	-2.53±0.73*	1.63±0.30 ^a	-1.88±0.73 ^{†a}	-3.51±0.80* [†]
Lactic Acid ²	-0.15±0.05 ^a	-0.70±0.11 ^a	-0.55±0.20*	-0.30±0.13 ^a	-1.55±0.24 ^{†a}	-1.25±0.32* [†]
Pyruvic Acid ³	-0.06±0.01 ^a	-0.12±0.04 ^a	-0.06±0.04	-0.04±0.01 ^a	-0.07±0.02 ^a	-0.03±0.03
L/P Arterial ⁴	36±4	34±3	-3±3	49±10	42±8	-7±8
L/P Venous ⁴	28±2	23±2	-5±3	35±7	39±7	4±4

¹ N = 6; values are mean ± SEM in mg/min/100 gm, a positive value denotes uptake

² N = 6; values as mean ± SEM in mg/min/100 gm, a negative value denotes production.

³ N = 5; values are mean ± SEM in mg/min/100 gm, a negative value denotes production

⁴ N = 5; values are mean ± SEM, L/P = lactic acid/pyruvic acid ratio

* p < 0.05.

[†] p < 0.05 relative to corresponding value before infusion

^a p < 0.05 relative to zero

Table 8. Glucose, lactic acid and pyruvic acid metabolism of jejunal segments perfused with normal saline or food before and during intra-arterial angiotensin II infusion.

Lumen Content	Before Angiotensin II			After Angiotensin II		
	Saline	Food	Difference	Saline	Food	Difference
Glucose ¹	2.10±0.35 ^a	-1.05±1.06	-3.15±1.20*	2.73±0.61 ^a	-0.14±1.16	-2.87±1.12*
Lactic Acid ²	-0.37±0.12 ^a	-1.33±0.31 ^a	-0.96±0.23*	-0.75±0.10 ^{†a}	-1.57±0.25 ^a	-0.82±0.28*
Pyruvic Acid ³	-0.06±0.02 ^a	-0.14±0.04 ^a	-0.08±0.03*	-0.04±0.01	-0.09±0.03 ^a	-0.05±0.03
L/P Arterial ⁴	26±3	23±2	3±2	22±3	23±4	1±1
L/P Venous ⁴	24±3	20±2	-3±1	20±2	21±3	1±2

¹ N = 6; values are mean ± SEM in mg/min/100 gm, a positive value denotes consumption.

² N = 6; values are mean ± SEM in mg/min/100 gm, a negative value denotes production.

³ N = 5; values are mean ± SEM in mg/min/100 gm, a negative value denotes production.

⁴ N = 5; values are mean ± SEM; L/P = Lactic acid/pyruvic acid ratio.

* p < 0.05

† p < 0.05 relative to corresponding value before infusion.

^a p < 0.05 relative to zero.

arterial-venous concentration difference of the appropriate compound, in mg/100 ml. For the glucose data, positive values represent uptake of glucose by the tissue and neative values correspond to glucose production or, more likely, glucose absorption from the lumen. Negative values for the lactic acid and pyruvic acid data indicates cellular production of these compounds.

The lactic acid/pyruvic acid ratio is determined by dividing the concentration of lactic acid in a blood sample by the concentration of pyruvic acid in that sample. This ratio can be used as an indicator of the means by which glucose is metabolized in a given tissue. A venous lactic acid/pyruvic acid ratio of 20-30 indicates that glucose is metabolized aerobically. As the amount of glucose metabolized anaerobically increases, the lactic acid/pyruvic acid ratio increases and can go as high as 140 in the anoxic heart (190). These values assume that the arterial lactic acid/pyruvic acid ratio remains at normal levels. If, however, the arterial lactic acid/pyruvic acid ratio is elevated, relative changes in the arterial and venous lactic acid/pyruvic acid ratios must be used to determine the changes in tissue glucose metabolism.

In both the mefenamic acid series (Table 7) and the angiotensin II series (Table 8), the jejunum consumed glucose and produced lactic acid and pyruvic acid when saline was present in the lumen. The venous lactic acid/pyruvic acid ratios indicate that the glucose utilized by the tissue was metabolized aerobically. When food was placed in the lumen in the mefenamic acid series, there was a significant decrease in glucose uptake, -2.53 ± 0.73 mg/min/100 gm, and an increase in lactic

acid production, -0.55 ± 0.20 mg/min/100 gm. In the angiotensin II series, the luminal presence of food also decreased glucose uptake, -3.15 ± 1.20 mg/min/100 gm, and increased lactic acid production, -0.96 ± 0.23 mg/min/100 gm. In addition, there was also a slight, but significant increase in pyruvic acid production, -0.08 ± 0.03 mg/min/100 gm and a slight decrease in the venous lactic acid/pyruvic acid ratio, -3 ± 1 .

The fact that the venous lactic acid/pyruvic acid ratios did not increase when food was placed in the lumen indicates that the lactic acid produced in both series under this condition was the by-product of aerobic glucose metabolism. Therefore, the increase in lactic acid production due to the presence of food in both series of experiments would have to have been due to an increase in glucose metabolism. The fact that glucose uptake decreased in these experiments indicates that glucose came from another source, specifically the glucose absorbed from the lumen.

The intravenous infusion of mefenamic acid did not significantly alter resting glucose uptake, lactic acid production, pyruvic acid production or the arterial or venous lactic acid/pyruvic acid ratio (Table 7). The values for the lactic acid/pyruvic acid ratios were considerably larger following mefenamic acid infusion than before. This was due to one animal in which there was a very large increase in the ratios; the remaining four animals showed little change. When food was placed in the lumen, the response was the same as before infusion with respect to pyruvic acid production and the lactic acid/pyruvic acid ratios. There was a significant increase in both lactic acid

production, -1.25 ± 0.32 mg/min/100 gm, and the decrease in glucose uptake, -3.51 ± 0.80 mg/min/100 gm. This indicates a significant increase in both glucose absorption and metabolism following mefenamic acid infusion. In one animal, the glucose was utilized primarily anaerobically.

Infusion of angiotensin II did not significantly change glucose uptake, pyruvic acid production, or the arterial or venous lactic acid/pyruvic acid ratio. There was, however, a significant rise in lactic acid production with saline in the lumen. The luminal placement of food during angiotensin II infusion significantly decreased glucose consumption and increased lactic acid production to the same extent as before; however, there was no change in the pyruvic acid production or the venous lactic acid/pyruvic acid ratio.

The data from the two series indicates that the metabolic response to food prior to pharmacological perturbation was primarily aerobic. Furthermore, decreasing resting blood flow by means of an intraarterial infusion of angiotensin II did not appreciably alter this response. Treatment of the segments with a cyclooxygenase inhibitor, however, profoundly altered the metabolic response to food. Following mefenamic acid infusion there is a significantly greater decrease in glucose uptake resulting in net glucose absorption and a significantly greater increase in lactic acid production. This increase in lactic acid production indicates an increase in glucose utilization, although it may be due in part to a shift to anaerobic glucose metabolism as is the case in one animal.

The changes in arterial and venous blood pH, pO_2 , and pCO_2 in

the mefenamic acid and angiotensin II series are indicated in Tables 9 and 10 respectively. In both series, there was a significant decrease in pO_2 across the segment during saline placement and in the angiotensin II series there was a slight increase in pCO_2 . As compared to saline, food did not significantly change the arterial-venous pO_2 difference in either series, but there was a significant increase in the arterial-venous blood pH difference. In addition, a significant arterial-venous blood pCO_2 difference developed in the mefenamic acid series when food was placed in the lumen.

Infusion of either mefenamic acid or angiotensin II decreased blood flow (Tables 5 and 6) and significantly increased the arterial-venous pO_2 difference (Tables 9 and 10). The infusion of mefenamic acid significantly increased the arterial-venous pCO_2 difference but, paradoxically, angiotensin II infusion eliminated the arterial-venous pCO_2 difference observed before infusion. Angiotensin II infusion did significantly increase the arterial-venous pH difference; this probably reflects the increase in lactic acid production (Table 10).

The presence of food in the lumen in both series of experiments following drug infusion was associated with a significant arterial-venous difference in pH, pO_2 , and pCO_2 . However, the arterial-venous pO_2 difference with food in the lumen was not significantly different than that with saline in the lumen. Following infusion of mefenamic acid, food significantly increased the arterial-venous pH difference, but did not alter the arterial-venous pCO_2 difference observed with saline in the lumen. In contrast, during angiotensin II infusion, food significantly increased the arterial-venous pCO_2

Table 9. Mean arterial and venous blood gases from jejunal segments perfused with saline or food before and after intravenous mefenamic acid infusion.

Lumen Content	Saline			Food		
	Arterial	Venous	Difference	Arterial	Venous	Difference
Before MA ¹						
ph ²	7.42±0.01	7.41±0.01	0.01±0.01	7.42±0.01	7.39±0.01	0.03±0.01 ^a
pO ₂ ³	90±5	34±2	56±4*	89±5	36±2	53±5*
pCO ₂ ³	32±2	33±1	-1±1	34±3	38±3	-4±1* ^a
After MA ¹						
ph ²	7.40±0.01	7.38±0.01	0.02±0.01	7.41±0.01	7.36±0.01 ^a	0.05±0.01* ^a
pO ₂ ³	99±5	28±1	71±4*†	98±5	31±1	67±5*†
pCO ₂ ³	34±2	37±3	-3±1*†	34±3	39±3	-5±1*

¹ MA = mefenamic acid; N = 6.

² Values are mean ±SEM.

³ Values are mean ± SEM in mm Hg.

* p < 0.05.

† p < 0.05 relative to the corresponding value before infusion.

^a p < 0.05 relative to the corresponding value with saline.

Table 10. Mean arterial and venous blood gases from jejunal segments perfused with saline or food before and during intra-arterial angiotensin II infusion.

Lumen Content	Saline			Food		
	Arterial	Venous	Difference	Arterial	Venous	Difference
Before A II ¹						
ph ²	7.39±0.01	7.38±0.01	0.01±0.01	7.39±0.01	7.36±0.01 ^a	0.03±0.01 ^a
pO ₂ ³	80±5	40±2	40±4	81±6	42±2	39±4
pCO ₂ ³	33±1	36±1	-3±1*	33±1	37±1	-4±1*
During A II ¹						
ph ²	7.40±0.01	7.37±0.01	0.03±0.01*†	7.40±0.01	7.36±0.01	0.04±0.01*
pO ₂ ³	87±6	39±2	48±5*†	88±7	40±2	48±5*†
pCO ₂ ³	33±1	33±1	0±1†	31±1	35±1	-4±1 ^a

¹ AII = angiotensin II, N = 5.

² Values are mean ± SEM.

³ Values are mean ± SEM in mm Hg.

* p < 0.05.

† p < 0.05 relative to corresponding value before infusion.

^a p < 0.05 relative to corresponding value with saline.

difference without altering the arterial-venous pH difference.

The changes in arterial and venous blood gases in these two experiments are complex. The essential data is that the decrease in resting blood flow due to drug infusion in both series of experiments was associated with an increase in the arterial-venous pO_2 difference. The presence of food in the lumen did not significantly alter the arterial-venous pO_2 difference in either series either before or after drug infusion. When food was present in the lumen, there were significant differences in arterial-venous pH, pO_2 and pCO_2 .

The effects of cyclooxygenase inhibitor infusion on jejunal motility are indicated in Table 11. The data presented in this table were derived from lumen pressure recordings from the segments in series three and from a series of experiments in which the effects of intravenous infusion of the cyclooxygenase inhibitors and their carriers on blood flow and motility were studied in isolated short jejunal segments. The blood flow data from this series has not been presented as it is not different from those in the series already included in this thesis.

The motility data are presented in terms of contraction frequency, basal lumen pressure and mean peak pressure. Of the three, only mean peak pressure was significantly altered, and only after infusion of mefenamic acid or indomethacin. The magnitude of lumen pressure when food was in the lumen was not significantly different from that with saline in the lumen.

Table 11. Mean frequencies, peak pressures and basal lumen pressures of jejunal segments with food or saline before or after infusion of cyclooxygenase inhibitors.

Lumen Content	Test Segment			Control Segment		
	Before Cyclooxygenase inhibitor ¹	Peak Pressure ³	Basal Pressure ⁴	Before carrier infusion ²	Peak Pressure ³	Basal Pressure ⁴
Saline	9±1	1.0±0.2	3.1±0.5	10±1	1.3±0.4	2.8±0.6
	9±1	1.9±0.9	3.5±0.4	11±1	1.8±0.4	4.0±1.5
Food	10±1	4.5±1.0*	3.6±0.6	10±1	2.0±0.8	3.5±0.7
	10±1	8.0±3.0*	4.5±0.7	10±1	2.5±0.7	4.2±0.8

¹ CI = cyclooxygenase inhibitor; N = 29

² N = 20.

³ Values are mean ± SEM.

⁴ Values are mean ± SEM in mm Hg.

* p < 0.05 relative to the corresponding value before infusion.

DISCUSSION

The pattern of the postprandial intestinal hyperemia in man (31, 39, 121, 137), subhuman primates (180), and dogs (28, 36, 37, 76, 78, 97, 178, 179) is well documented. The studies in conscious animals all point to a localization of the hyperemia in those organs one would expect to be functionally and metabolically active during the digestion and absorption of the meal. Within the small intestine, studies in anesthetized dogs indicate that the hyperemia is confined to the mucosal layer of those areas exposed to chyme (42, 43, 45, 78, 109, 113).

The stimulus for this vascular response in the small intestine appears to be the products of food digestion (45, 112, 113). However, the mechanism by which these chemicals induce the hyperemia is not clear, nor is it clear what function the hyperemia serves. One might expect that the increased flow serves to increase oxygen delivery in the face of an increase in oxygen demand. Indeed, there is an increase in both oxygen consumption and blood flow when digested food (164), digested food plus bile (46, 140, 162), glucose (110, 144, 158, 175), glucose plus bile (46, 110, 140, 163), or oleic acid plus bile (140) are placed in the lumen of the small intestine. Furthermore, there is a significant correlation between the percent change in oxygen consumption and the percent change in blood flow when digested food plus bile is placed in the lumen (164). However, bile, which does not change blood flow when placed in the jejunal lumen, enhances the hyperemic effect of glucose without altering the associated increase in oxygen consumption (46, 110).

Fara et al (61, 62) have suggested that cholecystokinin mediates the feline intestinal vascular response to food. The authors based this conclusion on the results of a cross-circulation study in which corn oil, L-phenylalanine, or acid were placed in the lumen of the duodenum of a donor cat and an intestinal vasodilation occurred in the recipient cat. This action as well as the accompanying changes in oxygen consumption, pancreatic enzyme output, gall bladder pressure and the volume of pancreatic and biliary flow in the donor cat were mimicked by intravenous infusion of CCK. The authors also suggested that the vasoactivity of CCK was related to a direct stimulation of metabolism as it did not dilate mesenteric artery strips in vitro.

Recently, Siregar and Chou (162) have proposed that histamine plays an important role in the vascular and metabolic response of the small intestine to food. They found that blockade of H-1 receptors with tripelenamine significantly reduced the food-induced hyperemia and increase in oxygen consumption. These findings do not necessarily contradict those of Fara et al (61, 62). There may be species-related differences in the vascular beds, or it may be that the regulatory mechanisms are complex and the disruption of any one step would have significant consequences. In either case, it appears that the release of endogenous chemicals may be important in the regulation of the postprandial intestinal hyperemia.

One class of compounds which are present in all areas of the gastrointestinal tract but which have not been studied in relation to the postprandial hyperemia are the prostaglandins. The prostaglandins have been implicated in the regulation of resting intestinal blood flow

(25, 77, 138, 153) and motility (153) as well as gastric blood flow and secretory activity (11, 41, 103, 149, 165, 167) and pancreatic secretion (107). Therefore, the cyclooxygenase inhibitors indomethacin and mefenamic acid were infused intravenously and intraarterially in this study in an attempt to determine what role, if any, prostaglandins play in the regulation of the postprandial intestinal hyperemia. In series 1, the intravenous infusion of either indomethacin or mefenamic acid reduced resting blood flow 30% (Table 1). Infusion of the carrier solution did not significantly change resting blood flow in series 2 (Table 1). This reduction in flow is similar to that reported by Bill (25) in rabbits, Goeffrey and Williamson (77) in dogs, and Nowak (138) in humans, but considerably less than that observed in cats by Sanders and Ross (153). Blood pressure in this series of experiments remained constant; therefore, resting vascular resistance increased significantly following infusion of the cyclooxygenase inhibitors (Table 2).

The food-induced jejunal hyperemia more than doubled in those segments treated with indomethacin or mefenamic acid (Table 1) and there was a five-fold increase in the food-induced decrease in resistance (Table 2). In the control series, the jejunal vascular response to food before infusion of the carrier was similar in magnitude to that in the test series. There was no significant change in the food-induced jejunal hyperemia following intravenous infusion of the carrier solution (Table 1), nor was there a significant change in the food-induced decrease in vascular resistance (Table 2).

In series 3, the effects of intraarterial infusion of the cyclooxygenase inhibitors and their carrier solutions were studied in

paired isolated jejunal segments. As seen in Tables 3 and 4, both the resting blood flows and the vascular responses to food in the two segments were nearly identical prior to infusion. Infusion of both the solutions significantly reduced resting blood flow and increased vascular resistance. However, the decrease in blood flow in the control segment following infusion of the carrier solution was significantly less than that in the test segment and the resting vascular resistance was significantly higher in the test segment.

The decrease in blood flow in the control segment may have been due to the prolonged infusion of a high pH solution ($\text{pH} = 8.4 - 8.6$) or simply the gradual increase in resistance over time usually seen in isolated intestinal preparations. In either case, it is not due to contamination of the control segment with cyclooxygenase inhibitors, as the total venous outflow collected from the treated segment during infusion was discarded and replaced with blood from a donor animal.

The increase in jejunal blood flow due to food doubled following intraarterial infusion of indomethacin or mefenamic acid, but there was no significant change in the blood flow response in the control segment. There was a significant increase in the food-induced decrease in vascular resistance in the control segment after carrier infusion but this was much smaller than that seen in the test segment. Thus, the data from series 1, 2, and 3 indicate that mefenamic acid and indomethacin significantly reduce resting blood flow and enhance the food-induced jejunal hyperemia. Furthermore, as the effects of the two drugs are the same whether infused intraarterially or intravenously, their site of action must be local rather than systemic.

Meyers and Honig (131) have shown that in skeletal muscle the vascular response to a dilator increases as initial resistance increases. A similar conclusion was reached by Granger and Norris (82) with regard to the intestinal circulation. They reported that vascular sensitivity, defined as the ratio of percent change in blood flow to percent change in oxygen consumption, increased as resting blood flow decreased. Therefore, we examined the relationship between initial resistance and the change in resistance due to food in series 1, 2, and 3 in order to determine if the enhancement of the hyperemia could be attributed simply to the decrease in resting blood flow.

Figures 5 and 6 indicate that in the first three series of experiments there was a significant correlation between initial resistance and the change in resistance due to food. Regression analysis indicates, however, that the relationship in the segments treated with the cyclooxygenase inhibitors was different from that in the untreated segments. As an additional check, the data from the treated segments in this preparation were compared with similar data from segments which had been treated with angiotensin II to produce an increase in initial resistance. As seen in Figure 7, the regression line for the angiotensin II data is similar to the regression lines for the untreated segments in Figures 5 and 6.

Therefore, the enhancement of the food-induced jejunal hyperemia following cyclooxygenase inhibitor infusion is not due solely to the accompanying increase in initial resistance. It is possible, however, that the decrease in resting blood flow following infusion of indomethacin or mefenamic acid altered the resting metabolic rate or

caused a shift in metabolism from aerobic to a combination of aerobic and anaerobic metabolism. It does not seem likely that this contributed to the response in the series in which the cyclooxygenase inhibitors were infused intraarterially. In that series, the resting blood flow following infusion of the carrier solution was very close to that in the test segment and yet the vascular response to food was enhanced only in the treated segment (Table 3). Nevertheless, the metabolic component of the jejunal response to food can play an important role in regulating the vascular response and must be examined.

In series 4, an attempt was made to determine the relative contributions of oxidative and anaerobic metabolism to the postprandial intestinal hyperemia both before and after intravenous infusion of mefenamic acid. As a control, the same measurements were made in series 5 before and during infusion of angiotensin II. Angiotensin II was infused intraarterially to reduce resting blood flow to a level similar to that in the cyclooxygenase inhibitor series. Oxygen consumption was used as a measure of oxidative metabolism and the relative proportions of glucose consumption and lactic acid and pyruvic acid production were taken as indicators of the level of anaerobic metabolism.

In both the test and control series, the metabolic demands of the jejunum with saline in the lumen appear to be met by means of aerobic metabolism. The resting oxygen consumption in both series of experiments (Tables 5 and 6) falls within the range of values reported by other authors (62, 140, 144, 158, 163, 164, 175, 184) and the venous pO_2 is not excessively low when compared to arterial pO_2 (Tables 9 and 10.) The resting glucose uptake and pyruvic and lactic acid

production of the segments are significantly different from zero in both series of experiments. The amount of glucose consumed is small, which agrees with the values observed by Sit et al (163), and supports the work done by Lester and Grim (115) in in vitro jejunal mucosal preparations. The authors reported that lipids were the primary substrate of cellular metabolism (115). The glucose that is consumed is apparently metabolized aerobically as the venous lactic acid/pyruvic acid ratio is low (190).

The presence of food in the lumen of the jejunum significantly altered most of these variables. The percent increase in oxygen consumption when food was perfused through the lumen was the same in both series of experiments before pharmacological perturbation (Tables 5 and 6). This increase in oxygen demand was met by an increase in delivery in both series rather than an increase in extraction. It is not surprising, therefore, to see that the steady state arterial-venous pO_2 difference was not significantly changed when the lumen content was changed from saline to food. There was a slight decrease in venous pH in both series, and an increase in venous pCO_2 in the mefenamic acid series (Tables 9 and 10).

The presence of food in the lumen significantly reduced the uptake of arterial glucose in both series of experiments and increased lactic acid production (Tables 7 and 8). Pyruvic acid production increased slightly in the angiotensin II series (Table 8), but did not change in the mefenamic acid series (Table 7). In both series, there was no significant increase in the venous lactic acid/pyruvic acid ratio.

The fact that lactic acid production increased under aerobic

conditions while glucose uptake apparently decreased would indicate that some of the glucose and fructose present in the food solution was absorbed and utilized as metabolic substrate within the segments. The concentration of free glucose in the digested food plus bile solution is approximately 5 mg/100 ml. Balint et al (10) have reported a difference between glucose absorbed from the lumen and glucose transported in the venous blood of approximately 3 mg/min when isotonic glucose was placed in the lumen. This represented approximately 30 % of the total absorbed glucose.

In summary, the metabolic state of the jejunum with saline in the lumen can be characterized as aerobic with a low level of glucose consumption. Perfusion of food through the lumen results in a moderate rise in oxygen consumption (14 %) which is met by an increase in delivery rather than extraction. There is a significant decrease in glucose uptake and an increase in aerobic lactic acid production. This is probably due to the absorption and utilization of carbohydrate from the lumen similar to that reported in vitro by Lester and Grim (115).

One hour after intravenous infusion of mefenamic acid, there were no significant changes in glucose uptake, oxygen consumption or lactic acid and pyruvic acid production. There were no significant differences in the arterial and venous lactic acid/pyruvic acid ratios either. There were significant increases in the arterial venous pO_2 and pCO_2 differences compared to control, and a decrease in resting blood flow.

Perfusion of food through the lumen following mefenamic acid infusion resulted in an increase in oxygen consumption which was twice that before infusion. This was accompanied by an enhanced hyperemic

response and a significant decrease in the arterial venous oxygen content difference. The food-induced decrease in glucose uptake was significantly greater following mefenamic acid infusion than before, and there was a net absorption of glucose. There were no significant changes in either pyruvic acid production or the arterial and venous lactic/pyruvic acid ratios, but the increase in lactic acid production was significantly greater than the food-induced increase prior to infusion. The arterial venous pO_2 and pCO_2 differences were not significantly increased when food was placed in the lumen after infusion but there was a significant decrease in venous pH.

The data indicate that there is a considerable increase in the metabolic response of the jejunum to food after the intravenous infusion of mefenamic acid. There is a significantly greater increase in oxygen consumption and glucose absorption; glucose metabolism and lactic acid production are also enhanced. All of these factors could contribute to the associated enhancement of the hyperemic response to food. Lactic acid is a vasodilator and its enhanced production when food is placed in the lumen following mefenamic acid infusion could directly contribute to the hyperemic response.

As Figure 8 indicates, there is a significant correlation between the change in blood flow when food is placed in the lumen and the change in oxygen consumption both before and after mefenamic acid infusion. This does not necessarily indicate a causative relationship, however, as oxygen consumption is calculated as the product of blood flow and the arterial venous oxygen content difference and may be expected to be correlated to some degree with either one.

This enhancement of the food-induced increase in oxygen consumption could be due, in part, to the increase in glucose absorption and metabolism following mefenamic acid infusion. Sit et al (163) have shown that the increase in oxygen consumption seen when glucose is placed in the jejunal lumen is related to both glucose absorption and metabolism. When 3-O-methyl-glucose (an analogue which is not metabolized) is placed in the lumen, both the increase in oxygen consumption and the jejunal hyperemia are significantly less than that seen with glucose. There is neither an increase in blood flow nor in oxygen consumption when 2-deoxy-glucose (a nonabsorbable analogue) is placed in the lumen.

In the control series, the reduction of resting blood flow by means of intraarterial angiotensin II infusion did not significantly alter either the vascular response, when expressed in terms of the percent change from control, or the metabolic response of the jejunum to food. There was a significant increase in lactic acid production with saline in the lumen during angiotensin II infusion; however, there were no significant differences in the food-induced changes in glucose uptake, lactic acid production, or the arterial lactic acid/pyruvic acid ratio. There were minor changes in the food-induced increase in pyruvic acid production and decrease in venous lactic acid/pyruvic acid ratio.

As the data in Table 11 indicate, the cyclooxygenase inhibitors stimulate intestinal motility as measured with a lumen pressure recording. There is no truly accurate method for the measurement of motility, but this technique produces the most representative data. One of the disadvantages of the technique, however, is that it is more

sensitive to changes in circular muscle activity then to longitudinal muscle activity. Visual observation of the segments after cyclooxygenase inhibitor infusion indicates that there is a pronounced relaxation of the longitudinal muscle layer as well as an increase in phasic circular muscle activity. This is indicated by a considerable elongation of the segment and frequent segmental contractions.

In this study, as well as in other studies in this laboratory, the placement of food in the lumen of the segment may cause a transient increase in motility but this ends within a few minutes and the segment remains quiescent. This pattern is not altered when resting motility is stimulated by cyclooxygenase inhibitor infusion, that is, there is no significant change in intestinal motility when food is placed in the lumen following infusion of indomethacin or mefenamic acid. It is unlikely, therefore, that the enhanced increase in metabolic activity due to food is due directly to an increase in intestinal motor activity.

There is no direct evidence that infusion of the cyclooxygenase inhibitors blocked prostaglandin synthesis in these experiments. An attempt was made to measure prostaglandin synthesis by examining the levels of prostaglandin E_2 , prostaglandin F_{2a} and thromboxane B_2 in the venous effluent of the segments under study. The data obtained was not reliable due to extreme variability within sample sets and has not been presented here.

The fact that resting blood flow decreased and motility increased following infusion of the inhibitors in a manner similar to that observed by other investigators in the field, however, does provide some indirect support. The data indicate, then, that inhibition of

prostaglandin synthesis results in a significant increase in the metabolic and vascular response of the jejunum to the presence of digested food plus bile in the lumen. Some ideas on the stimulus for release and possible mechanism(s) of action are provided in the following discussion.

Prostaglandin synthesis could be initiated by the absorption of prostaglandin precursors from the nutrient solution or by stimulation of phospholipase A_2 activity within the cell. Both linoleic and linolenic acid are present in vegetable oil and could possibly be converted to arachadonic acid or di-homo- γ -linolenic acid which are substrates for prostaglandin synthesis (176). However, studies in rats (91) and humans (152) indicate that only a small percentage of these compounds are so utilized.

Stimulation of phospholipase A_2 activity produces a turnover of cellular phospholipids and makes stored arachadonic acid available for prostaglandin synthesis. Phospholipase A_2 activity can be stimulated by slight chemical or mechanical stimulation of the cell membrane (146) and can therefore be activated by a variety of stimuli. In the jejunum, the stimuli could be mechanical compression due to smooth muscle contractions, nutrients absorbed from the lumen, or chemicals released from intestinal tissues.

The prostaglandins released appear to inhibit the increase in metabolic activity when food is placed in the lumen. As the change in blood flow due to food is correlated with the change in oxygen consumption, the data would suggest that metabolism is the determinant of blood flow in the jejunal response to food. If that were the case,

however, one would expect to see some increase in oxygen extraction in the steady state. That is to say, there must be an "error signal" to initiate and maintain the hyperemia.

In actuality, there is no increase in oxygen extraction or decrease in venous pO_2 when food is placed in the lumen before infusion of the cyclooxygenase inhibitor. After infusion of mefenamic acid, oxygen extraction is significantly reduced when the segment is exposed to food. While it is possible that the techniques used in this study to measure oxygen extraction and venous pO_2 are not sensitive enough to detect a small change in these variables when food is placed in the lumen before infusion, there is no question that the increase in blood flow after infusion is greater than that required to meet the increased metabolic demand. Therefore, it may be that oxygen consumption does play a role in determining the hyperemic response, but other factors may contribute as well. One possibility is a direct vasodilator effect of lactic acid.

The mechanism for the increase in the metabolic response is not certain, but at least two possibilities exist. The first is that the enhanced motility following cyclooxygenase inhibition increased mixing in the segments and thereby increased absorption of nutrients. Another, more direct mechanism, would be the lack of prostaglandin inhibition of glucose absorption. Several authors have shown that the E and F prostaglandins inhibit glucose absorption in the small intestine (10, 50, 126, 128). Therefore, the enhanced absorption of glucose in this study could have contributed directly to the enhancement of oxidative metabolism when food was placed in the lumen following mefenamic acid

infusion.

If the enhanced increase in metabolism due to food following mefenamic acid infusion were not responsible for the enhanced jejunal hyperemia, then the prostaglandins would have to have had a direct vascular effect or would have to have interacted with substances which do. There is no doubt that prostaglandins are vasoactive in the intestinal circulation, but the decrease in flow following cyclooxygenase inhibitor infusion would indicate that dilator prostaglandins are released under resting conditions. This is probably prostaglandin E_2 , as the motor activity following cyclooxygenase inhibition indicates that the prostaglandin released normally inhibits circular muscle and stimulates longitudinal muscle activity.

Even though the prostaglandin released at rest is a dilator, it is possible that the presence of food in the lumen stimulates release of a constrictor prostaglandin which acts as part of a negative feedback loop to limit the food-induced hyperemia. If the prostaglandin released were prostaglandin F_{2a} , it could also contribute to the enhancement of the metabolic response as prostaglandin F_{2a} also inhibits glucose absorption. Another possibility is that prostaglandins act as a negative feedback signal in a more sophisticated control system.

Siregar (162) has shown that histamine is important in the metabolic and vascular response of the small intestine to food. This activity appears to be mediated by the H-1 receptor as blockade of that receptor with tripeleamine significantly reduces both aspects of the response. Prostaglandins have been proposed as histamine antagonists in the stomach by several authors (11, 56, 149, 167) and have been shown to

mediate histamine tachyphylaxis in esophageal smooth muscle (5, 6, 108).

In this light, it is of particular interest to note that histamine stimulated prostaglandin release in the rabbit ear is mediated by H-1 receptors also (101). This release is due to an H-1 mediated increase in phospholipase A_2 activity as evidenced by an increase in arachadonic acid release following histamine infusion in this bed (101) and in the brain (171). Therefore, it is possible that the effects of H-1 receptor stimulation on the postprandial hyperemia are limited by the H-1 receptor mediated release of prostaglandins. That is to say, the stimulation of H-1 receptors by endogenously released histamine may also stimulate prostaglandin synthesis and release. This may in turn limit the action of histamine as the prostaglandins released by H-1 receptor stimulation may act as noncompetative inhibitors of histamine.

It is possible, then, that the presence of food in the lumen could result in the release of histamine within the wall of the jejunum. Histamine in turn would bind to both H-1 and H-2 receptors and might, in the case of the H-1 receptor, stimulate cellular metabolism and decrease vascular resistance. However, it might also stimulate prostaglandin synthesis which could result in an inhibition of metabolism and blood flow. There is no direct evidence to support this hypothesis in this study.

SUMMARY AND CONCLUSION

Intestinal blood flow increases following a meal in those regions of the intestine exposed to chyme. The mechanism of this vasodilation and its regulation are unclear. In this study, an attempt was made to determine what role, if any, the prostaglandins play in this process. The metabolic and vascular components of the jejunal response to food were characterized both before and after intravenous or intraarterial infusion of either indomethacin or mefenamic acid. These cyclooxygenase inhibitors were administered in a dose which has been shown to block prostaglandin synthesis.

1. Glucose metabolism in the resting jejunum is characterized by a low level of glucose consumption and lactic acid and pyruvic acid production. The lactic acid production appears to be due to aerobic metabolism of glucose as indicated by the venous lactic acid/pyruvic acid ratio.
2. The presence of food in the lumen of the jejunum results in a significant decrease in glucose uptake and an increase in lactic acid production. As the increase in lactic acid production occurred under aerobic conditions, this would imply that absorbed glucose is used as the substrate for glycolysis.

3. Infusion of the cyclooxygenase inhibitors significantly reduced resting blood flow compared to control. This decrease in blood flow was not of sufficient magnitude to lower resting oxygen consumption.

4. The food-induced jejunal hyperemia was significantly greater after a cyclooxygenase inhibitor infusion than before. This enhancement of the hyperemia was not due solely to an increase in initial resistance as infusion of angiotensin II at dose sufficient to increase vascular resistance to a similar level did not enhance the food-induced hyperemia.

5. The food-induced increase in jejunal oxygen consumption was also enhanced following mefenamic acid infusion. The change in blood flow due to food correlated well with the change in oxygen consumption; however, the hyperemic response following mefenamic acid infusion appears to be greater than that needed to satisfy the demand for oxygen.

6. Following mefenamic acid infusion, glucose absorption and metabolism were significantly greater with food in the lumen than before infusion. This may have contributed to the enhancement of the food-induced increase in jejunal oxygen consumption as glucose absorption and metabolism increase oxygen consumption.

7. There was a significantly greater increase in lactic acid

production when food was placed in the lumen following mefenamic acid infusion compared to the increase before infusion. This may have contributed directly to the enhanced hyperemic response to food.

8. In general, the presence of food in the lumen produced a significant decrease in venous pH, a significant increase in venous pCO_2 , and no significant change in pO_2 . The decrease in blood flow following mefenamic acid infusion resulted in a significant decrease in venous pH and pO_2 and a significant increase in venous pCO_2 . There were no further changes when food was placed in the lumen.

9. Infusion of the cyclooxygenase inhibitors stimulated intestinal motility. The increase in motility was characterized by rhythmic segmented contractions and elongation of the segment. This would indicate enhanced circular muscle activity and a decrease in longitudinal muscle tone.

10. Infusion of angiotensin II reduced resting blood flow to a level similar to that seen after cyclooxygenase inhibitor infusion. However, the decrease in blood flow per se did not significantly enhance the metabolic or vascular response of the jejunum to food.

The data indicates that prostaglandins are involved in the regulation of the postprandial intestinal hyperemia as well as resting blood flow and motility. Prostaglandins also act to limit the metabolic

activity of the jejunum when food is placed in the lumen. It is suggested that prostaglandins act as part of a negative feedback mechanism which regulates the postprandial intestinal hyperemia. It is speculated that prostaglandins interact with histamine which has been released due to the luminal presence of food.

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