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Stimulation of Colonic Blood Flow by Pentagastrin[1] (41392)

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Abstract. Pentagastrin, a synthetic gastrointestinal hormone, stimulates relative blood flow to the upper, middle, and lower third of the rat colon by two-, four-, and sixfold, respectively. Much smaller inductive effects are seen in the lung (30% increase) and kidney (62% increase), while no significant effects on relative blood flow are observed in the liver after pretreatment with pentagastrin. These effects on blood flow are consistent with pentagastrin-induced effects on DNA synthesis and benzo[α]pyrene hydroxylation activity.

Most of the work on intestinal blood flow and its control has focused on parameters affecting blood flow in the small intestine reflecting the central role of blood flow in the absorptive function of the small intestine. The area has been recently examined in an elegant review by Granger and his colleagues (1). Much less work has been focused on the large intestine, though other aspects of colonic function and regulation have been studied (2, 3). Johnson (2, 4) first reported the stimulation of colonic DNA synthesis by six injections of pentagastrin given to rats within 48 hr. Johnson and Guthrie (3) later showed that another gastrointestinal hormone, secretin, inhibits the pentagastrin stimulation of DNA synthesis in the colon. Fang and Strobel demonstrated the presence and functionality of a cytochrome *P*-450-dependent drug metabolism system in the colon (5, 6) and subsequently showed that the activity of the drug metabolism system of the colon is responsive to the gastrointestinal hormones (7, 8). Pentagastrin induction of colonic drug metabolizing activities was shown to require active protein synthesis for the two- to fourfold induction of hydroxylation activities to occur (8). The present paper reports the effects of the administration of pentagastrin on the blood flow characteristics of the colon and other tissues in order to define the factors affecting responses to gastrointestinal hormones in tissues of the alimentary system, as well as other systems. The use of radiolabeled ^{86}Rb, a nonmetabolizable element, in these studies enables definition of blood flow without problems of blockage in capillaries as might be the case with labeled microspheres (9).

Materials and Methods. *Animals and treatment procedures.* Male Sprague–Dawley rats weighing from 150 to 200 g were purchased from Timco Laboratories, Houston, Texas, and maintained on Purina Lab Chow and water *ad libitum*. The rats in the control were pretreated subcutaneously with 0.9% NaCl solution, while the experimental group was pretreated with pentagastrin (250 μg/kg body wt) daily for 3 days. Optimum dosage and time ranges for pentagastrin defined in previous work were used in these experiments in order to compare results (7, 8). Each group in each experiment contained six animals. The rats were fasted overnight before the experimental design was carried out.

Experimental protocol. Rats from the control or pentagastrin-pretreated groups were anesthetized with pentobarbital (50 mg per kg body wt) by intraperitoneal injection. The anesthetized rats were then carefully laparotomized in order to minimize bleeding and a $^{86}RbCl$ (0.5 μCi/g body wt) radioisotopic tracer was introduced into

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the circulation by injection through the left ventricle. The rubidium chloride was prepared in an aqueous solution such that the radioactivity was 1 mCi of ^{86}Rb/ml. After a 1-min equilibration period, samples of liver, lung, kidney, and the upper, middle, and lower parts of the colon were collected and wet weights obtained using preweighed counting containers. The content of ^{86}Rb in each sample was determined by counting each sample for 1 min with a Packard Autogamma Counter. The relative blood flow into each tissue was calculated according to the technique described by Setchell and Linzell (9):

$$\text{Relative blood flow} = \frac{\text{isotope content/g tissue}}{\text{dose of isotope injected/g body wt}}.$$

Each organ or tissue was sampled at least in triplicate and at least six groups of organs were used in these experiments. The isotope content of the tissues is stable between 30 and 90 sec after injection (variance between these time points is within or less than the interindividual variance for each time point).

Materials. Pentagastrin was obtained as a gift from Ayerst Laboratories, New York, New York. ^{86}Rubidium was purchased from Amersham Corporation, Arlington Heights, Illinois, as ^{86}RbCl in aqueous solution. Nembutol was obtained from Abbott Laboratories, North Chicago, Illinois.

Results. The effects of pentagastrin on relative blood flow of the three major organs of the rat are shown in Table I. A synthetic gastrointestinal hormone, pentagastrin, does not significantly alter relative blood flow to the liver. It does, however, produce minor changes in the blood flow to the lung and kidney. Pentagastrin pretreatment brings about a 30% increase in relative blood flow to the lung and a 62% increase in flow to the kidney. These effects, while significant, are small in comparison to the response of the colon, which is part of the gastrointestinal tract, to pentagastrin.

As shown in Table II, the effects of pentagastrin on the colon are much more pronounced than the effects on any tissue described in Table I. Pretreatment with pentagastrin causes a 235% increase in relative blood flow to the upper third of the rat colon (that portion nearest the cecum). The middle third of the colon shows a 425% increase in flow, while the lower third (that portion nearest the anus) shows a 565% increase in relative blood flow. Thus, these data show a dramatic and specific effect of pentagastrin on blood flow in the colon in comparison with other organs of the body.

Discussion. The dosage of pentagastrin used to elicit the blood flow effects presented here corresponds to the dosage giving the maximal increase in mucosal DNA synthesis as demonstrated by Johnson and Guthrie (3) and the maximal induction of benzo[α]pyrene hydroxylation activity as shown by Fang and Strobel (8). Further, the effects of pentagastrin on blood flow are much more pronounced in the colon than in other tissues. This specificity for the colon holds true for other parameters as well. Pentagastrin, as well as other gastrointestinal hormones, only slightly affects benzo[α]pyrene hydroxylation activity in the liver, whereas, the induction in the colon is 250% of control activity (8). Likewise, penta-

TABLE I. RELATIVE BLOOD FLOW IN RAT LIVER, LUNG, AND KIDNEY

Treatment group	Relative blood flow (ml/min)[a]		
	Liver	Lung	Kidney
Saline	2.13 ± 0.3	5.30 ± 0.24	1.81 ± 0.17
Pentagastrin[b]	2.27 ± 0.24	6.89 ± 0.59*	2.93 ± 0.20**

[a] Means ± SEM, $N = 6$.
[b] 250 μg/kg body weight daily for 3 days.
* Significantly different from control, $P < 0.02$ by Student's t test.
** Significantly different from control, $P < 0.01$, by Student's t test.

TABLE II. RELATIVE BLOOD FLOW IN REGIONS OF RAT COLON

Pretreatment group	Relative blood flow (ml/min)[a]		
	Upper colon[b]	Middle colon	Lower colon[c]
Saline	0.51 ± 0.11	0.38 ± 0.03	0.52 ± 0.07
Pentagastrin	1.20 ± 0.20*	1.62 ± 0.17**	2.92 ± 0.38***

[a] Mean ± SEM, $N = 6$.
[b] Region of colon nearest cecum.
[c] Region of colon nearest anus.
* Significantly different from control, $P < 0.03$ by Student's t test.
** Significantly different from control, $P < 0.01$, by Student's t test.
*** Significantly different from control, $P < 0.001$, by Student's t test.

gastrin does not stimulate trophic action in the kidneys or liver (4), while it does prompt marked trophic responses in the colon as judged by protein and DNA synthesis experiments (3, 4).

Clearly, the reported increases in both benzo[α]pyrene hydroxylation and DNA synthesis prompted by pentagastrin (3, 8) could be related to an effect on relative blood flow, i.e., an increased presentation of substrate be it carcinogen or thymine to the colon. On the other hand, the inhibition of pentagastrin effects on benzo[α]pyrene hydroxylation by cycloheximide demonstrates the requirement of active protein synthesis for this response to occur (8). Thus, it seems that pentagastrin has at least two levels of effects: stimulation of relative blood flow to the colon and induction of enzyme activities (e.g., DNA synthesis, benzo[α]pyrene hydroxylation).

It has been shown through epidemiological studies that most colon tumors are located in the descending and sigmoid colon areas (10). Additionally, studies on the induction of colonic tumors in experimental animals treated with azoxymethane (11, 12) have shown a gradient of tumors in the large bowel with the greatest concentration localized in that portion of the colon nearest the anus. These observations correlate well with our present data showing a four- to sixfold increase in relative blood flow to the lower two-thirds of the colon in response to treatment with pentagastrin. Thus, pentagastrin might play a role in carcinogenesis by providing more substrates to the colon by increased relative capillary blood flow.

Schuurkes and Charbon (13) have reported that pentagastrin injected into a brachial vein of the dog brings about a reduction of blood flow to the colon measured with flow probes on the colic branch of the caudal mesenteric artery. The results of these workers reporting blood flow to the colon, as well as other tissues of the dog, in response to pentagastrin are not in agreement with our results. The discrepancy may be due to the differences in technique which focuses on arterial flow, while our technique measures capillary blood flow, in species or in dosages or manner of injection of pentagastrin used (Schuurkes and Charbon injected 1–4096 ng/kg pentagastrin intravenously). Although any of the reasons suggested could account for the differences observed, resolution must await a direct comparison.

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