The Effect of Carcinoid Levels of Serotonin and Substance P on Hemodynamics

MICHAEL J. ZINNER, M.D., CHARLES J. YEO, M.D., BERNARD M. JAFFE, M.D.

From the Department of Surgery, Downstate Medical Center, Brooklyn, New York

Serotonin and substance P circulate in high concentrations in patients with the carcinoid syndrome. These studies were performed to evaluate the effects of intravenous infusions of serotonin and substance P to reproduce carcinoid levels of these agents on central hemodynamics, regional blood flow (using the radioactive microsphere technique), and endogenous hormone release. Serotonin did not affect mean arterial pressure but it significantly increased cardiac output, decreased systemic vascular resistance, and redistributed regional blood flow, increasing blood flow to the heart, adrenals, fundus, and antrum. Substance P significantly decreased mean arterial pressure and systemic vascular resistance, increased cardiac output, and increased blood flow to adrenal, fundus, antrum, liver, and all muscular layers of the stomach and small bowel. Neither serotonin nor substance P affected skin blood flow, nor altered circulating levels of glucose, insulin, or gastrin. Although both of these agents seem to participate in the pathogenesis of the carcinoid syndrome, our studies suggest that it is not possible to ascribe all the hemodynamic abnormalities to either.

IN 1907, OBERNDORFER PROPOSED the term "carcinoide" to describe a tumor of intestinal origin characterized by its small size, multicentricity, distinct histology, and low potential for local invasion.[1] Masson suggested that carcinoid tumors arise from the Kulchitzky cells of the intestinal mucosa, cells he considered to play an endocrine function.[2] In the early 1950s, a number of investigators described a clinical syndrome associated with argentaffin tumors of intestinal origin.[3,4] This syndrome, including cutaneous flushing, hypotension, gastrointestinal hypermotility, elevated cardiac output, bronchoconstriction, and right-sided cardiac valvular lesions, has come to be known as the carcinoid syndrome.[5] Based on Lembeck's observation that a carcinoid tumor contained high concentrations of serotonin (5-HT),[6] and reports of peripheral hyperserotoninemia[7] and increased urinary excretion of a 5-HT metabolite (5-hydroxyindole acetic acid),[8] serotonin has until recently been considered responsible for the clinical manifestations of these tumors.

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Reprint requests: Michael J. Zinner, M.D., Department of Surgery, Downstate Medical Center, Box 40, 450 Clarkson Avenue, Brooklyn, NY 11203.

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In recent years, the concepts of pathogenesis of the carcinoid tumors have broadened. Current theories favor a multihormonal view of carcinoid tumors,[9] with not only 5-HT, but also bradykinin, histamine, ACTH, and the undecapeptide substance P (SP), found in high concentrations in some carcinoid tumors.[10,11]

In the current study, we focused on 5-HT, the classic mediator of the carcinoid syndrome, and SP, a more recently proposed mediator. The simultaneous study of these two hormones is consistent with their dual brain-gut existence and their similar sites of localization in mucosal enterochromaffin (EC) cells in the mammalian gastrointestinal tract.[12,13] Furthermore, using biochemical and immunohistochemical techniques, both 5-HT and SP are found in many carcinoid tumors[14,15] and, in addition, elevated circulating concentrations of both 5-HT and SP are found in many patients with the carcinoid syndrome.[16,17]

The purpose of the current investigation was to reproduce, in conscious dogs, the elevated circulating levels of 5-HT and SP characteristic of the carcinoid syndrome. After achieving the supranormal circulating levels of 5-HT and SP, we monitored alterations in central hemodynamics, regional blood flow, and circulating hormone levels. The observations have allowed us to speculate as to the role of circulating 5-HT and SP as mediators of the carcinoid syndrome.

Methods and Materials

Hemodynamic Determinations

Under light thiopental anesthesia, twelve 19–29 kg mongrel dogs had a 7 French pigtail catheter placed via a femoral artery into the left ventricle (LV), where its position was confirmed by pressure manometry. A carotid artery was cannulated using PE 240 tubing, with the tip of the catheter left at the level of the aortic arch. A PE 360 catheter was used to cannulate the ipsilateral jugular

vein, which was adapted to fit an 8 French Seldinger introducer of the type used for percutaneous Swan-Ganz catheter insertion. All catheters were filled with heparin, tunneled subcutaneously, and the wounds closed. After a 24-hour recovery period, the conscious animals were supported in light fabric harnesses in the standing position, the cannulae retrieved, and the carotid and LV catheters connected to pressure monitoring transducers. A Swan-Ganz flow-directed catheter was positioned manometrically in the pulmonary artery via the jugular catheter in each animal. Arterial blood pressure (mmHg) was monitored via the carotid catheter. Cardiac output (l/min) was determined using a thermodilution cardiac output computer (Edwards Lab). Total systemic resistance (TSVR) was calculated as:

$$\text{TSVR} = \frac{\text{mean arterial pressure}}{\text{cardiac output}} \times 80$$

and recorded in dynes-sec/cm^5.

Quantitation of Regional Blood Flow

Regional blood flow was determined using 15 ± 5 μ radioactively labelled microspheres (3M Co., St. Paul, MN) with ^{46}Sc, ^{51}Cr, ^{85}Sr, or ^{141}Ce used in random order. At three time periods for each animal, approximately 1.5 to 2.0 × 10^6 microspheres, suspended in 10% dextran with 0.05% Tween, were vortexed and drawn into a syringe coated with 5% Tween-80, vortexed again, and injected via the LV catheter. Reference blood samples were collected from the carotid catheter for 30 seconds just prior to, during, and after the bolus microsphere injections using a constant rate withdrawal pump (Sage Co., Inc.). At the end of the experimental protocol, the animals were sacrificed using a potassium chloride bolus overdose, and the organs of interest harvested. Gastric and intestinal specimens were manually dissected into mucosa-submucosa and muscularis fractions. Multiple samples of each organ or the whole organ were weighed and placed into 12-ml polystyrene tubes for counting in a multichannel gamma spectrometer (Packard Instruments). Regional blood flow was calculated using the formula:[18]

$$\text{Regional blood flow} = \text{Regional cpm} \times \frac{\text{Reference blood flow}}{\text{Reference blood cpm}}$$

and was expressed as cc/min per 100 gr wet weight of tissue. No data were derived from tissues with less than 500 microspheres per sample. This technique has been validated in our laboratory[19,20] and others.[21,22,23] In the absence of exogenously infused hormones, blood flow data are stable over time. Portal vein blood flows were estimated as the sum of the blood flows to fundus, antrum, duodenum, jejunum, ileum, colon, spleen, and pancreas. Superior mesenteric artery blood flows were similarly estimated as the sum of the flows to the jejunum, ileum, and one-half of the flow to the duodenum, pancreas, and colon.

Experimental Protocols

After operation, recovery, and catheter retrieval, all animals received 15–20 ml/kg of intravenous normal saline over 30 minutes to assure adequate hydration. Following an additional 20-min stabilization period, a 20-min basal period was followed by a 60-min infusion period and a 20-min recovery period. During the 60-min infusion period, either serotonin (Sigma Co.) (n = 6) or substance P (Peninsula Labs) (n = 6) dissolved in normal saline (with a 1.0-ml sample of autologous dog plasma as carrier) was infused intravenously at 1.0 ml/min at doses of 26.8 μg/kg-min or 68.7 ng/kg-min, respectively. The infusate concentrations of 5-HT and SP were determined by radioimmunoassay from samples taken at the entry point of infusion tubing into each animal. To maintain consistency from previous lower dose infusions done in our laboratory, 5-HT was infused via peripheral hind-limb vein, while SP was infused via the distal port of the Swan-Ganz catheter in the peripheral pulmonary artery. This allowed for calculation of pulmonary inactivation of 5-HT and systemic inactivation of SP.

Mean arterial pressure, cardiac output, and total systemic vascular resistance were monitored at 5-min intervals. Blood samples were drawn at regular intervals into 7 ml EDTA tubes containing 0.1 ml aprotinin (Trasylol) per 1.0 ml of plasma. Arterial blood was sampled every 10 minutes during the basal period, every 5 minutes during the hormone infusions, and every 2 minutes during the recovery periods (to facilitate calculation of hormone half-life). Mixed venous blood from the right atrium, drawn through the proximal port of the Swan-Ganz catheter, was sampled every 10 minutes. Microspheres were injected once at the end of the basal period, then at 20 and 50 minutes into the hormone infusions.

Plasma Hormone Determinations

Blood samples were collected on ice, and within 30 minutes of the cessation of the infusion, were prepared for assay. Aliquots of whole blood for serotonin assay were immediately extracted by a previously described method.[24] The remainder of each sample was centrifuged at 3000 r.p.m. × 30 min at 4 C to obtain plasma specimens, which were stored at −20 C until assay. Glucose concentrations were determined by the glucose oxidase method using a Beckman Glucose Analyzer. Whole blood serotonin levels were determined by radioimmunoassay.[24] Substance P levels in extracted plasma were determined by a previously described radioimmunoassay developed

in our laboratory,[25] with the preparation of labelled tyrosine-8 substance P according to the protocol of Mroz and Leeman.[26] Insulin and gastrin levels were determined in our laboratory by previously described radioimmunoassays.[27,28] Cortisol was measured using an Amersham radioimmunoassay kit.

Statistics

Statistical analyses were performed by Student's t-test for paired data, with significance accepted at the 5% level. Results were expressed as mean ± SEM.

Results

Whole Blood Serotonin Levels During Serotonin Infusion (Fig. 1)

Basal values for whole blood 5-HT were 124 ± 11 ng/ml and 116 ± 9 ng/ml for mixed venous and arterial samples, respectively. Mixed venous 5-HT levels peaked 40 minutes into the infusion. Arterial 5-HT concentrations peaked 45 minutes into the infusions at 537 ± 153 ng/ml and remained elevated until the end of each infusion. Mixed venous concentrations were consistently greater than arterial concentrations because of the hindlimb vein infusion site. At the termination of the 5-HT infusion, samples taken every 2 minutes showed a downward trend in circulating 5-HT; however, basal levels of 5-HT were not reached by the end of the sampling period, precluding assessment of the half-life of 5-HT based on disappearance from whole blood samples. By integrating the mixed venous and arterial concentration curves at steady state (from 40 minutes to 60 minutes into the infusion), passage from mixed venous to arterial circulation (pulmonary inactivation) rendered 31.7% of exogenous 5-HT nonimmunoreactive.

Plasma Substance P Levels During Substance P Infusion (Fig. 1)

For plasma SP, basal levels were 0.30 ± 0.1 pg/ml and 0.25 ± 0.1 pg/ml for arterial and mixed venous samples, respectively. Arterial SP levels reached peak concentrations of 89 ± 18 pg/ml by 10 minutes into the infusion, remained elevated throughout, and returned to the basal range 2 minutes after the termination of each infusion. Mixed venous SP levels reached mean peak concentrations of 56 ± 13 pg/ml at 10 minutes into the infusion and remained elevated through each infusion. Mixed venous concentrations were always less than arterial concentrations because the SP infusion site was the distal port of the Swan-Ganz catheter (functionally the left atrium).

Using decay equations, the rapid disappearance of circulating SP from the arterial plasma at the termination of infusion allowed calculation of exogenous immunoreactive SP half-life as less than 25 seconds. Integration of arterial and mixed venous concentrations curves indicated that passage from arterial to mixed venous circulation (peripheral inactivation) rendered 47.7% of exogenous SP nonimmunoreactive.

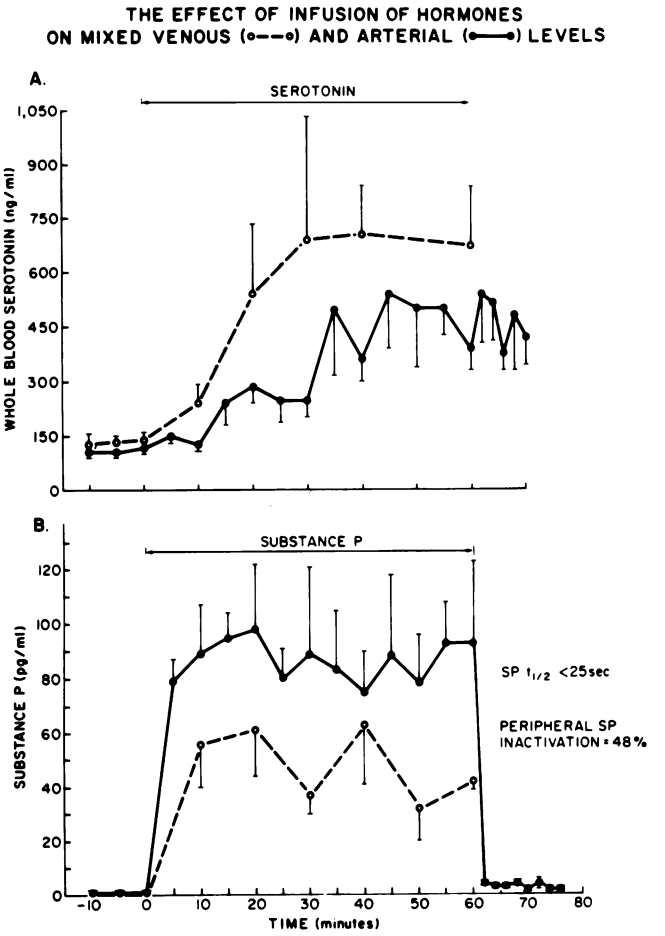

FIG. 1. (A) The effect of infusion of hindlimb intravenous serotonin (26.8 μg/kg-min) in mixed venous (O - - - O) and arterial (● —— ●) whole blood serotonin levels; and (B) the effect of infusion of substance P (68.7 ng/kg-min) effectively into the left atrium on arterial (● —— ●) and mixed venous (O - - - O) SP levels.

Central Hemodynamics (Fig. 2)

During or after 5-HT infusion, mean arterial pressure (MAP) did not change from mean basal values of 131 ± 3 mmHg. Cardiac output (CO) increased significantly from basal 3.98 ± 0.17 l/min to 4.73 ± 0.40 l/min at 20 minutes into the infusions ($p < 0.05$), and remained elevated until the termination of the infusions, when it returned toward basal values. Total systemic vascular resistance (TSVR) fell significantly from 2760 ± 184 dynes-sec/cm^5 to 2214 ± 343 dynes-sec/cm^5 at 30 minutes ($p < 0.05$), and remained diminished until 60 minutes, when it recovered toward basal.

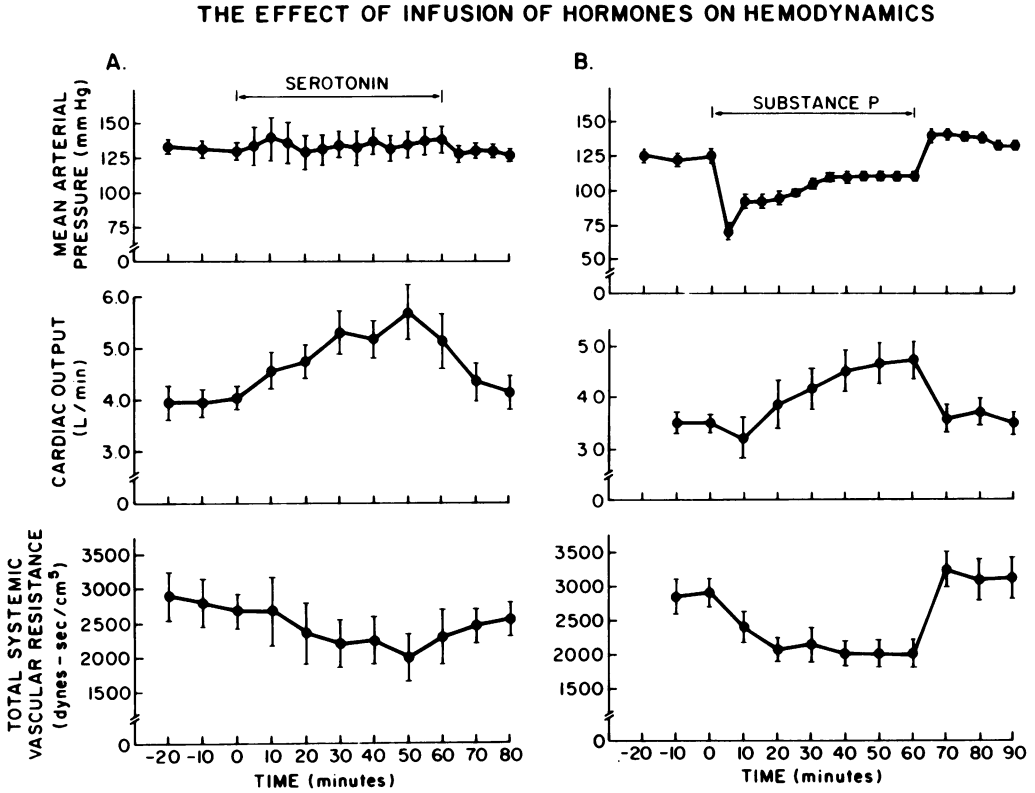

FIG. 2. The effect of serotonin and substance P infusion on mean arterial pressure, cardiac output, and total systemic vascular resistance.

SP infusion caused similar changes in CO and TSVR, but unlike 5-HT, proved a potent hypotensive agent. During SP infusion, MAP fell significantly from basal 124 ± 4 mmHg to 71 ± 6 mmHg at 5 minutes ($p < 0.01$), and remained decreased until 60 minutes. Following the end of each infusion, the MAP significantly overshot above basal to 141 ± 6 mmHg at 65 minutes ($p < 0.02$), then fell toward basal during the remainder of the recovery period. From a basal of 3.56 ± 0.14 l/min, CO initially decreased at 10 minutes, after which it increased significantly to 4.53 ± 0.41 l/min at 40 minutes into each infusion ($p < 0.05$). CO remained elevated until the recovery period, when it returned to basal levels. TSVR fell significantly from basal of 2821 ± 144 dynes-sec/cm^5 to 2074 ± 187 dynes-sec/cm^5 at 20 minutes ($p < 0.02$), remained decreased until 60 minutes, and then during the recovery period, was elevated above basal at 70 minutes, tending to return toward basal thereafter.

In summary, 5-HT and SP infusion caused increased CO and decreased TSVR, with SP but not 5-HT causing a profound decrease in MAP. With termination of SP infusion, MAP and TSVR initially rose above basal, then tended to return toward basal. Although SP caused salivation, no other changes in the animal were noted, *i.e.*, bronchoconstriction. It would be unrealistic to visually assess flushing in dogs.

Regional Blood Flow Changes During Hormone Infusion

Both 5-HT and SP caused multiple blood flow changes at the doses infused. For the purposes of interpretation of blood flow data, it should be noted that the concentration of the infused 5-HT and SP and the hemodynamic alterations produced by these hormones had reached steady state levels by 50 minutes into the infusions. Thus, the data most relevant for the study of chronically elevated, circulating 5-HT and SP levels are the blood flows at the 50-min time periods.

Serotonin infusion caused no significant changes in the blood flow to the brain, kidney, skeletal muscle, or gastrointestinal (GI) tract organs from the duodenum to the colon (Figs. 3 and 4). Significant decreases in flow occurred for the skin and solid organs of the GI tract, including the spleen, hepatic arterial inflow to the liver, and pancreas ($p < 0.05$), with the changes being decremental from the 20- to the 50-min time period. Significant increases in flow occurred for the heart, adrenal, fundus, antrum, and the muscular layers of the fundus, antrum, and jejunum (Fig. 5) ($p < 0.05$). The increased flow to the heart, fundus, and antrum was present by 20 minutes, and persisted unchanged to 50 minutes into the infusions. Adrenal flow decreased from the 20-min to the 50-min period, although it remained significantly elevated above basal at 50 minutes ($p < 0.02$).

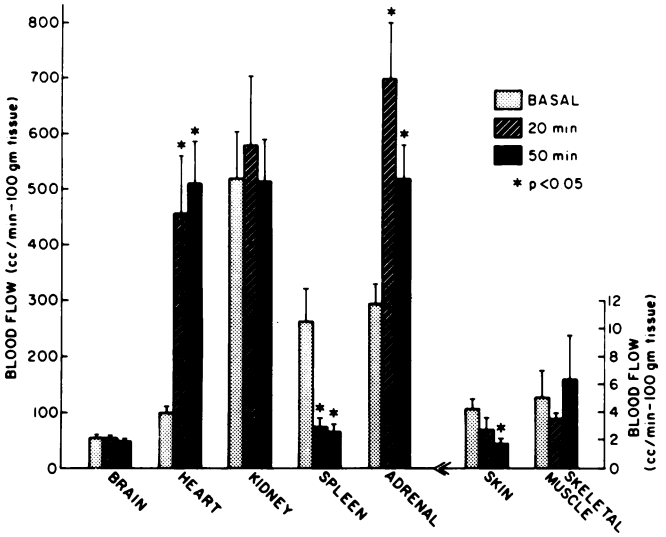

FIG. 3. The effect of serotonin infusion on regional blood flow.

Substance P infusion caused no significant changes in the blood flow to the brain, kidney, skin, skeletal muscle, pancreas, duodenum, ileum, or colon (Figs. 6 and 7). The only significant decreases in blood flow secondary to SP infusion occurred for the heart and jejunum at 20 minutes and the spleen at both 20 and 50 minutes ($p < 0.05$). SP caused significant increases in flow to the adrenal, hepatic artery, fundus, antrum, and the muscular layers (Fig. 8) of the fundus, antrum, duodenum, jejunum, and ileum ($p < 0.05$).

Neither 5-HT nor SP infusion significantly changed estimated portal vein or superior mesenteric artery blood flows, which were 707 ± 101 ml/min and 368 ± 52 ml/min, respectively, for 5-HT, and 724 ± 39 ml/min and 355 ± 33 ml/min, respectively, for SP. Total hepatic blood flow (calculated as the sum of hepatic arterial and portal venous flows) did not change from basal 1040 ± 156 ml/

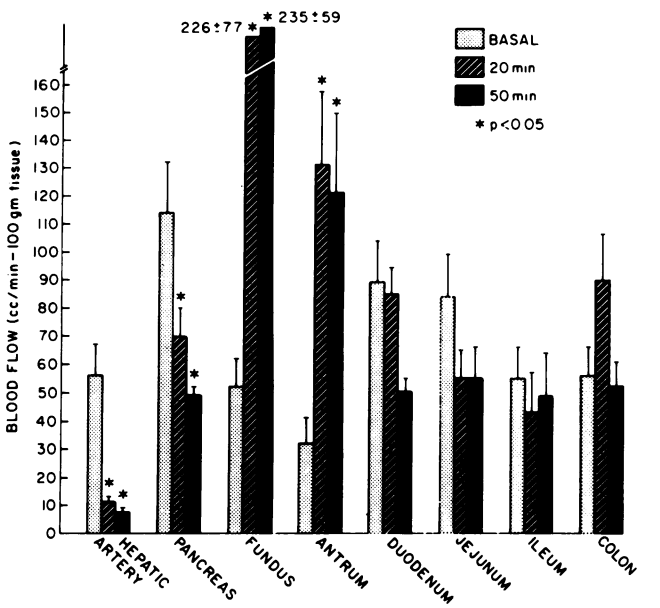

FIG. 4. The effect of serotonin on regional blood flow to the GI tract.

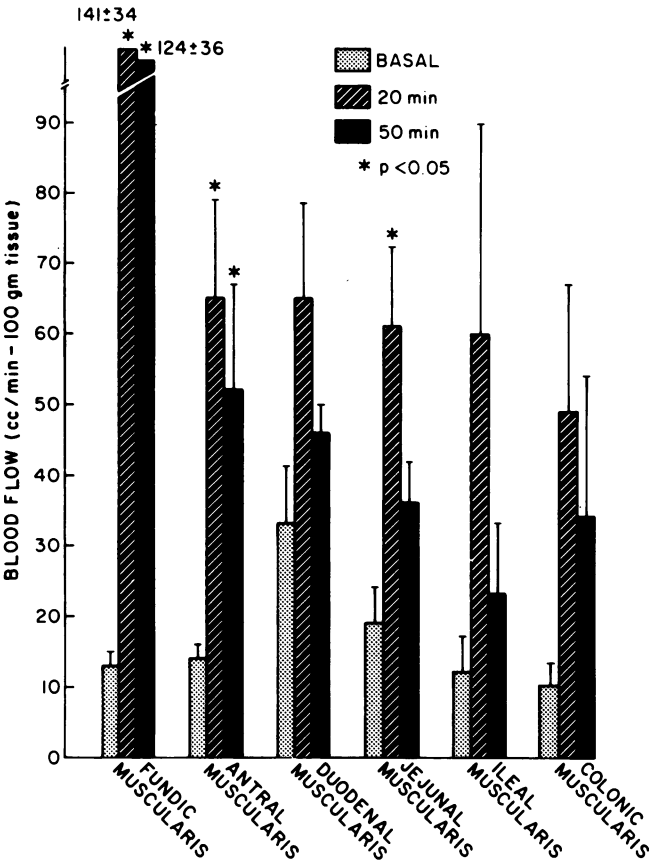

FIG. 5. The effect of serotonin intravenous infusion on regional blood flow to the muscular layers of the GI tract.

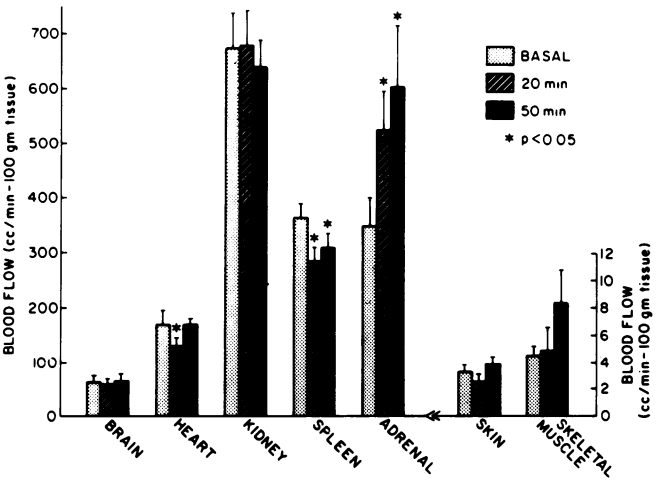

FIG. 6. The effect of SP infusion on regional blood flow.

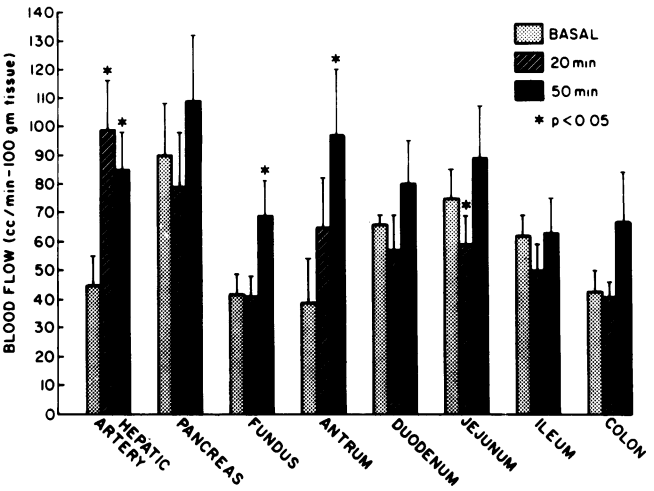

FIG. 7. The effect of SP infusion on regional blood flow to the GI tract.

min for 5-HT, but did significantly rise from 976 ± 74 ml/min to 1311 ± 129 ml/min at 50 minutes into the SP infusion ($p < 0.05$).

Notably, comparison of blood flow changes between 5-HT and SP infusions indicated directionally similar alterations in flows to the splenic, adrenal, fundic, and antral vascular beds, with opposite changes in the hepatic artery and pancreas. Both 5-HT and SP tended to increase blood flow to muscular layers of the gut, with 5-HT being more active proximally than SP. Neither infusion influenced flow to the brain, kidney, or skeletal muscle.

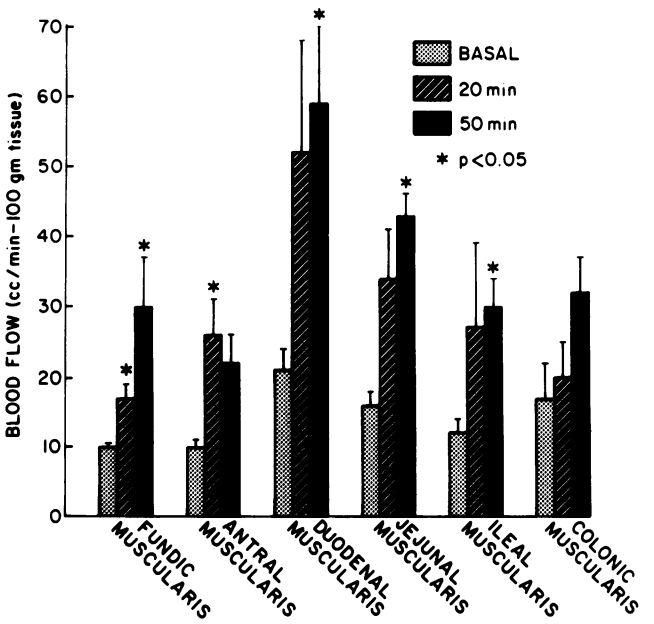

FIG. 8. The effect of SP infusion on regional blood flow to the muscular layers of the GI tract.

Glucose, Insulin, Cortisol and Gastrin

Glucose concentrations did not change significantly during infusion of 5-HT or SP, remaining at basal levels of 99 ± 2 mg/dl and 88 ± 2 mg/dl, respectively. Similarly, insulin did not change significantly from basals of 5.2 ± 1.0 μU/ml and 6.6 ± 1.0 μU/ml for 5-HT and SP, respectively. Both infusions tended to cause an early release of insulin measured in the peripheral circulation; however, statistical significance was not achieved for either hormone. Circulating cortisol levels rose in response to both infusions, with significant increases occurring for 5-HT from 10 minutes into the infusion ($p < 0.01$) and persisting thereafter. The mean increase at 60 minutes was from 2.9 ± 0.9 to 4.8 ± 0.1 μg/dl. Gastrin levels did not change from basal values of 19 ± 2 fmol/ml for 5-HT and 18 ± 2 fmol/ml for SP, respectively, during either infusion.

Discussion

In these experiments we have attempted to evaluate the effects of duplicating the supranormal levels of 5-HT and SP characteristic of patients with the carcinoid syndrome. Several investigators have confirmed that many carcinoid patients have circulating venous 5-HT levels varying from the normal of 168 ± 13 ng/ml to greater than 3000 ng/ml (with most patients ranging between 500 and 1600 ng/ml).[16,29] For SP, levels in carcinoid patients have been less well studied. Using unextracted plasma, 3- to 4-fold elevations of circulating SP levels above normal have been documented.[17] In our laboratory and assay system, using extracted plasma, three carcinoid patients have had basal circulating SP concentrations above normal (greater than 10 pg/ml) with a range of 82 to 130 pg/ml. We have therefore reproduced, by intravenous infusion, the circulating levels of 5-HT and SP found in many patients with the carcinoid syndrome.

Characteristic cardiovascular and hemodynamic alterations have been described in the carcinoid syndrome, and these include flushing, hypotension, increased cardiac output, pulmonic and tricuspid valvular lesions, and cardiac failure.[5,30] In our acute canine infusion experiments, we have demonstrated that both 5-HT and SP caused significant reductions in systemic vascular resistance and increases in cardiac output, suggesting that either or both may mediate changes in carcinoid patients. SP, but not 5-HT, proved to be a potent hypotensive agent, and may be responsible for hypotensive episodes of carcinoid patients. Our experiments were not designed to visually identify cutaneous flushing. However, our blood flow data failed to produce increased skin blood flow during either infusion, which suggests that neither 5-HT nor SP act as mediator of the carcinoid flush. This is consistent with

previous investigations which have questioned the role of 5-HT in carcinoid flushing[31] and suggests that circulating kinins[32] or other agents[33] may be more directly responsible. The alternative possibility is that 5-HT opens arteriovenous shunting in the skin causing flushing and decreasing the appropriate blood flow measured by 15μ microspheres.

The etiology of the characteristic carcinoid-related fibrostenotic lesions of the right-sided cardiac valves remains obscure.[34] Our acute infusion experiments caused no gross pathologic changes to the endocardium or the tricuspid or pulmonary valves. This finding was not unexpected, as the structural cardiac abnormalities are most certainly slowly evolving, chronic lesions.

The regional blood flow alterations caused by 5-HT and SP in doses which reproduce carcinoid levels were striking. Previous investigators have studied these blood flow changes in anesthetized animals using electromagnetic flow meters or venous effluent techniques to measure blood flow. In these studies, 5-HT has been shown to vasoconstrict large arteries, vasodilate small arteries, and to variably affect blood flow dependent on the extent of intrinsic vascular tone.[35-37] With similar techniques, it has been demonstrated that SP acts as a general vasodilator in multiple vascular beds.[38,39]

In the current study, using a conscious canine model and the radioactive microsphere technique, we were able to document 5-HT- and SP-induced organ-specific blood flow changes in multiple vascular beds. Serotonin, at carcinoid-like doses, caused a redistribution of flow, which increased flow to major organs such as heart, adrenal, fundus, and antrum, and decreased flow to spleen, skin, hepatic artery, and pancreas. Such redistribution of flow, with bidirectional changes, supported the importance of the state of intrinsic vascular tone in the response to infused 5-HT.[35] SP, unlike 5-HT, appeared to act more as a generalized vasodilator. During SP infusion, the adrenal, hepatic artery, fundus, antrum, and all muscular layers of the bowel received increased flow. The sole organ with a sustained reduction in blood flow during SP infusion was the spleen, which may reflect the ability of the canine splenic capsule to contract and reduce its volume during various stimuli.[40]

Our results have demonstrated that both SP and 5-HT are active in augmenting blood flow to the muscular layers of the GI tract, with 5-HT being most active proximally, and SP equally active throughout. This increase in muscularis blood flow may be related to the known stimulation of GI motility by 5-HT and SP,[41,46] and may possibly be related to the GI hypermotility and diarrhea characteristic of the carcinoid syndrome.

Carcinoid mediated hyperserotoinemia is reported to be associated with abnormal glucose metabolism and insulin secretion,[43] peptic ulcer disease,[44,45] and hypercorticism.[46] While patient data suggested that 5-HT exerts tonic inhibition of insulin secretion,[43] our experiments suggested no role for either 5-HT or SP in the acute regulation of circulating glucose or insulin levels in intact dogs. The failure of circulating gastrin levels to rise during 5-HT or SP infusion in our experiments suggests that the reported 18–38% incidence of peptic ulceration in carcinoid patients[44,45] is not related to elevated circulating gastrin. Finally, our experiments are consistent with reports from *in vitro* systems,[46] in which serotonin was found to stimulate cortisol production. The elevated adrenal blood flow produced by 5-HT infusion in our model may partially explain this elevation of circulating cortisol levels or reflect increased hormonal activity.

This study of the effects of products elaborated by carcinoid tumors has provided a mechanism to begin to explain the pathophysiology of the carcinoid syndrome. This study is in agreement with previously performed studies in our laboratory at physiologic doses of 5-HT (4 and 10 μg/kg-min)[47] and SP (7 ng/kg-min).[48] Our studies suggest that the classical carcinoid mediator, 5-HT, may be responsible for elevated cardiac output, redistribution of regional blood flow, and gastrointestinal muscularis hyperemia with associated hypermotility. In contrast, SP, a more recently identified constituent of many carcinoid tumors, may be responsible for generalized vasodilation, increased cardiac output, hypotension, and GI hypermotility. However, neither 5-HT nor SP appear to be responsible for the carcinoid flush.

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