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Vasoactive Intestinal Polypeptide: Inactivation in Liver and Potentiation in Lung of Anesthetized Dogs[1] (38469)

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(Introduced by Andres Goth)

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Vasoactive intestinal polypeptide (VIP), recently isolated from small intestine of hogs (1–3), exerts multiple biological actions, including peripheral vasodilation, systemic hypotension, increased cardiac output, enhancement of respiration, stimulation of glycogenolysis, and relaxation of several smooth-muscle organs (2, 4, 5). The possible physiologic and pathologic importance of this peptide remains to be determined, as do the factors regulating its release and metabolism.

The present investigation was conducted to explore the fate of the peptide in the circulation and the sites of its biological inactivation. If VIP is released from intestine, the portal blood would normally carry it to the liver where it could be metabolized. In view of the participation of the lung in the metabolism of numerous vasoactive hormones (7), we also investigated the role of this organ in the inactivation or potentiation of the biological effects of VIP.

For measurement of the biological activity of the peptide *in vivo*, we monitored arterial blood pressure and respiration, in anesthetized dogs. Earlier (1), it was demonstrated that VIP lowers diastolic and mean blood pressure, as a result of peripheral vasodilation, and augments respiration, partly due to direct stimulation of chemoreceptors, and partly secondary to the hypotension. The peptide was infused by three different routes; into the right ventricle, the left ventricle and the portal vein, in four different submaximal doses; 0.29, 0.57, 1.10, and 2.23 μg/kg. Comparisons of the responses to these infusions permit the conclusions that: (a) The hypotensive and respiratory stimulant effects of VIP are either abolished or markedly reduced during circulation through the liver; and (b) the biological activity of the peptide is moderately enhanced during its passage through the lung, possibly because of the release of other vasoactive compound(s).

Methods. Five mongrel dogs, weighing between 12 kg and 14 kg, were anesthetized with a mixture of chloralose (50 mg/kg) and urethane (750 mg/kg) and were heparinized (4000 units). Each dog breathed room air spontaneously through an endotracheal tube. In order to eliminate the possible influence of vagal reflexes, bilateral vagotomy was carried out at the start of the experiment.

For infusion of the peptide, catheters were placed in three locations in each dog: (a) the portal vein, via a mesenteric vein; (b) the right ventricle, via the right jugular vein; and (c) the left ventricle, via the left carotid artery. These particular sites of infusion were chosen so that VIP would pass initially through (a) the liver, (b) the lung, or (c) neither of these organs. The locations of the catheters were verified at autopsy.

Highly purified VIP (free of secretin or cholecystokinin-pancreozymin, and prepared as described in Ref. 2, at the Karolinska Institute, Stockholm) was dissolved in saline (10 μg/ml) and infused for one minute at each of four infusion rates; 0.42, 0.82, 1.60 and 3.14 ml/min, using a Harvard infusion pump. At these infusion rates, the mean doses of the peptide were. respectively, 0.29, 0.57, 1.10, and 2.23 μg/kg. Each dog received four doses, given through each of three routes (a total of 12 infusions), at intervals

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which were meant to allow blood pressure and respiration to return to control values before the next infusion was begun.

A catheter was also placed in a femoral artery for continuous measurement of arterial blood pressure by means of a Sanborn (Hewlett–Packard) 267 B transducer; mean pressure was obtained by electronic averaging. Airway pressure was measured by a similar transducer, and airflow by a pneumotachygraph (Instrumentation Associates, Inc.), attached to the airway. Tidal volume was obtained by electronic integration of the airflow signal, and minute ventilation was calculated as the product of tidal volume and frequency.

Data on blood pressure and minute ventilation from all experiments were analyzed statistically using the paired τ test. Comparisons were made between the results from the three different methods of infusion at each dose level in each dog.

Results. The responses in five dogs to progressively larger doses of VIP, given by three different routes, are summarized in Table I. Due to the relatively long duration (approximately 6 hr) of anesthesia, there was a moderate fall in control arterial blood pressure, and an increase in respiratory rate toward the end of the experiment.

Fall of systemic arterial pressure after VIP infusion (Table I). The fall in aortic blood pressure following infusions of the peptide was expressed in terms of: (a) the magnitude of fall in mean pressure, percent of control value; (b) the duration of the fall, i.e., the duration required for the experimental value to return in the range of the control; and (c) the product of a and b.

The peptide elicited a hypotensive response which became more pronounced with increasing doses. For any given dose, the magnitude of hypotension was always smallest, and its duration shortest, after infusions into the portal vein ($P < 0.01$). In one dog, even the largest doses infused into the portal vein failed to lower mean blood pressure measurably (Fig. 1). In the other dogs, at least twice and up to six times as much peptide, had to be infused into the portal vein as into the right ventricle in order to produce the same hypotensive response.

Increase of minute ventilation after VIP infusion (Table I). Except for the smallest dose, infusions of VIP into the right or left ventricle were always followed by an increase in minute ventilation. Portal infusions of the peptide, however, were totally without effect on ventilation in two dogs (Fig. 2); and the mean respiratory stimulation in all five dogs following portal infusions was significantly smaller than that resulting from right ventricular infusions ($P < 0.01$).

Discussion. The above observations provide a comparison of the relative potency of VIP as a hypotensive agent and a stimulant of ventilation, when infused into the right ventricle, the left ventricle and the portal vein of dogs.

Measurements of arterial blood pressure and of minute ventilation confirm the earlier impression that, in dogs, VIP is effectively inactivated in the liver (2). Thus, in doses ranging from 0.29 to 2.23 μg/kg, intraportal infusions had no significant effect on blood pressure or ventilation, and in one animal portal infusions in all doses were totally ineffective (Figs. 1 and 2). Comparison of the doses required to produce equal responses by intra-portal and by right ventricular infusion, allows the estimate that passage through the liver reduced the biological activity of VIP by at least 50% and by up to 100%. The tendency for portal infusions to become relatively more effective at higher dose levels suggests that the mechanisms of hepatic inactivation may be saturable, becoming less effective at larger concentrations of the peptide.

The inactivation of VIP during passage through the liver implies that, should this peptide be proven a normal hormone, its actions may be confined to the gastrointestinal tract, the liver and the portal circulation. Such effects of VIP include: suppression of gastric secretion (9), stimulation of intestinal secretion (10) and adenylate cyclase activity (11), relaxation of gastric and gallbladder smooth-muscle (5), glycogenolysis (4), increased flow of bile (12), and dilation of splanchnic vessels (12). In the presence of liver failure or excessive release of VIP, however, the peptide could escape hepatic inactivation, and reach the circula-

TABLE I. EFFECT OF VIP INFUSIONS ON ARTERIAL BLOOD PRESSURE AND VENTILATION[a]

Mean dose μg/kg	Site of Inf.	Arterial blood pressure: Control exper. mm Hg		Fall %	Duration min	Fall × duration	P^b	Ventilation: V_T Control exper. ml		f Control exper, breaths/min		$\dot{V}_E$ Control exper. ml		Increase %	Increase P
0.29	R.V.	145 ± 5	137 ± 6	5.2 ± 0.9	1.9 ± 0.3	11 ± 3	<0.05	286 ± 16	284 ± 18	8.5 ± 1.5	8.9 ± 1.5	2424 ± 473	2509 ± 473	3 ± 2	NS
0.29	L.V.	142 ± 6	137 ± 5	3.9 ± 0.5	1.8 ± 0.5	8 ± 3	<0.01	284 ± 20	280 ± 19	8.5 ± 1.4	8.7 ± 1.4	2393 ± 415	2419 ± 420	1 ± 1	NS
0.29	P.V.	140 ± 6	138 ± 5	1.6 ± 0.9	0.6 ± 0.2	1 ± 1	<0.025	280 ± 21	280 ± 21	9.0 ± 1.5	9.0 ± 1.5	2457 ± 411	2457 ± 411	0 ± 0	NS
0.57	R.V.	140 ± 5	129 ± 5	7.7 ± 1.1	3.2 ± 0.3	25 ± 6	<0.005	276 ± 22	278 ± 22	9.3 ± 1.5	10.4 ± 1.4	2484 ± 364	2820 ± 336	16 ± 4	<0.01
0.57	L.V.	138 ± 7	135 ± 5	5.7 ± 1.1	2.4 ± 0.3	15 ± 4	<0.0025	276 ± 24	270 ± 22	8.8 ± 1.3	9.4 ± 1.2	2403 ± 406	2555 ± 399	7 ± 4	<0.01
0.57	P.V.	141 ± 6	136 ± 6	3.6 ± 1.0	1.4 ± 0.5	7 ± 4	<0.0025	276 ± 23	274 ± 23	9.4 ± 1.3	9.6 ± 1.3	2582 ± 418	2624 ± 437	1 ± 1	NS
1.10	R.V.	137 ± 9	117 ± 9	15.4 ± 2.4	5.0 ± 0.8	76 ± 18	<0.0025	262 ± 23	256 ± 24	9.1 ± 1.3	12.5 ± 1.7	2373 ± 406	3182 ± 482	36 ± 7	<0.0025
1.10	L.V.	137 ± 12	122 ± 10	10.5 ± 2.9	4.0 ± 0.6	45 ± 16	<0.0025	262 ± 28	258 ± 28	9.8 ± 1.2	12.0 ± 1.3	2578 ± 448	3099 ± 483	21 ± 5	<0.0025
1.10	P.V.	132 ± 15	124 ± 14	5.6 ± 2.7	3.1 ± 0.9	27 ± 16	<0.05	256 ± 25	254 ± 25	11.1 ± 1.2	12.1 ± 1.4	2786 ± 364	3042 ± 413	9 ± 5	<0.0025
2.23	R.V.	132 ± 12	108 ± 11	18.5 ± 2.8	5.4 ± 0.5	103 ± 23	<0.05	244 ± 19	256 ± 26	11.8 ± 1.1	16.7 ± 1.7	2886 ± 378	4231 ± 580	49 ± 11	<0.01
2.23	L.V.	129 ± 13	107 ± 12	16.5 ± 3.0	4.9 ± 0.8	87 ± 27	<0.0005	248 ± 20	256 ± 28	11.8 ± 0.9	14.8 ± 1.0	2964 ± 384	3758 ± 425	28 ± 7	<0.0025
2.23	P.V.	124 ± 14	111 ± 15	10.6 ± 3.9	3.4 ± 1.3	51 ± 32	<0.025	246 ± 26	242 ± 33	14.3 ± 2.2	17.3 ± 2.1	3468 ± 492	4116 ± 691	21 ± 12	NS

[a] Abbreviations: R.V., right ventricle; L.V., left ventricle; P.V., portal vein; V_T, tidal volume; f, frequency of respiration; $\dot{V}_E$, minute ventilation. Values are means ± SEM.

[b] Values for R.V.–L.V., and L.V.–P.V. comparisons are listed to left, and for R.V.–P.V. comparisons to right.

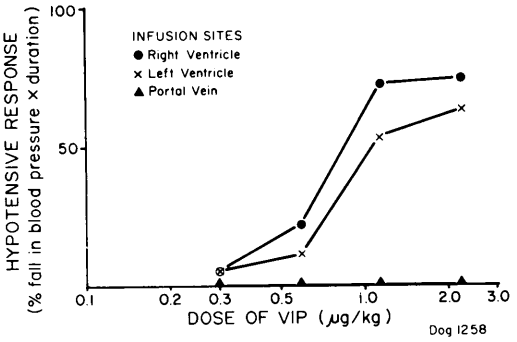

FIG. 1. Hypotensive response to increasing doses of vasoactive intestinal peptide (VIP), infused into the right ventricle, left ventricle, or portal vein of anesthetized dog.

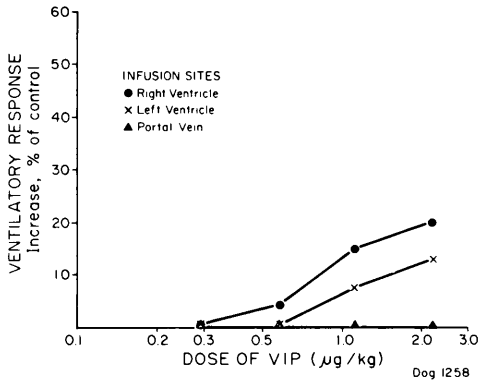

FIG. 2. Ventilatory response (increase in minute ventilation, percent of control value), in same experiment as plotted in Fig. 1.

tion beyond the portal bed. The cardiovascular and respiratory effects of the peptide in dogs (1) notably mimic some of the features of hepatic cirrhosis in humans, e.g., peripheral vasodilation, increased cardiac output and hyperventilation (8). Increased plasma levels of VIP have already been reported in patients with certain peptide-secreting tumors (unpublished observations, 13), and in hepatic cirrhosis (14). Glucagon, a closely related peptide, also is degraded in the liver, and its circulating level is abnormally high in cirrhotics (15).

The increase in biological activity of VIP during passage through the lung is difficult to relate to any physiological role that the peptide may have. This apparent potentiation may result from metabolic alteration in the peptide, or from secondary release of other active substances. We have no data favoring either of these possibilities. Additional active agents that VIP might possibly release from the lung include histamine and prostaglandins. Several basic peptides are capable of releasing histamine (16), and VIP, itself strongly basic (2,3), releases histamine from peritoneal mast cells of rats, though only at high concentrations (25% release at a mean concentration of 10 μg/ml, Dr. Andres Goth, personal communication). Significant release of histamine by VIP is, however, unlikely in doses such as we employed since this peptide relaxes tracheobronchial smooth muscle *in vitro* (17) and *in vivo* (unpublished observations), and enhances alveolar ventilation (1). Release of prostaglandins of the E series could more readily explain the greater systemic hypotension and respiratory stimulation following right ventricular, relative to left ventricular, infusions of VIP. E prostaglandins are vasodilator and bronchodilator compounds whose increased synthesis and release by the lung may be provoked by a variety of physical and chemical stimuli (6).

Summary. The role of the liver and the lung in the inactivation or potentiation of the biological activity of the vasoactive intestinal polypeptide (VIP) was examined in five anesthetized dogs. Infusions of the peptide were made into the right ventricle, the left ventricle, and the portal vein. Each animal received 4 doses, ranging from 0.29 to 2.23 μg/kg. Systemic arterial blood pressure, tidal volume, breathing frequency, and minute ventilation were continually monitored. The biological effects of the peptide were measured in terms of (a) the fall in arterial blood pressure; and (b) respiratory stimulation. Infusions of the peptide into the portal vein produced either no effect or significantly weaker effects ($P < 0.01$) than infusions into the right ventricle. The latter infusions were moderately more potent ($P < 0.05$) than infusions into the left ventricle. VIP thus appears to be effectively inactivated during passage through the liver. The apparent increase in biological potency of the peptide during its passage through the lung may be attributable to the release of addi-

tional vasodilator substances, or to further activation of the peptide.

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