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Effect of Vasoactive Intestinal Polypeptide (VIP) on the Lower Esophageal Sphincter Pressure (LESP) (39740)

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Vasoactive intestinal polypeptide (VIP) is a highly basic peptide which resembles secretin, glucagon, and to some extent gastric inhibitory polypeptide (GIP). First isolated from porcine small intestine, VIP exerts a variety of biological actions (1-5).

The lower esophageal sphincter (LES) remains in a continuous state of closure at rest and opens on swallowing in order to let the bolus pass into the stomach (6). The mechanisms which control the resting sphincter pressure and its relaxation are not properly understood.

Recent studies have shown that VIP is widely distributed throughout the gastrointestinal tract and causes relaxation of various smooth muscles of the gastrointestinal tract (3, 7). Furthermore, it has been specifically localized in the esophagus in the myenteric plexus as well as in the muscular area (7, 8). The purpose of the present investigation was to study the effect of VIP on LES smooth muscle *in vivo*.

Materials and methods. The present studies were conducted in 11 opossums (*Didelphis virginiana*) because in this species the lower end of the esophagus, including LES, is smooth muscle and resembles that of man (9). The animals were anesthetized by intraperitoneal administration of pentobarbital sodium (40 mg/kg) and strapped supine on an animal board. The animals were breathed with a mechanical respirator (Harvard Apparatus Co., Millis, Mass.). The brachial vein was cannulated for intravenous administration of agents. The animals were made to swallow a specially designed catheter system (10) which consisted of four polyvinyl catheters fused together with tetrahydrofuran, and interposing central idle polyvinyl tubing. All of these catheters had side openings at the distal end 1 cm apart. The proximal ends of these catheters were connected to Statham pressure transducers. All of these catheters were constantly perfused with bubble-free water under pressure, as already described (10). The perfusion rate of water under the present arrangement was 0.33 ml/min. The compliance in this system of perfusion even at a lower rate of water perfusion was insignificant. Initially, the catheter assembly was introduced into the stomach. All the pressures were recorded on a Beckman dynograph recorder (Model R411, Beckman Instruments, Schiller Park, Ill.) through Statham pressure transducers (Statham, Model P23Db, Statham Instruments, Oxnard, Calif.). One of the common carotid arteries was cannulated for direct measurement of blood pressure. At this point, the abdominal cavity of the animals was exposed employing midline laparotomy incision. The catheter assembly was slowly pulled until one of the middle openings recorded pressures from the high pressure zone of the LES, while the lower ends of the esophagus and upper part of the stomach were under direct vision. The catheter assembly openings lying proximal and distal to the opening resting in the LES recorded intraesophageal and intragastric pressures, respectively. The lower end of the esophagus, along with the upper part of the stomach, was gently held, and the relationship of the catheter assembly with the LES was secured using two ordinary pins which passed through esophageal wall and the central idle polyvinyl tubing. The details of this technique are described elsewhere (10). All the pressures in the esophagus, LES, and stomach were measured in relation to the atmospheric

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pressure and at the peak of respiratory excursion.

All agents were either dissolved or diluted in a 0.15 *M* NaCl solution and administered as 30-sec single intravenous boluses, unless otherwise mentioned. Different doses of VIP were administered in a random fashion and at least 30 min were given between different doses. The anesthesia was maintained by occasional intravenous administration of pentobarbital sodium (3 mg/kg) whenever needed. Tetrodotoxin (10 μg/kg) was administered very slowly over 2 min and, 10 min following tetrodotoxin, LES response to esophageal distention was observed. The details of the balloon used for esophageal distention have been given elsewhere (10). The administration of tetrodotoxin was continued in this fashion until LES relaxation in response to esophageal distention was completely abolished (10). During tetrodotoxin administration, the circulatory system of the animal was supported using slow continuous infusion of lactated Ringer with 5% dextrose (0.1 ml/min). The following agents were used: vasoactive intestinal polypeptide (VIP) in the form of pure peptide (natural porcine) (GIH Laboratory, Karolinska Institute, Stockholm); propranolol (Ayerst Laboratories, New York); and tetrodotoxin (Calbiochem, San Diego, Calif.).

Results. Effect of vasoactive intestinal polypeptide (VIP) on the lower esophageal sphincter (LES). VIP produced a dose-related fall in the lower esophageal sphincter (Fig. 1). The smallest dose which produced any detectable response on the LES was 0.25 μg/kg. A dose of 8 μg/kg produced a maximal fall of 36.8 ± 2.9 (SEM) mm Hg (80.5 ± 4.5% of the resting pressure) in the LES pressure. The fall in LES pressure with 8 μg/kg of VIP commenced within 20 to 40 sec and lasted for 3 to 10 min. The effect of VIP on initial and final LESP and absolute fall in LESP are detailed in Table I. The administration of 0.15 *M* NaCl alone did not produce any change in LES pressure.

Influence of propranolol on the effect of VIP on the LES. Propranolol, a β-adrenergic antagonist, was administered intravenously in the dose of 1 mg/kg. Ten minutes following propranolol, the effect of 8 μg/kg of VIP was studied. This dose of VIP produced a fall of 44.3 ± 17.3 mm Hg before and 36.0 ± 6.0 mm Hg after administration of propranolol ($P > 0.05$; $n = 3$ in three animals, one observation each). The resting LESP before and after propranolol treatment at the time of VIP administration was 61.0 ± 17.2 and 49.3 ± 6.4, respectively (*P*

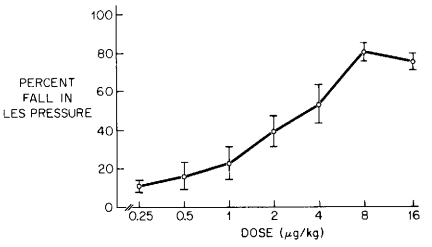

FIG. 1. The dose-response curve of the effect of vasoactive intestinal polypeptide (VIP) on the lower esophageal sphincter (LES). The doses of VIP varied from 0.25 to 16 μg/kg. The response is represented by percentage of fall in the sphincter pressure. The dose of 8 μg/kg gave the maximal response of 80.5 ± 4.5% (SEM) fall in the sphincter pressure. This dose-response curve was constructed from experiments conducted in five animals. The number of observations at each dose level was in four to five animals, one observation each.

TABLE I. EFFECT OF DIFFERENT DOSES OF VIP ON THE LOWER ESOPHAGEAL SPHINCTER PRESSURE.

Dose of VIP (μg/kg)	Number of observations	Initial pressure[a] (mm Hg)	Final pressure (mm Hg)	Fall in pressure[a] (mm Hg)
0.25	5	42.4 ± 3.0	38.4 ± 4.1	4.0 ± 1.3
0.5	5	39.2 ± 4.2	33.2 ± 4.8	6.0 ± 2.3
1	5	48.0 ± 3.0	37.0 ± 3.2*	11.0 ± 3.1
2	5	49.2 ± 7.0	31.2 ± 7.0*	18.0 ± 2.0
4	5	46.4 ± 3.2	22.6 ± 4.4*	23.8 ± 2.4
8	5	45.6 ± 2.2	8.8 ± 2.1*	36.8 ± 2.9
16	4	39.5 ± 3.4	10.2 ± 1.8*	29.2 ± 2.2

[a] Mean ± SEM of one observation in four to five different animals.
* Significant difference from their corresponding initial pressures ($P < 0.05$).

> 0.05; $n = 3$ in three animals, one observation each).

Influence of tetrodotoxin on the effect of VIP on the LES. The dose of tetrodotoxin which abolished the response of esophageal distention on the LES in different animals varied from 10 to 40 μg/kg. VIP in control experiments produced an LES pressure fall of 44.3 ± 17.3 mm Hg (from 61.0 ± 11.2 to 15.7 ± 1.8 mm Hg), and in the presence of tetrodotoxin the fall was 45.0 ± 4.0 (from 60.7 ± 6.6 to 15.7 ± 4.7 mm Hg) (Fig. 2). These differences were not statistically significant ($P > 0.05$; $n = 3$ in three animals, one observation each).

Discussion. These studies show that VIP inhibits the lower esophageal sphincter in intact opossums. Moreover, this inhibition is not a neurally mediated response, as it is not influenced by neural block with tetrodotoxin (11). β-Adrenergic antagonism also did not modify the inhibitory effect of VIP. The effects of muscarinic and nicotinic antagonists were not examined because there are no inhibitory muscarinic or nicotinic receptors on the sphincter muscle (12). Similarly, α-adrenergic receptor stimulation causes only contraction of the LES (13). The effect of VIP on the LES is similar to its inhibitory effect on rat stomach strips and guinea pig trachea (14).

In contrast to its effect on the LES, VIP has been reported to cause contraction of the duodenum and ileum. These effects are due to VIP stimulation of excitatory neurons as they are antagonized by tetrodotoxin (15).

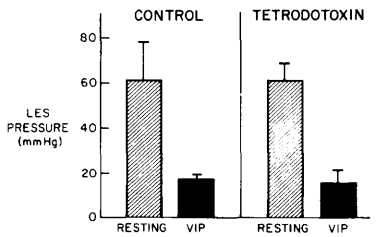

FIG. 2. The influence of tetrodotoxin on the effect of VIP on the LES. In control experiments (left panel), the resting sphincter was 61.0 ± 11.2 (SEM) mm Hg, and it fell to 16.7 ± 1.8 mm Hg with 8 μg/kg of VIP. In the presence of tetrodotoxin (right panel), the resting sphincter pressure was 60.7 ± 6.6 mm Hg, and it was reduced to 15.7 ± 4.7 mm Hg with VIP. The resting and the final sphincter pressures with VIP were not modified by tetrodotoxin ($P > 0.05$).

The inhibitory effect of VIP on the LES may turn out to be of considerable physiological importance. VIP has been shown to be localized to the esophageal wall, both in the region of the myenteric plexus and the muscle layer (8). VIP has also been found in high concentrations in brain and neural cell lines (8, 16), and especially in synaptosomes (nerve endings) (17), suggesting the possibility that it may act as a neurotransmitter.

It would be of interest, therefore, to investigate a possible physiological role of VIP in the control of the LES.

Summary. The effect of vasoactive intestinal polypeptide (VIP) on the lower esophageal sphincter (LES) was studied in anesthetized opossums. Intravenous administration of VIP caused a dose-related fall in LES pressure. A dose of 8 μg/kg produced a "maximal" fall of 36.8 ± 2.9 mm Hg (80.5 ± 4.5%) in sphincter pressure. The effect of VIP (8 μg/kg) was not antagonized by tetrodotoxin in the doses which antagonized neural activity in the LES. β-Adrenergic antagonist, propranolol, also failed to antagonize this inhibitory effect of VIP. These studies show that VIP exerts an inhibitory effect on the LES. Moreover, this inhibitory effect may be due to a direct action on the sphincter muscle.

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