Effect of dopamine on esophageal motor function

ARUN K. MUKHOPADHYAY AND NORMAN WEISBRODT
Department of Medicine, Baylor College of Medicine, and Department of Physiology,
University of Texas Medical School, Houston, Texas 77030

Mukhopadhyay, Arun K., and Norman Weisbrot. Effect of dopamine on esophageal motor function. Am. J. Physiol. 232(1): E19-E24, 1977 or Am. J. Physiol.: Endocrinol. Metab. Gastrointest. Physiol. 1(1): E19 E24, 1977. Intravenous administration of dopamine produced a dose-dependent decrease in lower esophageal sphincter pressure and a dosee-dependent increase in contractile activity of the body of the esophagus. The threshold dose of dopamine was 0.25 µg/kg, and the effect reached a plateau at about 6 µg/kg. A dose of 6 µg/kg of dopamine produced 83% ± 3 (SE) reduction in the lower esophageal sphincter pressure and 12 ± 1 (SE) contractions in the body of the esophagus within 5 min of the bolus injection. Atropine, phentolamine, propranolol, and bilateral cervical vagotomy did not modify the effect of dopamine. Both haloperidol and bulbocapnine potently antagonized the effect of dopamine. The amplitude of esophageal contraction in the lower esophagus in response to pharyngeal stimulation and esophageal distention was significantly increased after administration of haloperidol. It is concluded that intravenous administration of dopamine has potent effects on the motor function of the lower esophageal sphincter and the body of the esophagus. The effect of dopamine is not mediated via the vagal centers in the brain or cholinergic muscarinic and adrenergic receptors. The response of the smooth muscle segment of opossum esophagus to intravenous dopamine is mediated via specific dopamine receptors. The inhibitory dopamine receptors may play a physiological role in controlling the amplitude of esophageal contractions.

THE SMOOTH MUSCLE SEGMENT of the esophagus is supplied by cholinergic, adrenergic, as well as by non-cholinergic, nonadrenergic nerves. The neurotransmitter responsible for the operation of noncholinergic, non-adrenergic nerves is not known. We have recently reported that dopamine, administered intravenously, produces initial relaxation of the lower esophageal sphincter followed by contractions in the body of the esophagus (12). We suggested that such dopamine-induced alterations in smooth muscle function of the esophagus may be mediated through adrenergic, cholinergic, or dopaminergic receptors. The purpose of the present investigation was to characterize the type of receptors involved in dopamine response in esophageal smooth muscle.

METHODS
Studies were performed in 36 adult opossums of either sex. The animals weighed from 1.8 to 3.1 kg and were anesthetized with barbital sodium, 150 mg/kg of body weight injected intraperitoneally. Each experiment lasted for 5-8 h during which time the animals usually did not need additional barbital injection. When necessary, small doses of barbital were injected intravenously to maintain anesthesia at a constant level. Intraluminal pressures in the body of the esophagus and the lower esophageal sphincter (LES) were monitored with a water-filled and continuously perfused assembly of intraluminal catheters having three recording sites. Each catheter (ID = 0.86 mm, OD = 1.17 mm) had a side opening, and all were continuously perfused with bubble-free water with a constant infusion (Harvard apparatus) pump. An infusion rate of 0.12 ml/min was utilized for measurements of LES pressure and the number of contractions of the esophageal body. Rates of 0.42, 1.08, and 2.20 ml/min were utilized for measurements of the amplitude of contractions of the esophageal body. These rates were used in the light of the observation that the rate of infusion affects the recordings of intraluminal pressure (15). The catheter assembly was passed through the mouth of the animal until all openings were in the stomach. Subsequently, the catheter assembly was withdrawn slowly, 0.25 cm at a time. The lower esophageal sphincter was localized and the point at which the sphincter pressure was highest was noted. Throughout the experiment, this position was strictly maintained. On occasions when the catheter assembly moved either proximally or distally, it was replaced in the previously noted position. The catheters were so arranged that the side openings were 2 cm apart. The external jugular vein was exposed and catheterized for intravenous injections. A constant infusion of saline (0.05 ml/min) was utilized to keep the intravenous catheter patent. All drugs were injected intravenously. The following drugs were used: Dopamine HCl (Sigma Chemical Co.), phentolamine mesylate (CIBA Pharmaceutical Company), propranolol hydrochloride (Ayerst Laboratories), atropine sulphate (Eli Lilly and Company), haloperidol (McNeil) and bulbocapnine hydrochloride (ICN Life Sciences Group, Cleveland). All drug concentrations are expressed as the salt. Different doses of dopamine between 0.06 and 12 µg/kg were injected as intravenous boluses. The doses of drugs were given at random and not in ascending order. The pharmacologic antagonists were given as slow intravenous infusions over 15-min periods. The cervical vagus nerves were exposed and cut
bilaterally in four animals as described previously. Data were obtained before bilateral vagotomy and 1 h later.

Pressures in the lower esophageal sphincter and the body of the esophagus were recorded at the peaks of respiratory excursions in reference to atmospheric pressure. The absolute pressure before and after drug administration and the percent change in LES pressure were determined. The data on percent changes of LES pressure were analyzed statistically after appropriate conversion of percentages to arc sine values. The response of the body of the esophagus was measured by determining the number of contractions per 5-min period. Primary peristalsis was induced by pharyngeal stimulation with a wet cotton swab. Secondary peristalsis was produced by balloon distention 6 cm proximal to the lower esophageal sphincter. The balloon, attached to a catheter (ID = 1 mm, OD = 1.5 mm), was introduced through the mouth of the animal and inflated with 4 m of air to produce distention. The amplitude of esophageal contractions in response to both primary and secondary esophageal peristalsis was measured at a distance 2 cm proximal to the lower esophageal sphincter.

RESULTS

Effect of Dopamine on the Smooth Muscle Area of the Esophagus

A representative response of the lower esophageal sphincter and the distal smooth muscle area of the body of the esophagus to dopamine is shown in Fig. 1. Within half a minute after dopamine (6 μg/kg), there was prompt relaxation of the LES. LES relaxation was followed by repetitive contractions in the body of the esophagus as well as of the lower esophageal sphincter. The duration of LES relaxation and subsequent contractions in the body of the esophagus and the LES was brief and lasted for about 2 min. The repetitive contractions following dopamine injection in the body of the esophagus were seen at 2 cm as well as 4 cm proximal to the LES. There was no evidence of tachyphyllaxis with dopamine.

Relationship of the Dose of Dopamine to the Response of the LES

To examine if the LES relaxation to dopamine was dose-related or not, we tested the effect of doses of dopamine between 0.06 μg/kg and 12 μg/kg. Figure 2 illustrates that increasing doses of dopamine produced increasing degrees of LES relaxation. The threshold dose of dopamine was 0.25 μg/kg and the effect reached a plateau at about 6 μg/kg. It should be noted that 6.0 μg/kg of dopamine produced a reduction in LES pressure of 83.1% ± 2.8 (SE).

Relationship of the Dose of Dopamine to the Response of the Esophageal Body

Figure 3 shows that dopamine produced a dose-dependent increase in esophageal body contractions. Note that a dose of 0.25 μg/kg produced 0.75 ± 4.75 (SE) contractions within 5 min after the injection, whereas a dose of 6 μg/kg produced 11.6 ± 0.77 (SE) contractions within 5 min after the injection. Increasing the dose of dopamine from 6 μg/kg to 12 μg/kg produced slight increase in the number of contractions.

Effect of Pharmacological Antagonists on the Response of the Esophagus to Dopamine

In order to characterize the type of receptors mediating the response to dopamine, we tested the ability of various pharmacological antagonists to inhibit the response of the LES in the body of the esophagus. The doses of the antagonists were selected from previously published studies (6, 9, 10, 17).

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**FIG. 1.** A representative response of LES and distal portion of body of esophagus to intravenous administration of dopamine, 6 μg/kg. Lowest channel represents LES and upper two channels body of esophagus 2 cm and 4 cm proximal to lower esophageal sphincter.
Effect of antagonists on the response of the LES to dopamine. Figure 4 illustrates that the cholinergic muscarinic receptor blocking agent atropine (30 μg/kg), the adrenergic alpha-receptor blocking agent phentolamine (4 mg/kg), and the adrenergic beta-receptor blocking agent propranolol (2 mg/kg) did not antagonize LES relaxation induced by dopamine (3 μg/kg). The percent LES relaxations produced by dopamine (3 μg/kg) after atropine, phentolamine, and propranolol were 69.5 ± 1.8 (P > 0.5), 68.4 ± 2.4 (P > 0.5), and 69.5 ± 1.5 (P > 0.5), respectively. However, haloperidol (5 mg/kg), a dopamine receptor blocking agent, significantly antagonized the response of the LES to dopamine (P < .001). The antagonism exhibited by haloperidol was also observed with higher doses of dopamine (Fig. 5A). Although haloperidol antagonized the LES response to dopamine, the antagonism was not complete. Therefore, we tested the effect of another dopamine receptor blocking agent, bulbocapnine (5 mg/kg), on the response. Fig. 5B illustrates that bulbocapnine nearly completely abolished the response of the LES to dopamine. The percent LES relaxation produced by 3, 6, and 12 μg/kg of dopamine after treatment with bulbocapnine was 4.3 ± 1.36 (SE) (P < .001), 7.6 ± 2.39 (SE) (P < .001), and 16.7 ± 2.75 (SE) (P < .001) respectively.

Effect of antagonists on the response of the body of the esophagus to dopamine. Figure 6 illustrates that atropine (30 μg/kg), phentolamine (4 mg/kg), and propranolol (2 mg/kg) did not antagonize the contractile activity of the body of the esophagus that was induced by dopamine. The total number of esophageal contractions produced by dopamine (12 mg/kg) after atropine, phentolamine, and propranolol were 12.3 ± 0.66 (P > 0.5), 16.0 ± 0.57 (P > 0.2), and 9.2 ± 0.85 (P > 0.2), respectively. However, haloperidol (5 mg/kg) antagonized the dopamine response of the body of the esophagus. The total number of esophageal contractions produced by dopamine after haloperidol treatment was 2.6 ± 1.15 (P < .001). Because haloperidol itself stimulated contractions of the body of the esophagus, we tested the effect of bulbocapnine (5 mg/kg), another dopamine receptor blocking agent, on the response of the body of the esophagus.
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FIG. 5. A: effect of haloperidol (5 mg/kg) on response of LES to 3, 6, and 12 µg/kg doses of dopamine. Each bar represents mean ± SE of 7-10 experiments in five animals. Open bars indicate control data and hatched indicate data after administration of haloperidol. Different doses of dopamine are shown under each set of bars. B: effect of bulbocapnine on response of LES to 3, 6, and 12 µg/kg doses of dopamine. The bars have the same indications as those described in Fig. 5A. Bulbocapnine antagonized response of LES to doses of 3 µg/kg (P < .001), 6 µg/kg (P < .001), and 12 µg/kg (P < .001) of dopamine. Comparison of Fig. 5A and B indicates that at a dose of 5 mg/kg bulbocapnine is a much better dopamine receptor antagonist than haloperidol.

Intravenous administration of dopamine. The percents of LES relaxation produced by dopamine (12 µg/kg) before and after bilateral cervical vagotomy in four animals were 84.6 ± 4.33 (SE) and 83.3 ± 1.74 (SE), respectively. The difference was not statistically significant (P > 0.5). The numbers of esophageal contractions in the body of the esophagus produced by intravenous dopamine (12 µg/kg) before and after bilateral cervical vagotomy were 12.2 ± 1.24 (SE) and 14.8 ± 1.49 (SE), respectively. The difference was not statistically significant (P > 0.05).

Effect of Pharmacological Antagonists on Response of Body of Esophagus to Dopamine

Figure 6 illustrates that bulbocapnine nearly completely abolished the response of the body of the esophagus to dopamine. Figure 7 illustrates that bulbocapnine nearly completely abolished the response of the body of the esophagus to dopamine. The numbers of esophageal contractions produced by 3 µg/kg and 12 µg/kg of dopamine after bulbocapnine treatment were 1.4 ± 0.42 (P < .001) and 2.8 ± 0.96 (P < .001), respectively. No contractile response was seen with 3 µg/kg of dopamine (N = 12) after treatment with bulbocapnine.

Effect of Bilateral Cervical Vagotomy on the Response of the LES and Esophagus to Dopamine

Bilateral cervical vagotomy did not modify the response of the LES and the body of the esophagus to dopamine. Figure legends are same as that described in Fig. 6. Note that 3 µg/kg of dopamine uniformly failed to produce any contractile activity after bulbocapnine. Response of body of esophagus to 6 µg/kg of dopamine and 12 µg/kg of dopamine was also significantly antagonized by bulbocapnine. *Indicates significant differences (P < 0.01).
**Effect of Haloperidol and Bulbocapnine on Esophageal Response to Pharyngeal Stimulation and Esophageal Distention**

In order to examine if dopamine receptors played any role under physiological circumstances, we tested the effect of haloperidol (5 mg/kg) and bulbocapnine (5 mg/kg) on the response of the lower one third of the esophagus to pharyngeal stimulation and esophageal distention. Both pharyngeal stimulation as well as esophageal distention produced peristaltic contractions in the body of the esophagus and relaxation of the lower esophageal sphincter during control experiments as well as after administration of the antagonist. However, the amplitude of contractions in the lower one-third of the body of the esophagus in response to both pharyngeal stimulation and esophageal distention was significantly increased after administration of haloperidol (Table 1), as well as bulbocapnine (Table 2).

**TABLE 1. Amplitude of contraction in smooth muscle segment of esophagus in response to pharyngeal stimulation and esophageal distention during control periods and after administration of haloperidol**

<table>
<thead>
<tr>
<th>Rate of Total Water Infusion through Esophageal Catheters</th>
<th>Amplitude of Contraction, mmHg</th>
<th>Pharyngeal Stimulation</th>
<th>Esophageal Distention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>After haloperidol</td>
</tr>
<tr>
<td>0.42 ml/min</td>
<td></td>
<td>n = 13</td>
<td>n = 12</td>
</tr>
<tr>
<td></td>
<td>29.6 ± 3.8</td>
<td>55.3 ± 3.8</td>
<td>28.3 ± 2.4</td>
</tr>
<tr>
<td>1.08 ml/min</td>
<td></td>
<td>n = 12</td>
<td>n = 13</td>
</tr>
<tr>
<td></td>
<td>50.2 ± 1.82</td>
<td>83.6 ± 5.9</td>
<td>48.8 ± 3.0</td>
</tr>
<tr>
<td>2.2 ml/min</td>
<td></td>
<td>n = 13</td>
<td>n = 11</td>
</tr>
<tr>
<td></td>
<td>78.0 ± 1.82</td>
<td>105 ± 3.9</td>
<td>67.5 ± 3.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. Haloperidol, 5 mg/kg, in three animals.

**TABLE 2. Amplitude of contraction in smooth muscle segment of esophagus in response to pharyngeal stimulation and esophageal distention during control periods and after administration of bulbocapnine**

<table>
<thead>
<tr>
<th>Rate of Total Water Infusion through Esophageal Catheters</th>
<th>Amplitude of Contraction, mmHg</th>
<th>Pharyngeal Stimulation</th>
<th>Esophageal Distention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>After bulbocapnine</td>
</tr>
<tr>
<td>0.42 ml/min</td>
<td></td>
<td>n = 12</td>
<td>n = 7</td>
</tr>
<tr>
<td></td>
<td>23.6 ± 1.86</td>
<td>47.2 ± 2.64</td>
<td>22.1 ± 2.00</td>
</tr>
<tr>
<td>1.08 ml/min</td>
<td></td>
<td>n = 8</td>
<td>n = 7</td>
</tr>
<tr>
<td></td>
<td>47.0 ± 2.54</td>
<td>73.4 ± 5.37</td>
<td>42.1 ± 3.48</td>
</tr>
<tr>
<td>2.2 ml/min</td>
<td></td>
<td>n = 11</td>
<td>n = 8</td>
</tr>
<tr>
<td></td>
<td>73.1 ± 3.12</td>
<td>98.3 ± 3.02</td>
<td>72.4 ± 3.97</td>
</tr>
</tbody>
</table>

Values are means ± SE. Bulbocapnine, 5 mg/kg.

**DISCUSSION**

The present study demonstrates that dopamine, administered intravenously, produces a dose-dependent relaxation of the LES, and a dose-related increase in the contractile activity of the body of the esophagus. The response of the smooth muscle area of the esophagus to dopamine could be mediated by adrenergic, cholinergic, or dopaminergic receptors. The present study demonstrates that the effect is not mediated by cholinergic muscarinic and adrenergic alpha- or beta-receptors. Both haloperidol and bulbocapnine have been shown to be dopamine receptor blocking agents (9, 18), and both antagonized the smooth muscle response of the esophagus to dopamine. Thus, in terms of pharmacological antagonists, the response of the LES and the body of the esophagus to intravenous dopamine is mediated through specific dopamine receptors.

The evidence that dopamine receptor stimulation mediates relaxation of the LES and contraction of the body of the esophagus generates several questions. First, is this a vagally mediated response? Because bilateral cervical vagotomy did not alter the smooth muscle response, it is unlikely that the dopamine response is mediated by vagal centers in the brain stem. Second, where are these receptors located? DeCarle and Christensen (5) have recently demonstrated that strips from the smooth muscle area of the opossum esophagus contain dopamine receptors. Thus, the receptors that respond to intravenous dopamine are likely to be those in the wall of the esophagus. The present study, as well as the in vitro study with smooth muscle strips, clearly indicate the noncholinergic, nonadrenergic character of the dopamine response. Moreover, the dopamine response in esophageal smooth muscle is not tetrodotoxin sensitive (5, 14), thus indicating that the effect is likely to be direct on smooth muscle. Third, what is the significance of dopamine-induced esophageal contractions? Is this a stimulatory effect of dopamine? Dopamine may have both stimulatory and inhibitory effects in different areas of the same organ (1). Cools and VanRossum (4) have recently described two populations of dopamine receptors: excitation-mediating dopamine receptors and inhibition-mediating dopamine receptors. They have proposed that balance between the two types of receptors is an essential prerequisite for normal function of the neural structures having dopamine receptors. Although the dopamine receptors in the esophagus are likely to be on the smooth muscle rather than on the nerves (6), one can argue that the dopamine-induced relaxation of the lower esophageal sphincter represents the effect of inhibitory receptors, and the dopamine induced contractions in the body of the esophagus and the LES represent the effect of stimulatory receptors. DeCarle and Christensen (5), in their in vitro study, also noted contractile activity in the strips taken from the body of the esophagus as well as the LES. The effect was unresponsive to 10^-7 tetrodotoxin. Both in our study, as well as the in vitro study, the contractions in the body of the esophagus always followed the initial inhibitory response observed in the lower esophageal sphincter. Thus, another explanation for the dopamine-induced contractions may be that these are rebound...
contractions (3). Last, are the dopamine receptors physiologically important? Dopamine is generally considered important only as a precursor substance in the biosynthesis of norepinephrine. However, there is growing evidence that in addition to its role as a precursor substance, endogenous dopamine may perform other important functions. Dopamine is the predominant catecholamine present in a number of organs and tissues, including the gastrointestinal tract of several species (7). Dopamine is the main catecholamine present in the nervous system in mollusks (12), where it appears to meet several of the criteria proposed for the identification of a synaptic transmitter for the slow inhibitory postsynaptic potential, as well as a modulator of the slow excitatory postsynaptic potential in mammalian sympathetic ganglion cells (16, 17). Finally, dopamine has been found in the small intensely fluorescent cells in sympathetic ganglia (2). The pattern of smooth muscle response of the esophagus to dopamine in the present study is similar to that seen after stimulation of the distal cut end of the vagus nerve, pharyngeal stimulation, and esophageal distention. In all of the above situations, the LES relaxation is brisk, and the onset of LES relaxation precedes the arrival of esophageal contractions to the LES. Therefore, one might speculate that dopamine could play a role in the control of LES relaxation produced by dopamine. J. Pharmocol. Exptl. Therap. 168: 303-309, 1976.

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Thus, dopamine is unlikely to be the substance released after pharyngeal stimulation, esophageal distention, and electrical field stimulation although it is recognized that the interaction of endogenously released dopamine and its receptor may not be fully accessible to the antagonists used. The significant increase in the amplitude of esophageal contractions after dopamine receptor blockade by two structurally different dopamine antagonists indicate that dopamine receptors may be involved in the regulation of the amplitude of esophageal contractions under physiological circumstances. This also indicates that the predominant effect of dopamine receptors in the body of the esophagus is inhibitory. This concept is in agreement with the observation that dopamine inhibited the "off" response contractions in the strips taken from the body of the esophagus (5).

In summary, the present study demonstrates that the opossum esophagus responds to intravenous dopamine via the mediation of the specific dopamine receptors. These dopamine receptors are inhibitory to both the lower esophageal sphincter and the body of the esophagus. The inhibitory dopamine receptors in the body of the esophagus may have a physiological role in controlling the amplitude of esophageal contractions during swallowing and in response to esophageal distention.

We thank Drs. J. R. Johnson, G. Eknoyan, and G. A. Castro for helpful suggestions and comments.

This work was supported in part by the Kelsey and Leer Foundation Grant (962), Houston, Texas and the National Institute of Health Grant AM 16305.

Dr. Weisbrodt was the recipient of the Public Health Service Research Scientist Development Award DA 00022.

Received for publication 5 April 1976.