Motor Effect of Dopamine on Human Sigmoid Colon

Evidence for Specific Receptors

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The effect of dopamine on human sigmoid motility has been studied in 26 subjects. To record mechanical activity of the sigmoid colon, two small, air-filled balloons mounted on a probe introduced through a sigmoidoscope were used. The recordings were made at a distance of 25 and 15 cm from the anal edge. Dopamine was infused for 10 min after a 30-min control infusion of physiologic solution. Mean amplitude, mean duration, mean frequency, percentage of motor activity, and motility index of the pressure waves were determined. The motor response to dopamine was characterized by an increased baseline pressure with phasic waves superimposed. Dopamine produced a significant response at the dose of 5 μg/kg/min. Alpha and beta antagonizing agents failed to oppose the effect of dopamine, while anticholinergic drugs enhanced its motor action. These studies suggest that dopamine may stimulate the motor function of human large bowel through specific receptors.

The role of the adrenergic system in the regulation of human colonic motility has not been fully elucidated. Although cathecolamines usually exert an inhibitory motor effect on the gastrointestinal tract, in our previous work (1) we showed that a beta-stimulating agent is able to elicit a motor response in human sigmoid colon.

Dopamine (D), 3,4-dihydroxyphenylethylamine, the third endogenous cathecolamine, has similar properties to other adrenergic-stimulating agents. Acting on alpha agonists it produces peripheral vasoconstriction (2); as a beta agonist it increases heart rate and myocardial contractility (3). Dopamine also differs from endogenous and synthetic amines by exerting vasodilatation on intracerebral (4), renal, and mesenteric vascular beds (3); by reducing the lower-esophageal sphincter pressure; and by contracting the lowermost part of the body of the opossum esophagus, an action not opposed by alpha and beta antagonists (5).

At the present time it is widely accepted that D has a physiologic role as a neurotransmitter in the central nervous system, and there is some evidence that it may act as a transmitter in the peripheral nervous system as well (6, 7): (1) specific dopaminergic receptors exist in blood vessels and esophageal muscle; they are blocked by dopaminergic antagonists including butyrophenones and phenothiazines (8–10); (2) D is excreted in the urine in amounts 10–20 times that of free adrenaline and noradrenaline (11); (3) D is present in the sympathetic ganglia and other regions of the human body (12, 13).

In the gastrointestinal tract D has been found in pancreas, gastric juice, liver, intestinal mucosa, and spleen (14), and it has been reported to stimulate pancreatic secretion (15). The purpose of this study is: (1) to evaluate the effect of D on human sigmoid motility, and (2) to clarify the presence of specific dopaminergic receptors.

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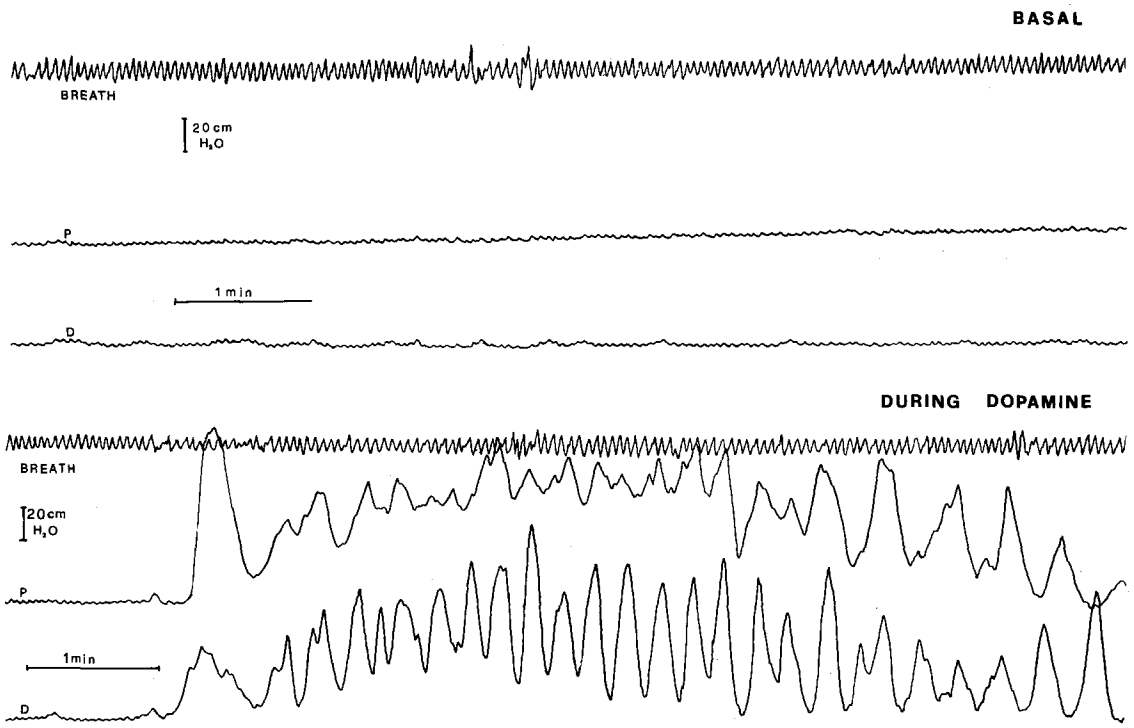

Fig 1. Mechanical recording of colonic sigmoid motility from proximal (P) and distal (D) balloon during basal condition (upper part) and during infusion of dopamine 5 μg (lower part).

MATERIALS AND METHODS

We studied colonic motility in 26 subjects; 23 of them were affected by various colonic diseases: irritable bowel, idiopathic constipation, chronic ulcerative colitis; 3 subjects were considered to be normal. We considered all the cases studied as belonging to one group only, because a uniform motor behavior was noted after the infusion of D. To record colonic mechanical activity, we used an intraluminal probe with two small, air-filled balloons (2.5 × 1 cm) mounted 10 cm apart on it. The balloons were positioned through a sigmoidoscope, the proximal one usually lying 25–30 cm from the anal edge. The pressures were recorded using Statham transducers (model P231a).

All patients had a small enema of 200 ml of warm tap water 3 hr before sigmoidoscopy. Forty-five minutes were allowed for the patient to recover after the introduction of the probe, then basal recording was performed for 30 min with the patient lying in the left lateral decubitus position. During this 30 min of basal recording, a physiologic solution (1 ml/min) was infused in the cubital vein of the left arm. Then D, 5 μg/kg/min, diluted in 10 ml of the same solution, was infused for 10 min.

We chose this amount of the drug after a preliminary

TABLE 1. EFFECT OF 5 μG/KG/MIN OF DOPAMINE ON FREQUENCY, DURATION, AMPLITUDE, PERCENTAGE OF THE WAVES, AND MOTILITY INDEX (MI)*

	Frequency		*Duration*		*Amplitude*		*Percentage*		*MI*	
	B	*D*	*B*	*D*	*B*	*D*	*B*	*D*	*B*	*D*
Mean	0.76	1.96	24.3	24.2	12.3	21.04	35.22	76.6	496	1718
SE	0.12	0.19	2.7	1.7	1.6	2.5	5.5	5.7	109	286
P		<0.01		N.S.		<0.01		<0.01		<0.01

*B = basal; D = dopamine.

study where D was administered intravenously at different doses: 1 (5 cases), 5 (5 cases), 10 (2 cases), and 20 μg/kg/min (2 cases). Each dose was tested for a period of 10 min. At the dose of 1 μg the pressure increase did not reach statistical significance; however, with the dose of 5 μg a statistically significant increase occurred. With the higher doses the study was limited to 4 patients only, because nausea and agitation developed in 3 of them. The motor response to D was evaluated during the 10-min infusion only, because of the immediate cessation of the effect after the termination of the drug infusion.

In some tests, physiologic solution was administered again after D for 30 min, then the infusion of D for 10 min was repeated at the same dose in association with a probable antagonist: a beta-antagonizing agent (propranolol 1 mg/min for 10 min in 5 cases), an alpha-antagonizing agent (phentolamine 1 mg/kg for 10 min in 5 cases), and atropine (1 mg intravenously, a bolus injection 5 min before the administration of D in 5 cases).

The following parameters have been calculated to analyze the pressure recordings obtained from the proximal balloon: mean frequency, mean amplitude, mean duration of the pressure waves, percentage of motor activity (whole duration time of the waves × recording time in min (%), and motility index (MI) obtained multiplying the mean amplitude by the percentage duration of activity.

Heart rate and systolic blood pressure were monitored during the whole test. The action of the drug during the 10-min infusion was compared to the 30 basal min in which physiologic solution was administered and to the 10 min when D was associated with a probable antagonist. The values obtained were evaluated with the Student's *t* test for paired data. The nature and the consequences of the test were explained to the patients who gave informed consent.

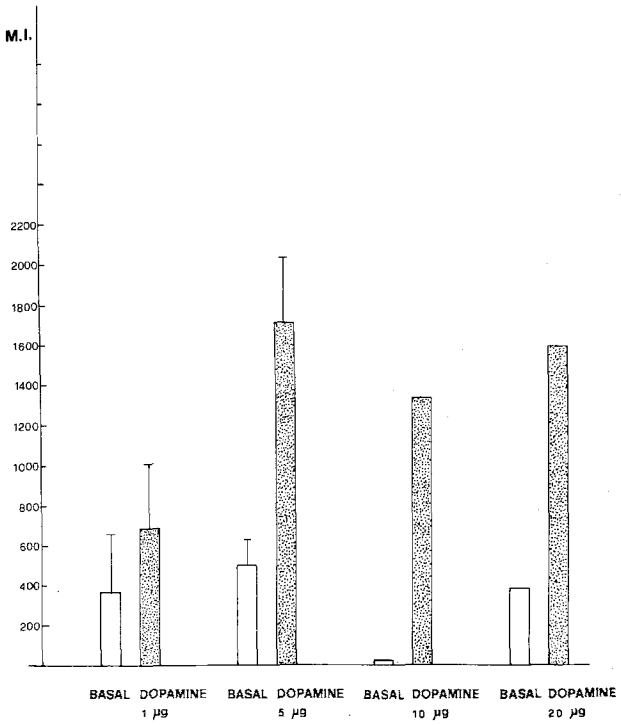

Fig 2. Bar graph of motility index (mean ± SE) in basal condition and after dopamine 1 μg in 5 cases (N.S.); after 5 μg in 17 cases ($P < 0.01$); after 10 μg in 2 cases, and after 20 μg in 2 cases.

RESULTS

Motor response to D started in the first minute of the infusion and was very strong. There was an increase in the basal pressure with secondary waves superimposed (Figure 1). The mean frequency of the pressure waves was 2 or 3/min, and the maximum achieved was 4. The active phase lasted half of the total infusion time, then decreased to basal level before the termination of the drug infusion. When recordings from both the balloons were satis-

TABLE 2. EFFECT OF DOPAMINE*

	Basal			*Dopamine*		
	MI	*HR*	*BP*	*MI*	*HR*	*BP*
5 cases with 1 μg/kg/min	355 ± 248	69 ± 4.7	98 ± 2.4	686 ± 333 N.S.	73 ± 4.7 $P < 0.02$	99 ± 3.1 N.S.
17 cases with 5 μg/kg/min	496 ± 109	65 ± 2	103 ± 2	1718 ± 286 $P < 0.01$	72 ± 2 $P < 0.01$	107 ± 2 $P < 0.01$
2 cases with 10 μg/kg/min	0	70	115	1339	79	123
2 cases with 20 μg/kg/min	365	70	112	1568	86	157

*MI = motility index; HR = heart rate; BP = blood pressure (mean ± SE).

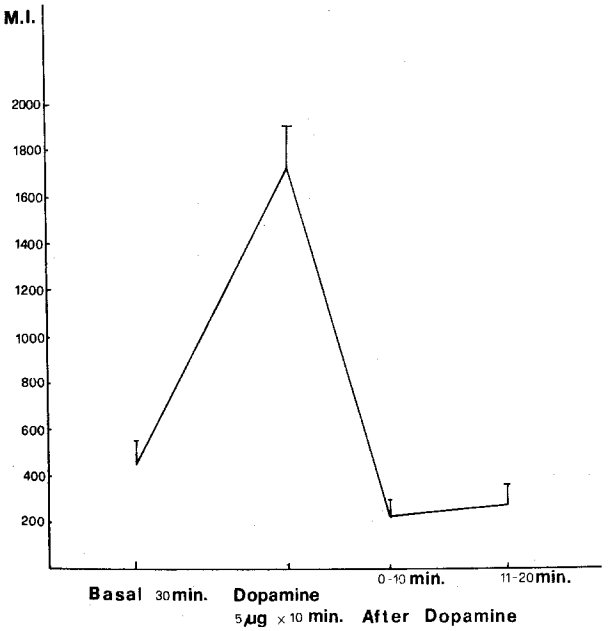

Fig 3. Behavior of motility index (mean ± SE) before, during, and after dopamine infusion, 5 μg, in 17 patients. The increase of motility index during dopamine and the decrease in the 10 min after dopamine is different from the values obtained in the basal condition ($P < 0.01$).

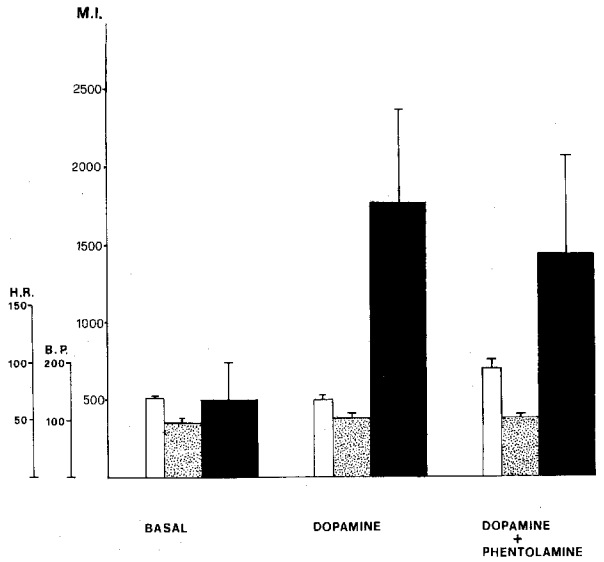

Fig 4. Effect of dopamine 5 μg and dopamine 5 μg + phentolamine 10 mg on heart rate, blood pressure, and motility index (mean ± SE) of sigmoid colon in 5 subjects. An alpha-antagonist, given in combination with dopamine, does not significantly change the values of motility index obtained with dopamine alone.

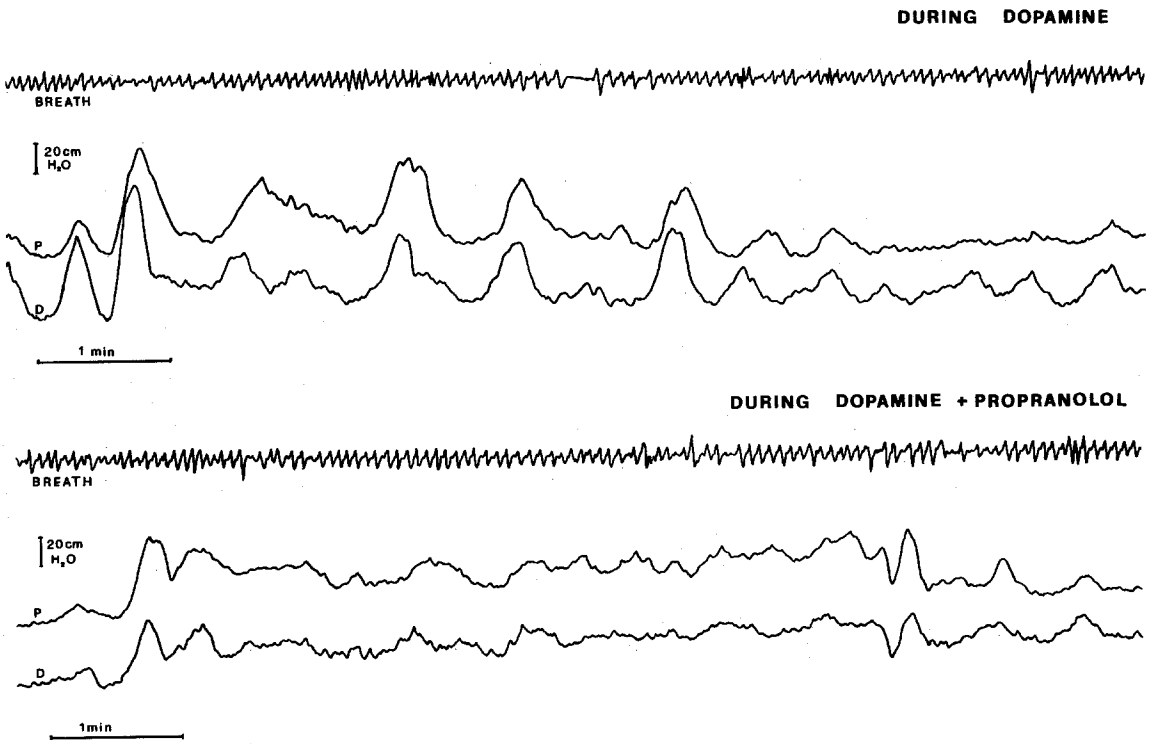

Fig 5. Mechanical recording of colonic sigmoid motility from proximal (P) and distal (D) balloon during dopamine 5 μg (upper part) and during dopamine 5 μg + propranolol 10 mg (lower part).

factory, no quantitative difference was noted in the two trains of waves, but qualitatively, at times, all the distal waves induced by D preceded the proximal ones by 5 sec.

Increasing doses of D did not induce a constant increase of the sigmoid motor activity (Figure 2): in fact the values of the parameters studied after the dose of 1 μg were higher than the basal, but none was significantly more than in the basal period. At the dose of 5 μg, all the parameters considered, except the mean duration of the pressure waves, increased significantly (Table 1). At doses 10 and 20 μg/kg/min there seemed to be a decrease of the effect, but it was not possible to make a statistical evaluation because of the low number of cases studied (Table 2).

Systolic blood pressure and heart rate both increased significantly at the dose of 5 μg/kg/min (Table 2). The motor activity of the 10 min following the suspension of D decreased to levels significantly inferior to the basal values, then after 20 min the values returned to basal level (Figure 3).

Alpha- and beta-adrenergic antagonizing agents administered in combination with D did not modify the motor activity from the values obtained with D alone (Figures 4–6). When atropine was given be-

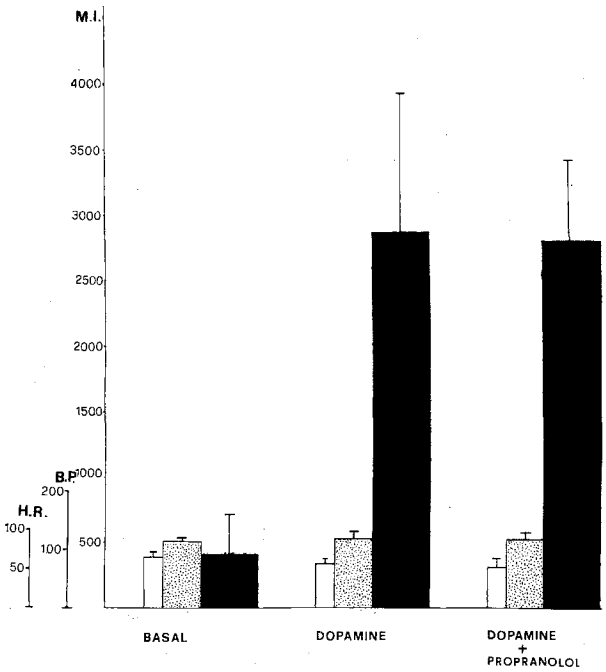

Fig 6. Effect of dopamine 5 μg and dopamine 5 μg + propranolol 10 mg on heart rate, blood pressure, and motility index (mean ± SE) of sigmoid colon in 5 subjects. A beta-antagonist, given in combination with dopamine, does not significantly change the values of motility index obtained with dopamine alone.

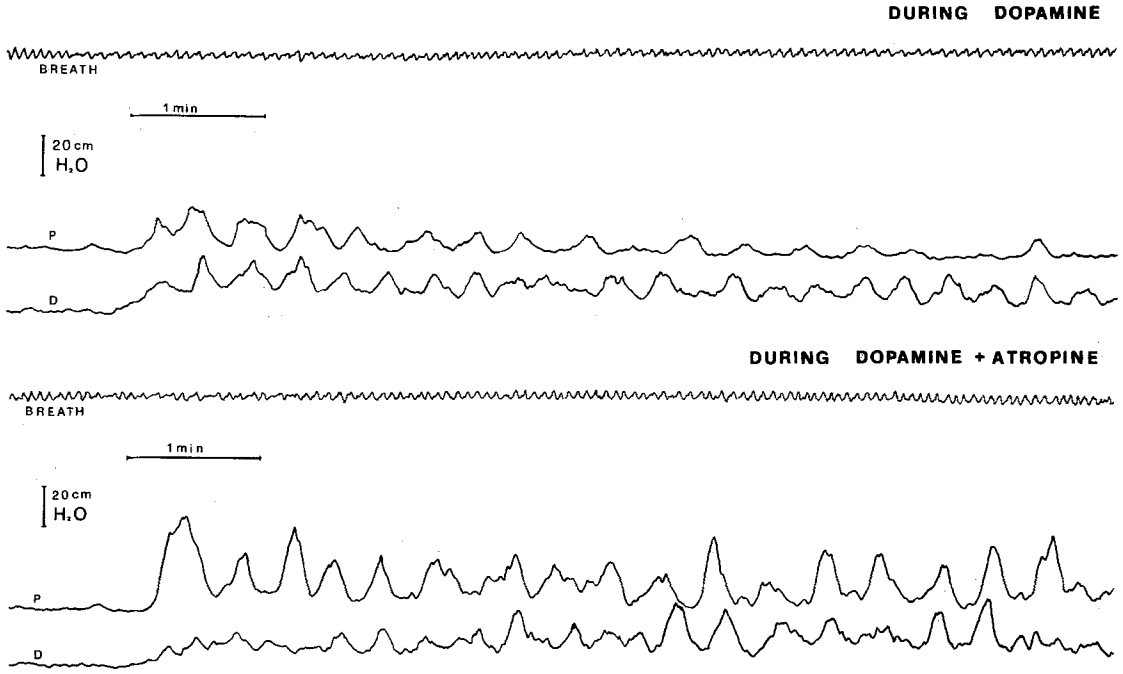

Fig 7. Mechanical recording of colonic sigmoid motility from proximal (P) and distal (D) balloon during dopamine 5 μg (upper part) and during dopamine 5 μg + atropine 1 mg (lower part).

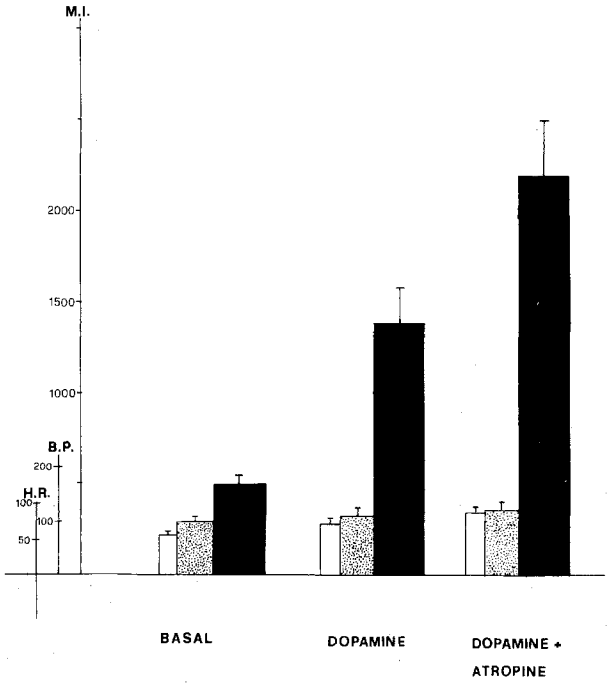

Fig 8. Effect of dopamine 5 μg and dopamine 5 μg + atropine 1 mg on heart rate, blood pressure, and motility index (mean ± SE) of sigmoid colon in 5 subjects. A cholinergic antagonist, given in combination with dopamine, induces a significant increase of motility index in comparison with the values obtained with dopamine alone ($P < 0.01$).

fore D, the response to D was increased to values significantly higher than when it was infused alone ($P < 0.01$) (Figures 7 and 8): MI with D alone was 1430 ± 201; MI with D + atropine, 2238 ± 291. This increase was maintained throughout the infusion period.

DISCUSSION

The motor effect of D on the human sigmoid colon, as well as on the cardiovascular system, may be due to direct action on the colon or it may be secondary to a primary response elsewhere. As the action of D is not opposed by alpha and beta antagonists, D does not act as a precursor of noradrenaline or adrenaline, nor does it combine with alpha- or beta-adrenergic receptors. Furthermore, D does not act through a cholinergic mediation because atropine fails to inhibit its motor-stimulant effect; on the contrary, there was a significant increase in this effect after cholinergic blockade. The reason for this is not quite clear, but presumably some atropine-sensitive cholinergic system opposes the action of D. Another possible explanation may be that atropine prolongs the biologic half-life of D; this phenomenon has been previously noted regarding beta-antagonizing agents in comparison to beta-stimulating agents (16). Our data suggest that D acts on a nonadrenergic, noncholinergic system or on an adrenergic system with specific receptors for D, but do not reveal whether the dopamine receptor leading to motor effect on the large bowel is present there or elsewhere.

Regarding the propulsion effect of the contents, some data indicate that D induces a nonpropulsive type of motility. In patients where motility was satisfactorily recorded at two different sites simultaneously, no coordination between the two trains of waves was noted after D, and occasionally the direction of the waves was distal to proximal. In addition, spot-fluorographic studies (unpublished data) in 5 subjects, with a film analysis every 2 min, show that the motor response to D is located in the whole large bowel and that it is of segmentary type, with no consistent progression of contents.

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