EFFECT OF DOPAMINE ON SMOOTH MUSCLES OF THE RAT STOMACH AND CHARACTERISTICS OF α ADRENORECEPTORS OF MUSCLE CELLS OF THE GASTROINTESTINAL TRACT

I. V. Komissarov and G. I. Reutskaya

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Dopamine and phenylephrine lower the tone of the smooth muscles of isolated strips of rat stomach in concentrations of 10^{-6} M or more. The concentration–effect curves have the same slope. The effect of dopamine is unchanged in the presence of propranolol ($5 \cdot 10^{-6}$ g/ml). Phentolamine (and also dihydroergotamine and tropaphen*) exhibits equal antagonism to phenylephrine and dopamine. It is concluded that dopamine and phenylephrine relax the smooth muscles of the stomach by their action on α adrenoreceptors. The latter differ from the α adrenoreceptors of the vas deferens (rats) in their high sensitivity to the blocking effect of certain neuroleptics, namely haloperidol, trifluoroperazine, and chlorpromazine, pA_2 for which (8.11-8.64) is of the same order as pA_2 for α adrenolytics (7.76-8.46). The similarity and difference between α adrenoreceptors of muscles of the gastrointestinal tract and inhibitory dopaminergic receptors of nerve cells are discussed.

KEY WORDS: catecholamines; dopamine; adrenoreceptors; smooth muscles.

Dopamine has mainly a direct sympathomimetic action on the smooth muscles, including the gastrointestinal tract [5, 11]. Since the inhibitory effect of catecholamines on smooth muscles of the mammalian stomach and intestine can be mediated by both α and β adrenoreceptors [8], it is not clear which of them is responsible for the dopamine effect.

This paper gives the pharmacological characteristics of adrenergic receptors of the smooth muscles of the rat stomach responsible for transmitting the inhibitory effects of dopamine.

EXPERIMENTAL METHOD

Isolated strips of the gastric fundus of albino rats weighing 150-200 g were kept in oxygenated Tyrode's solution at 37°C. Changes in tone were recorded by Engelmann's lever with a ratio of 1:20 between the arms and with a weight of 1 g attached to the preparation. The effect of dopamine (hydrochloride) and phenylephrine on tone of the muscle strip was investigated in concentrations of 10^{-8}-10^{-2}M. The effect was expressed as a percentage of the maximal relaxation. The values of pA_2 were found by Schild's method [17] for phentolamine, dihydroergotamine, tropaphen, chlorpromazine, haloperidol, trifluoroperazine, and perphenazine, chosen as antagonists of dopamine and phenylalanine. The duration of action of the antagonists on the strip was 7 min. The values of pA_2 for phentolamine and haloperidol also were determined in experiments on the rat vas deferens, kept in oxygenated Krebs' solution.

Each series of experiments was carried out on 6 to 8 isolated preparations. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS AND DISCUSSION

In low concentrations, dopamine and phenylephrine caused only slight contractions of the smooth muscles of the strip of stomach, but in concentrations of 10^{-6} M or higher they reduced their tone (Fig. 1: 1,2). Phenyl-

*The tropine ester of β-acetoxyphenyl-α-phenylpropionic acid (a sympatholytic).

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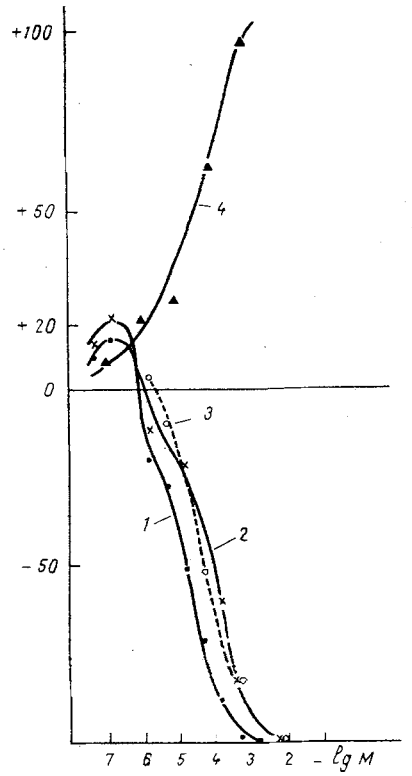

Fig. 1. Effect of phenylephrine, dopamine, and apomorphine on tone of smooth muscles of rat stomach. Abscissa, concentration of substances on logarithmic scale; ordinate, contraction of strip of stomach as a percentage of maximal relaxation. 1) Phenylephrine, 2) dopamine, 3) dopamine in the presence of propranolol, $5 \cdot 10^{-6}$ mg/ml, 4) apomorphine.

ephrine was almost 5 times as active as dopamine: EC_{50} was $1.6 \cdot 10^{-5}$ and $7.9 \cdot 10^{-5}$ M respectively ($P \leq 0.05$). Maximal relaxation of the strip produced by dopamine (79 ± 16 mm) was about 80% of the maximal effect of phenylephrine. However, the gradients of the effect curves of dopamine and phenylephrine (0.78 and 0.7 respectively; $P > 0.5$) did not differ significantly.

The coincidence of the gradients of the concentration–effect curves is evidence that the two amines share a common mechanism of action. Since phenylephrine is regarded as a sympathomimetic with selective action on the intestinal α adrenoreceptors [7], it can be postulated that dopamine causes relaxation of the smooth muscles of the rat stomach through their intervention also. This suggestion is confirmed by the steepness of slope of the concentration–effect curve of dopamine, which is characteristic of α but not of β adrenomimetics [1, 7], by the absence of effect of propranolol ($5 \cdot 10^{-6}$ g/ml) on the effects of dopamine (Fig. 1:3), and also by agreement between the values of pA_2 of phentolamine, which exhibits an equal degree of antagonism with respect to both phenylephrine and dopamine (Table 1). It will also be clear from Table 1 that an equal degree of antagonism toward dopamine and phenylephrine is also shown by other α adrenolytics – dihydroergotamine and tropaphen. This same degree of antagonism to both amines is a feature of most of the neuroleptics studied: chlorpromazine, trifluoperazine, and haloperidol. The equal sensitivity of the α-adrenoreceptors of the gastric muscles to the blocking effect not only of α adrenolytics, but also of many neuroleptics, distinguishes the α adrenoreceptors of the smooth muscles of the gastrointestinal tract from the α adrenoreceptors through which catecholamines cause excitation and contraction of the smooth muscles of other organs. This provides further grounds for the separation of adrenergic receptors into excitatory α_1 and inhibitory α_2 adrenoreceptors [3]. The activity of phentolamine as a blocker of α_1 adrenoreceptors of the rat

TABLE 1. Values of pA_2 of Some Antagonists of Phenylephrine and Dopamine, Determined on Strips of Rat Stomach (M ± m)

Antagonist	Agonist	
	phenylephrine	dopamine
Phentolamine	7,76±0,27	7,76±0,18
Dihydroergotamine	8,92±0,28	8,41±0,14
Tropaphen	7,42±0,38	8,46±0,23
Chlorpromazine	8,32±0,22	8,49±0,14
Trifluoperizine	8,76±0,19	8,11±0,22
Haloperidol	8,58±0,15	8,64±0,31
Perphenazine	5,82±0,21	6,17±0,23

TABLE 2. Values of pA_2 of Antagonists of Sympathomimetics Found in Experiments on the Rat Vas Deferens (M ± m)

Agonist	Antagonist	
	phentolamine	haloperidol
Noradrenalin	8,53±0,08	5,65±0,15
Dopamine	8,58±0,16	5,60±0,03
Phenylephrine	7,81±0,28	5,74±0,22

vas deferens is 2-2.5 orders of magnitude greater than the analogous activity of haloperidol (Table 2). As a blocker of α_2 adrenoreceptors, haloperidol is somewhat more active than phentolamine (Table 1).

The results of several investigations indicate that haloperidol, other butyrophenones, and many phenothiazine neuroleptics [14] selectively block specific dopaminergic receptors (DA receptors). The high activity of haloperidol and the other neuroleptics revealed in the experiments on strips of stomach (Table 1) necessitates a discussion of the problem that the DNA receptors of certain nerve cells may be identical with the α_2 adrenoreceptors of the muscle cells of the gastrointestinal tract. Evidence of the similarity of these receptors is given by the possibility of abolishing changes in the membrane potential of mollusk ganglionic neurons evoked by dopamine by means of both ergotamine and phentolamine [12] and haloperidol and fluphenazine [13], and also by the common nature of the ionic mechanisms of action of dopamine on mollusk neurons [16] and the action of noradrenalin on the smooth muscles of the rat intestine [15] and stomach [2]. The dopaminomimetic apomorphine does not inhibit the neuronal activity of Helix aspersa [18] and does not lower the tone of the smooth muscles of the rat stomach (Fig. 1: 4). Conversely, apomorphine causes marked contractions of strips of stomach. The contractions are cholinergic in nature for they are abolished by atropine (10^{-7}-10^{-6} g/ml) but not by diphenyhydramine (10^{-5} g/ml) or methysergide (10^{-7} g/ml).

However, the α_2 adrenoreceptors of the muscles of the gastrointestinal tract are not identical with the DA receptors of mollusk neurons, for the latter have higher sensitivity to dopamine than to noradrenalin, and phenylephrine does not activate them even in high concentrations [19]. DA receptors of a completely different type, blocked exclusively by neuroleptics, are found in the neurons of the caudal mesenteric ganglion of cats [4] and of the caudate nucleus of rats [6, 10].

It is possible that α_2 adrenoreceptors are localized in the membranes of certain nerve cells, of the superior cervical ganglion for example, where the inhibitory effect of dopamine on cholinergic conduction is depressed equally by phentolamine and haloperidol [4]

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