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Effects of dopamine in isolated rat colon strips

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Abstract: The aim of the present work is to investigate the effects of dopamine on isolated rat colon strips, and whether dopamine receptors are involved in these effects. Experiments on spontaneous motility and under potassium contraction were performed with dopamine and isoprenaline, both in the absence and presence of antagonists (distal colon strips, isotonic recording, Tyrode solution, 31 °C, 1 g of resting tension). At higher concentration (10^{-4} mol/L), dopamine abolished spontaneous motility of the rat colon and this effect was not modified by antagonists. In isolated rat colon strips that were depolarized with potassium, dopamine produced concentration-dependent relaxation, without significant differences in reserpinized rats. Preincubation with sulpiride or Sch 23390, dopamine antagonists, did not modify the effects of dopamine. Propranolol shifted the concentration-response curve to the right, though in a noncompetitive manner. Prazosin and yohimbine (α-antagonists) did not modify the response to dopamine. Isoprenaline produced a concentration-dependent relaxant response to the KCl-induced contraction antagonized by propranolol, but not by prazosin, in a noncompetitive manner. In conclusion, dopamine exhibits a relaxant effect on the isolated rat colon, which is not mediated by specific dopamine receptors or α-adrenoceptors but it may be mediated by atypical β-adrenoceptors.

Key words: dopamine, isolated rat colon, dopamine receptors.

Résumé : Le présent travail a pour but d'examiner les effets de la dopamine sur des bandelettes de côlon isolé de rats et de déterminer si les récepteurs de la dopamine jouent un rôle dans ces effets. On a effectué des expériences sur la motilité spontanée et lors de contractions induites par le potassium, en utilisant de la dopamine et de l'isoprénaline tant en absence qu'en présence d'antagonistes (bandelettes de côlon distal, enregistrement isotonique, solution de Tyrode, 31 °C, tension de repos 1 g). À concentration élevée (10^{-4} mol/L), la dopamine a supprimé la motilité spontanée du côlon, et cet effet n'a pas été modifié par les antagonistes. Dans les bandelettes isolées dépolarisées avec du potassium, la dopamine a provoqué une relaxation concentration dépendante, et il n'y a pas eu de différence significative chez les rats traités à la réserpine. La préincubation avec les antagonistes de la dopamine, sulpiride ou Sch 23390, n'a pas modifié les effets de la dopamine. Le propranolol a déplacé la courbe concentration-réponse vers la droite, quoique de manière non compétitive. Les antagonistes alpha, prazosine et yohimbine, n'ont pas modifié la réponse à la dopamine. L'isoprénaline a induit une réponse relaxante dépendante de la concentration à la contraction induite par le KCl, laquelle a été antagonisée de manière non compétitive par le propranolol, mais pas par la prazosine. Ainsi, la dopamine a un effet relaxant sur le côlon isolé de rat; cet effet n'est pas transmis par les récepteurs spécifiques de la dopamine ou les adrénorécepteurs alpha, mais pourrait être induit par des adrénorécepteurs bêta atypiques.

Mots clés : dopamine, côlon isolé de rat, récepteurs de la dopamine.

[Traduit par la Rédaction]

Introduction

The colon shows more interspecies variation in its anatomy and physiology than most organs. For example, rat colon is less sensitive to noradrenaline than human and rabbit taenia coli (Burleigh et al. 1984), and the electrophysiological properties of the colon circular muscle are very different among species (Huizinga and Daniel 1991). Moreover, the effects of different agents on the intestine depend on experimental conditions or drug used (Gagnon et al. 1972; Aguilar et al. 1986; Martínez-Abad et al. 1996).

Endogenous dopamine plays a physiological role in the gastrointestinal tract, but whether dopamine receptors are involved remains controversial (Lefebvre 1990; Walker et al. 2000). Additionally, it is well-known that dopamine not only interacts with dopamine receptors, but also with α- and β-adrenoceptors (Goldberg et al. 1978).

In dogs, dopamine did not modify the contraction of the ascending and transverse colon, but increased the activity of the descending colon (Bueno et al. 1984). In vitro experiments showed that dopamine relaxed the dog isolated colon strips, and that effect was antagonized by α- and β-blocking

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agents (Grivegnee et al. 1984). In mouse colon, dopamine produced concentration-dependent contractions that were reversed into relaxation when dopamine was added at concentrations above 10^{-5} mol/L, probably because of interactions with α-adrenoceptors (Fontaine et al. 1984). In contrast, in rat distal colon, catecholamines induced responses that were not mediated by α-adrenoceptors because the responses to noradrenaline were resistant to the classical α-adrenoceptor antagonist, phentolamine, and to cirazoline and UK 14304, selective α_1- and α_2-adrenoceptor antagonists (McLaughlin and MacDonald 1990). Ek et al. (1986) suggested that β_1- and β_2-adrenoceptors could inhibit rat colonic motility, and Bianchetti and Manara (1990) described the existence of β-adrenoceptors different from classical β_1 and β_2 subtypes for rat proximal colon. Moreover, a nonadrenergic-noncholinergic system mediated by nitric oxide release has been observed in rat colon (Serio et al. 1995). In isolated guinea pig, colon atypical adrenoceptors have also been described (Horinouchi et al. 2003).

All these results support the views of Walker et al. (2000), who suggested that the mechanisms by which dopamine influences gastrointestinal tract motility are incompletely understood and complicated by tissue- and species-specific differences in dopaminergic function. The aim of the present work is to investigate the effects of dopamine on isolated rat colon strips, and whether dopamine receptors are involved in these effects.

Materials and methods

Adult Wistar rats weighing 200–250 g were used. Animals were housed under laboratory standard conditions on a 12 h light: 12 h dark cycle (lights on 8:00 a.m.; lights off 8:00 p.m.) in the rooms in which temperature (20–22 °C) and relative air humidity (50% ± 5%) were strictly regulated. Food and water were available ad libitum. Rats were used in accordance with the Institutional Guideline for the Care and Use of Laboratory Animals.

Tissue preparation

Rats were killed by cervical dislocation. The abdomen was opened to expose the intestine, and the distal colon (immediately adjacent to the caecum) was rapidly removed and immersed in Tyrode solution. Longitudinal muscle strips, about 20 mm × 4 mm, were prepared by cutting the distal colon along the longitudinal axis and were suspended under a load of 1 g in a 20 mL organ bath containing Tyrode solution at 31 °C. The composition of the latter was, in mmol/L: NaCl 136, KCl 2.7, $CaCl_2$ 1.4, $MgSO_4$ 0.04, KH_2PO_4 0.4, $NaHCO_3$ 11.9, and glucose 5.6. This solution was aerated with carbogen (5% CO_2 : 95% O_2) to maintain the pH of the solution between 7.3 and 7.4. Mechanical activity of the longitudinal muscle strips was recorded by an isotonic transducer (Ugo Basile model 7004, Milan, Italy) and a recorder (Ugo Basile model Gemini 7070, Milan, Italy).

The preparations were allowed to equilibrate in the Tyrode solution for at least 30 min before any drug was added. At the end of the equilibration period, 2 experiments were performed as follows: (*i*) dopamine concentration response-curves (10^{-11}–10^{-4} mol/L) were obtained by adding the drug cumulatively before and after the addition of antagonists. (*ii*) A submaximal, well-maintained plateau contraction was obtained by adding KCl (37 mmol/L) and then concentration-response curves for dopamine (3×10^{-8}– 3×10^{-4} mol/L) or isoprenaline (10^{-11}–10^{-6} mol/L) were performed as described above. The well-maintained-plateau contraction elicited by potassium was stable for the length of time required to assess the agonist effects.

Antagonists were incubated for 15 min before the agonist was added in the same way as in the control. Since an indirect effect of dopamine on other tissues has been previously described (Koga et al. 1980; Martínez-Mir et al. 1987), experiments were performed on the isolated rat colon strips of reserpine-treated rats (5mg reserpine/kg body mass i.p., 24 h before sacrifice).

Inhibitory responses under basal conditions were obtained as a percentage of the of the basal colonic activity modification (frequency of contractions/10 min × mean of amplitude of the contractions (mm)). Relaxant responses to drugs were expressed as the percentage of inhibition of the KCl-induced contraction. Effective concentration 50% (EC_{50}) was calculated graphically from a plot of log concentration versus percentage of the maximum response (E_{max}) produced by the agonist in individual experiments, and then transformed into pD_2 values or –log of EC_{50}. The calculation of the pA_2 value was made according to the method of Arunlakshana and Schild (1959), as previously described (Aguilar et al. 1986).

Statistical analysis

All data are shown as mean ± SE. Significance of differences was assessed with unpaired Student's two-tailed *t*-test at the 5% significance level.

Drugs

Drugs that were used in the study included dopamine hydrochloride, isoprenaline hydrochloride, propranolol hydrochloride, reserpine, yohimbine hydrochloride (Sigma, St Louis, Mo.), prazosin hydrochloride (Pfizer, Groton, Conn.), Sch 23390 maleate (Schering, Kenilworth, N.J.), and sulpiride hydrochloride (Delagrange, Brussels, Belgium). All drugs were dissolved in distilled water. Final dilutions were made in Tyrode solution. EDTA (Sigma, St Louis, Mo.) 0.04 mmol/L was added to the catecholamine solution to prevent oxidation.

Results

Effect of dopamine on the spontaneous motility of the isolated rat colon

Isolated rat colon exhibited spontaneous motility with a frequency of 30 ± 0.3 contractions/10 min.

Dopamine (10^{-11} mol/L to 10^{-5} mol/L) did not modify spontaneous motility of isolated rat colon. However, when a concentration of 10^{-4} mol/L was used, spontaneous motility was completely abolished. This inhibitory response was not antagonized by sulpiride (10^{-7} mol/L), propranolol (10^{-7} mol/L), nor prazosin (10^{-7} mol/L) (Fig. 1; $n = 5$ for each group). Spontaneous motility of isolated rat colon strips was recovered after washing with Tyrode solution.

Fig. 1. Effect of dopamine on the spontaneous motility of the isolated rat distal colon. (A) Dopamine (DA) alone, (B) dopamine and propranolol (PRO), (C) dopamine and prazosin (PRZ), and (D) dopamine and sulpiride (SUL). 11, 10^{-11} mol/L; 9, 10^{-9} mol/L; 7, 10^{-7} mol/L; 4, 10^{-4} mol/L.

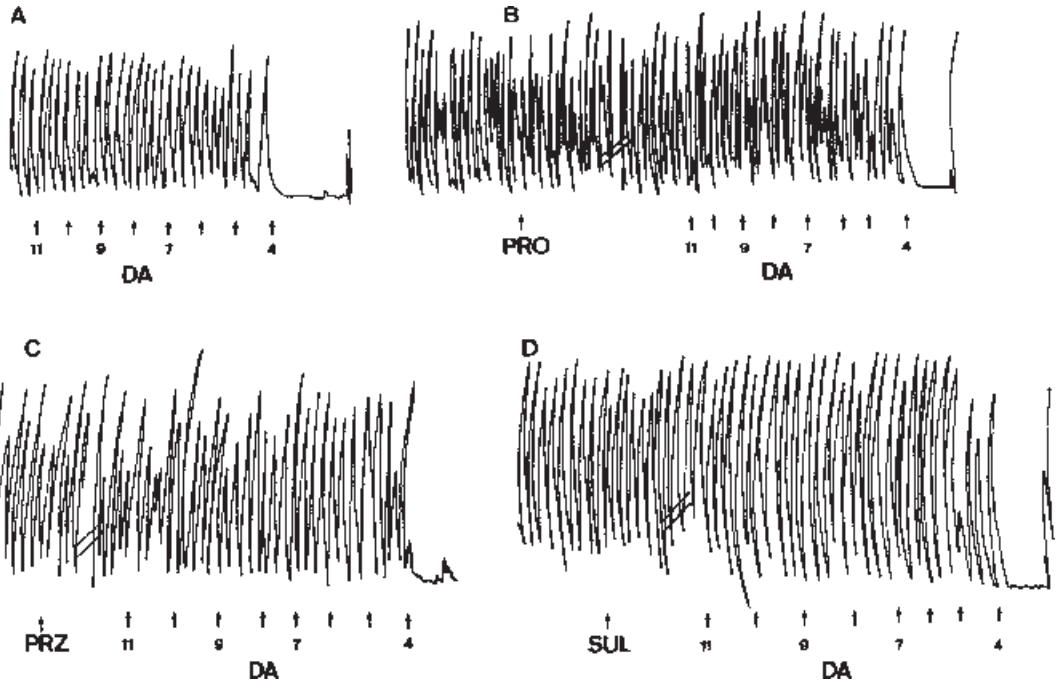

Fig. 2. Dopamine concentration-response curves for isolated rat distal colon strips depolarized with potassium from nonreserpinized and reserpinized rats.

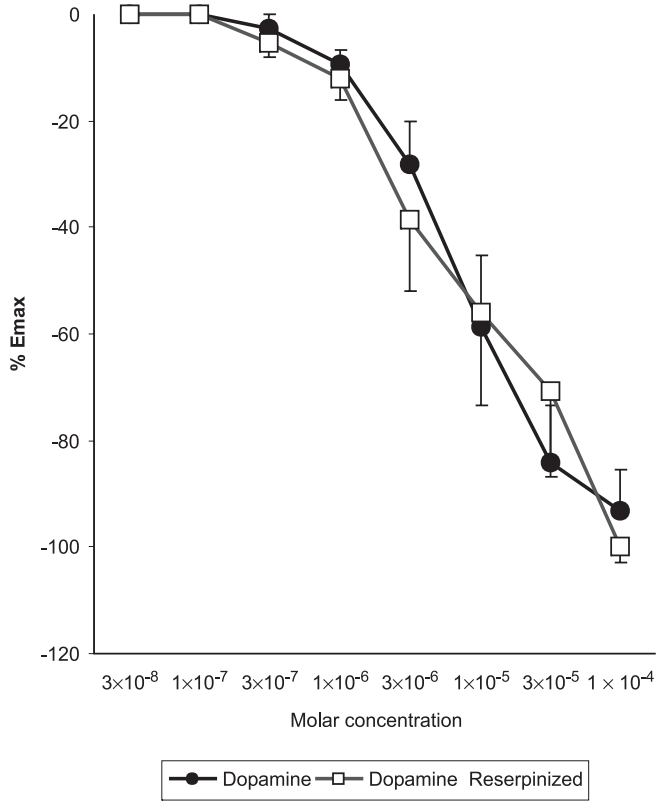

Table 1. Maximum effect (E_{max}) and pD_2 of the first and second concentration-response curves (CRC) to dopamine in non-reserpinized and reserpinized rats.

	n	E_{max} (%)	pD_2
Dopamine	17	–92.5±7.5	5.14±0.21
Dopamine 2nd CRC	15	–91.8±6.9	5.16±0.09
Dopamine in reserpinized rat	5	–100±0.9	5.25±0.25
Dopamine in reserpinized rat 2nd CRC	5	–100±6.1	4.65±0.12

Effects of dopamine on the isolated rat colon strips depolarized with KCl

Dopamine (3×10^{-8} to 3×10^{-4} mol/L) produced a concentration-dependent relaxant response to KCl-induced contraction (Fig. 2). The effect of dopamine was reproducible after a 30-min interval. E_{max} and pD_2 values are shown in Table 1. Depletion of catecholamine stores by reserpine did not produce any significant modification of dopamine concentration-response curves in the depolarized rat colon (Fig. 2), and the effect was always reproducible after a 30 min interval.

The selective DA_1-dopamine antagonist, Sch 23390 (10^{-7} mol/L), did not alter the dopamine concentration-response curve (n = 10). Similarly, sulpiride (10^{-7} mol/L), a DA_2-antagonist, did not modify the dopamine-induced relaxation in KCl-depolarized rat colon (Fig. 3*;* n = 7).

Propranolol (10^{-9} mol/L), a β-adrenoceptor antagonist, did not modify the dopamine-induced relaxation in the KCl-depolarized rat colon. However, at 10^{-8}, 3×10^{-8}, and 10^{-7} mol/L, propranolol shifted the dopamine concentration-response curve to the right, though this displacement was not pro-

Fig. 3. Concentration response curves to dopamine in isolated rat distal colon strips depolarized with potassium in the presence of (A) Sch 23390 and (B) sulpiride.

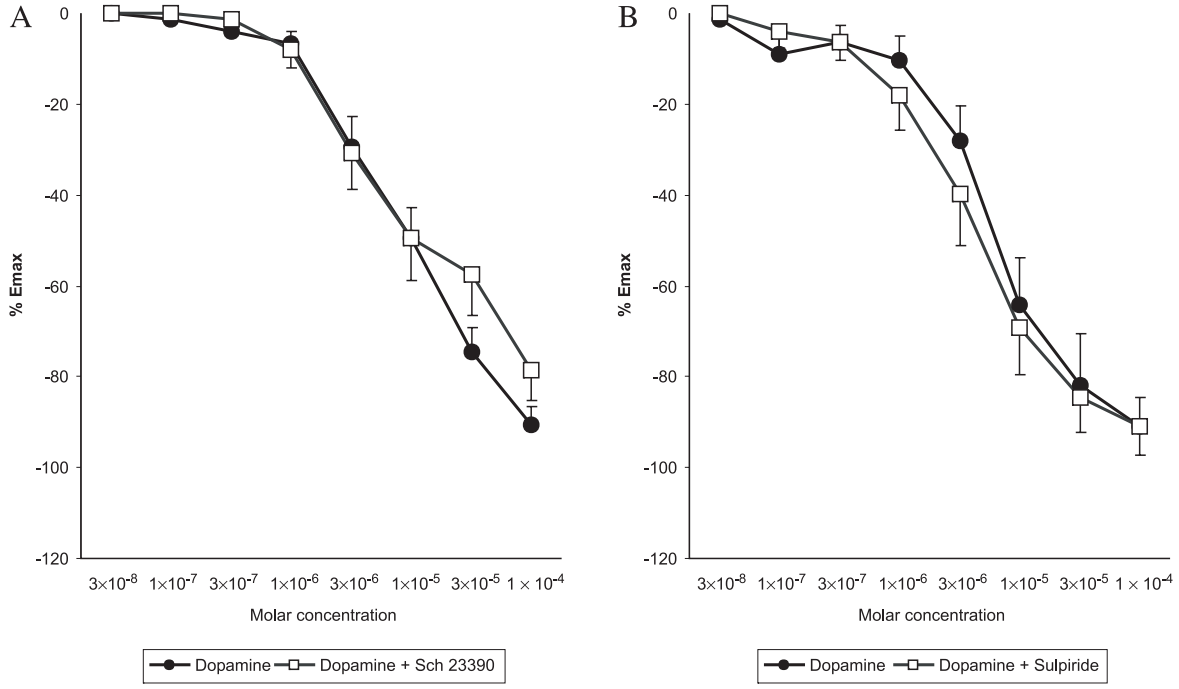

Table 2. Maximum effect (E_{max}) and –log of the effective concentration 50% (EC_{50}) of the dopamine (DA) concentration-response curves in the absence (Control) and presence (Mixtures) of different concentrations of propranolol, prazosin, both propranolol and prazosin, or yohimbine.

				Control		Mixtures	
DA + Propranolol (mol/L)	DA + Prazosin (mol/L)	DA + yohimbine (mol/L)	n	E_{max} (%)	–log (EC_{50})	E_{max} (%)	–log (EC_{50})
10^{-7} mol/L			5	–89.3±6.8	5.29±0.07	–64.4±10.4*	4.39±0.25*
3×10^{-8} mol/L			7	–94.5±2.2	4.96±0.05	–74.3±4.1*	4.26±0.14*
10^{-8} mol/L			5	–87.9±80	4.75±0.11	–76.2±4.5*	4.28±0.15*
10^{-9} mol/L			5	–96.8±1.9	5.22±0.17	–100±3.1	5.18±0.26
	10^{-6} mol/L		5	–91.2±5.4	5.01±0.19	–96.3±2.1	4.51±0.21
	10^{-7} mol/L		5	–90.7±7.7	5.11±0.15	–97.4±2.6	4.75±0.20
	10^{-5} mol/L		6	–91.2±8.8	5.46±0.14	–95.6±4.4	5.44±0.17
	10^{-7} mol/L		5	–91.2±8.8	5.46±0.14	–93.0±2.8	5.26±0.08
10^{-8} mol/L	10^{-7} mol/L		5	–91.2±8.8	5.46±0.14	–77.3±6.7*	4.64±0.19*
		10^{-8} mol/L	6	–95.4±4.5	5.48±0.14	–98.8±0.8	5.52±0.12
		10^{-7} mol/L	5	–95.4±4.5	5.48±0.14	–94.6±2.8	5.65±0.14

Note: *, $p < 0.05$ vs. its control. n is the number of trials.

duced in a dose-dependent manner. Dopamine E_{max}, in the presence of 10^{-8}, 3×10^{-8}, and 10^{-7} mol/L propranolol, was lower than with dopamine alone (Table 2). Propranolol produced a shift of the dopamine-response curve, but the antagonism was noncompetitive, with a Schild plot slope of 0.21 ± 0.2, significantly different from 1 ($p < 0.05$).

Prazosin, an α_1-adrenoceptor antagonist, did not modify dopamine-induced relaxation in the KCl-depolarized rat colon at 10^{-8}, 10^{-7}, or 10^{-6} mol/L. Dopamine effects in the presence of prazosin (10^{-7} mol/L) and propranolol (10^{-8} mol/L) were not significantly different to those observed in the presence of propranolol 10^{-8} mol/L alone ($p < 0.05$). At 10^{-8} and 10^{-7} mol/L, yohimbine, the α_2-adrenoceptor antagonist, did not modify the dopamine-induced relaxation in the KCl-depolarized rat colon (Table 2).

Effect of isoprenaline on the isolated rat colon depolarized by KCl

Isoprenaline (10^{-11}–10^{-6} mol/L) produced a concentration-dependent relaxant response to KCl-induced contraction. E_{max} was –88.0% ± 6.6% and the pD_2 was 7.3 ± 0.1 ($n = 5$). Propranolol at 10^{-10} and 10^{-9} mol/L did not modify the isoprenaline-induced relaxation. However, propranolol at 10^{-8} and 10^{-7} mol/L shifted the concentration response curve for

isoprenaline to the right, though this displacement was not produced in a dose-dependent manner. The antagonism elicited by propranolol against isoprenaline was noncompetitive in nature, as demonstrated by the slope of the regression line of the Schild plot (0.54 ± 0.01) which was significantly different from 1 ($p < 0.05$).

Discussion

The rat colon can be divided into 3 regions (proximal, distal, and caecum) both morphologically (Christensen et al. 1984) and functionally (Ferre and Ruckebusch 1985). In the present study we investigated the effects of dopamine on the distal portion of the colon, in which the actions of dopamine have been described as inhibitory (Lefevre 1990).

Under basal conditions, and using concentrations of less than 10^{-4} mol/L, dopamine did not modify spontaneous motility of the isolated rat colon, though with higher concentrations (10^{-4} mol/L), colon activity was completely inhibited, which is in agreement with the results from studies of other species and regions (Tayo et al. 1979; Fontaine et al. 1983; Lefebvre et al. 1983). However, the ability of dopamine to suppress colon activity at only higher concentrations suggests that this effect may be caused by indirect mechanisms. That spontaneous motility was reversible after washing indicates the tissue viability. It is not possible to block the inhibitory effect of dopamine with α-, β-, or dopamine antagonists, in concordance with the observations of Grivegnee et al. (1984) in dog isolated colon. In view of these results, experiments in KCl-depolarized isolated rat colon were carried-out.

Dopamine in isolated, KCl-depolarized rat distal colon strips produced a concentration-dependent relaxant effect, in agreement with different authors, and this response was reproducible after a 30-min interval. The potency of dopamine in this preparation was similar to that observed in isolated guinea pig atria and isolated rat uterus (Martínez-Mir et al. 1987; Estañ et al. 1988).

Dopamine has been shown to cause the release of noradrenaline in different tissues (Koga et al. 1980). However, the relaxant response to dopamine found in this work was not modified by reserpine. This result agrees with observations in other species and tissues such as the guinea pig airway (Cortijo et al. 1984), isolated guinea pig atria (Martínez-Mir et al. 1987), and isolated rat uterus (Estañ et al. 1988), thus indicating that the effect of dopamine in these preparations was not mediated by the release of endogenous catecholamines.

Sch 23390, a selective D_1-antagonist, did not modify the concentration-dependent relaxant response induced by dopamine, and sulpiride, a DA_2-antagonist, also failed to modify this response, suggesting that dopamine receptors do not participate in the effects of dopamine in our preparation. Since we were aware of the controversy about selectivity of DA-receptor antagonists, Sch 23390 and sulpiride were used because they exhibit minimal nonspecific effect on other receptor systems (Walker et al. 2000).

Our results are partly in agreement with those of Lefebvre et al. (1983), who showed that dopamine had an inhibitory effect with no evidence of dopamine receptors in rat gastric fundus preparation, even when they used selective dopamine agonists such as quinpirole or fenoldopam. However, this effect was partially antagonized by phentolamine, suggesting α-receptor antagonism.

In our experiments, prazosin failed to modify the relaxant response induced by dopamine. This suggests nonparticipation of this receptor type in the effects of dopamine. This finding is similar to that reported by McLaughlin and MacDonald (1990), who observed that the effects of noradrenaline in rat distal colon depolarized with potassium were not antagonized by phentolamine. Yohimbine, under our experimental conditions, did not modify the effects of dopamine, this likewise being in agreement with the observations of McLaughlin and MacDonald (1990), with cirazoline and UK 14304.

It is known that dopamine interacts with α- and β-adrenoceptors (Goldberg et al. 1978). For this reason we have performed experiments in the presence of the nonselective β-adrenoceptor antagonist, propranolol. At low concentrations, this drug did not modify the relaxant effect of dopamine, but when the antagonist was used at higher concentrations, the effects of dopamine were antagonized in a noncompetitive manner. These results are, in part, coincident with the observation in rat uterus, in which propranolol antagonized the effects of fenoldopam in a similar way (Estañ et al. 1993).

It has been suggested that modifications similar to those exhibited by propranolol over the dopamine concentration-response curves could be explained by catecholamine extraneuronal uptake, but for our in vitro experiments of rat distal colon, we discarded this suggestion, because the propranolol antagonism was similar in the presence and absence of the extraneuronal uptake blocker hydrocortisone (Iversen and Salt 1970). These results are in agreement with those observed in other species and regions (Estañ et al. 1988; Lefebvre 1992).

In our experimental conditions, the noncompetitive nature of the antagonism elicited by propranolol is in agreement with the results of McLaughlin and MacDonald (1990) for in vitro rat distal colon, suggesting that receptors mediating relaxation are similar to those mediating lipolysis in adipocytes of rat. These receptors were regarded as atypical β-adrenoceptors in guinea pig gastrointestinal smooth muscle by Blue et al. (1989) and Horinouchi el al. (2003), and has also been described in human colon (De Ponti et al. 1999). This suggests that the effects of dopamine in our preparation may be due to interactions with this type of atypical β-adrenoceptors.

Experiments with isoprenaline were performed to determine the colon response of a typical β agonist. The results obtained, specifically that the antagonism against propranolol was noncompetitive in nature (MacLaughlin and MacDonald 1990; Bianchetti and Manara 1990), supported the hypothesis that β-adrenoceptors in rat distal colon could be atypical β-adrenoceptors.

In conclusion, dopamine shows a relaxant effect on isolated rat distal colon, without participation of specific dopamine receptors or α-adrenoceptors. The relaxant effect of dopamine on depolarized isolated rat distal colon may be mediated by atypical β-adrenoceptors.

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