J. Pharm. Pharmacol. 1992, 44: 330–336
Received August 19, 1991

The Inhibitory Effect of Dopamine on Cat Gastric Smooth Muscle

R. A. LEFEBVRE

Heymans Institute of Pharmacology, University of Gent Medical School, De Pintelaan 185, B-9000 Gent, Belgium

Abstract—The inhibitory effect of dopamine has been studied in longitudinal and circular muscle strips of the cat gastric fundus. When tone was raised by transmural electrical stimulation and by administration of methacholine, dopamine concentration-dependently relaxed the strips but the inhibitory effect of dopamine was clearly more pronounced on electrically-induced tone. The effect of dopamine was not influenced by the presence of cocaine or hydrocortisone. The relaxant effect of dopamine, when tone was raised by methacholine, was not influenced by α- and dopamine receptor antagonists but it was significantly reduced by propranolol and ICI 118551 (erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol). The inhibitory effect of dopamine on the electrically-induced tone was significantly reduced by phentolamine; domperidone tended to reduce the effect of the lower concentrations of dopamine. In the presence of propranolol, phentolamine and rauwolscine concentration-dependently antagonized the inhibitory effect of dopamine on electrically-induced tone, while prazosin was without influence. These results indicate that the inhibitory effect of dopamine in the cat gastric fundus is mainly due to interaction with postjunctional β_2-adrenoceptors on the smooth muscle cells and with prejunctional α_2-adrenoceptors on the intramural cholinergic neurons

The influence of dopamine on gastric motility is in general inhibitory. Dopamine not only interacts with dopamine receptors but also with α- and β-adrenoceptors (Goldberg et al 1978). In most in-vitro studies, the inhibitory effect of dopamine on gastric smooth muscle cell activity has been attributed to an interaction with α- and β-adrenoceptors but some studies have suggested the involvement of gastric dopamine receptors (Lefebvre 1990). Little information is available on the influence of dopamine on cat gastric motility. In-vivo, the dopamine receptor agonist apomorphine has been shown to induce gastric relaxation by central activation of the vagal non-adrenergic non-cholinergic fibres to the stomach (Abrahamsson et al 1973); this is probably due to interaction with the dopamine receptors in the chemoreceptor trigger zone (Stefanini & Clement-Cormier 1981), similar to the effect we have shown for the apomorphine-induced gastric relaxation in the dog in-vivo (Blancquaert et al 1985). This does not exclude the possibility that dopamine and dopamine receptor agonists could interact with gastric dopamine receptors, influencing motility. Thus dopamine was shown to induce irregular propagation of slow waves and alterations in slow wave frequency in a muscle strip, containing corpus and antrum material of the cat stomach; as the dopamine-induced changes were inhibited by domperidone, an interaction with gastric dopamine receptors was suggested (Jo et al 1989).

In the present study, the influence of dopamine on longitudinal and circular muscle strips of the cat gastric fundus has been investigated. In contrast to the corpus and the antrum, the fundus mainly has a reservoir function and has a great relaxant capacity (Meyer 1987). Our results suggest that the inhibitory effect of dopamine in the cat gastric fundus is due to a postjunctional effect at muscular β_2-adrenoceptors, and to a prejunctional effect, mainly at α_2-adrenoceptors on intramural cholinergic neurones.

Materials and Methods

Tissues

Cats of either sex, 1·5–3·5 kg, were reserpinized (3 mg kg^{-1} i.p.) and fasted for 24 h with free access to water. After pentobarbitone anaesthesia (30 mg kg^{-1}), the stomach was excised and 2 longitudinal and 2 circular muscle strips (15 mm long, 2 mm wide) were prepared from the ventral part of the fundus after the mucosa was removed (Lefebvre et al 1986). All strips were used immediately. The strips were mounted under a load of 1 g between 2 parallel platinum plate electrodes (48–8 mm) in 18 mL organ baths containing Tyrode solution of the following composition (mM): NaCl 136·8, KCl 2·7, $CaCl_2$ 1·8, $MgCl_2$ 1·6, NaH_2PO_4 0·4, $NaHCO_3$ 11·9, glucose 5·6; the solution was kept at 37°C and bubbled with 95% O_2–5% CO_2. Changes in length of the strips were recorded auxotonically (Harvard heart-smooth muscle transducer) on a Beckman Type R Dynograph recorder, and an S88 Grass stimulator and a constant current unit were used to stimulate the strips transmurally (supramaximal voltage, 0·5 ms). The strips were rinsed every 15 min during the 60 min equilibration period, and thereafter every 5 min in between drug administration and periods of transmural stimulation.

During the preliminary experiments, we observed that the basal tension of the strips tended to increase with time. This effect was marked after some hours and disturbed the protocol. Further experiments were therefore performed in the presence of indomethacin (3×10^{-5} M), by which the increase in tone was avoided. The Tyrode solution also

contained eserine ($7{\cdot}3 \times 10^{-8}$ M) to potentiate the electrically-induced contractions and ascorbic acid ($5{\cdot}7 \times 10^{-4}$ M) as an antioxidant.

Protocols

Effect of dopamine. After the equilibration period, transmural stimulation (1 Hz) was performed twice during 2 min with an interval of 10 min; 2 min of stimulation was sufficient to obtain a plateau contraction. Thereafter, a cumulative concentration-response curve was performed with methacholine in order to determine the concentration of methacholine needed to induce a contraction of similar amplitude to that induced electrically. This concentration ranged between 3×10^{-8} and 3×10^{-7} M. Once this information was obtained, transmural stimulation was performed over 15 min. The contractile response was usually well maintained; when it declined during the stimulation period, appropriate corrections were introduced (see below). Fifteen min later, transmural stimulation was applied again and, once a stable plateau contraction was reached, dopamine was added in increasing concentrations until no further relaxation occurred. The strip was then rinsed until the contraction induced by electrical stimulation (applied for 2 min at intervals of 10 min) reached the same amplitude as that before addition of dopamine. Methacholine was then added at the concentration determined at the beginning of the experiment and the same protocol as used for electrically-induced contractions was repeated for the methacholine-induced contraction. The whole sequence was performed twice to study the reproducibility of the effect of dopamine; in half of the experiments, the effect of dopamine was first studied on methacholine-induced contraction.

To study the influence of tetrodotoxin (3×10^{-6} M) on the relaxant effect of dopamine during methacholine-induced contractions, the protocol described above was used except that the effect of dopamine was not studied during electrical stimulation-induced contractions. Fifteen min before the relaxant effect of dopamine was studied for the second time, tetrodotoxin (3×10^{-6} M) was added to the Tyrode solution.

Influence of uptake blockers and α-, β- and dopamine receptor antagonists on the effect of dopamine. The protocol as described above was used, but before studying the effect of dopamine during electrically- and methacholine-induced contractions for the second time, the Tyrode solution was changed to one containing either 3×10^{-5} M cocaine or 3×10^{-5} M hydrocortisone (uptake blockers), 10^{-6} M phentolamine (α-adrenoceptor antagonist), 10^{-6} M SCH 23390 or 10^{-6} M domperidone (dopamine receptor antagonists), 10^{-5} M propranolol, 10^{-5} M practolol or 10^{-5} M ICI 118551 (erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol) (β-adrenoceptor antagonists). Except when studying hydrocortisone and propranolol, strips of the same cats were tested in parallel without addition of the uptake blocker or antagonist. For SCH 23390, the solvent was added to the control strips.

Influence of the dopamine receptor antagonist domperidone and of α-adrenoceptor antagonists on the effect of dopamine during electrically-induced contractions. The Tyrode solution used in these experiments contained from the beginning 3×10^{-5} M cocaine, 3×10^{-5} M hydrocortisone and 10^{-5} M propranolol, to block uptake and β-adrenoceptors, respectively. After the equilibration period, the strips were stimulated electrically (1 Hz) twice for 2 min with an interval of 10 min. At the 80th min, transmural stimulation was applied for 15 min; 15 min later, transmural stimulation was applied again and the effect of dopamine was studied as described above. This sequence, an electrically-induced control contraction and an electrically-induced contraction with a concentration-response curve for dopamine was then obtained a further 3 times in the presence of increasing concentrations of domperidone, phentolamine, prazosin or rauwolscine. The antagonist was added 5 min before the control contraction and was thus present for more than 35 min when dopamine was added.

Experiments where no antagonist or the solvent for domperidone was added were performed in parallel in gastric smooth muscle strips from the same cats.

Analysis of data

All values are given as means ± s.e.m. where n always refers to smooth muscle strips from different cats. The relaxant effect of dopamine was expressed as a percentage of the contraction present before addition of dopamine. When necessary, correction for spontaneous relaxation was done by taking into account the degree of relaxation present during the foregoing control contraction at the corresponding time interval.

The effect of dopamine in the presence of one of the uptake-blockers or antagonists was compared with that before, by a signed-rank test. When possible, concentration ratios after or before α-adrenoceptor antagonist were calculated for the concentration of dopamine causing 50% relaxation of the electrically-induced contraction. This was performed for each concentration of antagonist. The data obtained were pooled to construct Schild plots (Arunlakshana & Schild 1959). The x-intercept of the regression line was taken as the pA_2 value if the 95% confidence limits of the slope of the regression line contained unity.

Drugs

The following drugs were used: ascorbic acid (Merck, Belgium); atropine sulphate (Merck); cocaine hydrochloride (Belgopia, Belgium); domperidone (Janssen Pharmaceutica, Belgium); dopamine HCl (Sigma, USA) eserine salicylate (Boehringer Ingelheim, Germany); hexamethonium chloride (Federa, Belgium); hydrocortisone (Roussel, France); ICI 118551 (ICI, UK); indomethacin (Certa, Belgium); (±)-*O*-acetyl-β-methylcholine chloride (Schuchardt, Germany); practolol (ICI); prazosin hydrochloride (Pfizer, Belgium); phentolamine mesylate (Ciba-Geigy, Belgium); (±)-propranolol hydrochloride (ICI, UK); SCH 23390 maleate (Schering Co, USA); tetrodotoxin (Sankyo Co, Japan). For domperidone, practolol and phentolamine, commercially available ampoules were used; for domperidone, the manufacturer also provided the solvent. Most drugs were dissolved or diluted in distilled water. Dopamine was dissolved in isotonic NaCl solution, containing 10^{-3} M ascorbic acid and the solution was kept on ice. SCH 23390 was dissolved in 0·5 mL of 0·1 M HCl and made up to volume with distilled

water. For reserpine, a stock solution of 5 mg mL^{-1} dissolved in 10% ascorbic acid was used. Hydrocortisone and indomethacin were dissolved in ethanol before addition to the Tyrode solution; the final concentration of ethanol in the Tyrode solution was $1{\cdot}7 \times 10^{-2}$ M.

Results

Dopamine did not change the basal tension of the strips. Therefore, its effect was studied during contractions elicited either by transmural electrical stimulation or by addition of *O*-acetyl-*β*-methylcholine chloride (methacholine). The characteristics of these contractions were determined in preliminary experiments, each experiment being repeated in strips of at least 4 different cats. In both types of strips, transmural electrical stimulation (supramaximal voltage, 0·5 ms, 0·25–16 Hz) elicited frequency-dependent contractions, which were stabilized and potentiated by $7{\cdot}3 \times 10^{-8}$ M eserine. The electrically-induced contractions in the presence of eserine were not influenced by 5×10^{-4} M hexamethonium and completely blocked by 3×10^{-6} M tetrodotoxin except that in 1 circular muscle strip out of 4, some contractile response persisted at a stimulation frequency of 8 and 16 Hz. For further experiments, a stimulation frequency of 1 Hz was used. Methacholine (10^{-8}–10^{-6} M), in Tyrode solution containing eserine $7{\cdot}3 \times 10^{-8}$ M, induced concentration-dependent contractions, which were not influenced by 5×10^{-4} M hexamethonium and 3×10^{-6} M tetrodotoxin, but completely blocked by 10^{-6} M atropine.

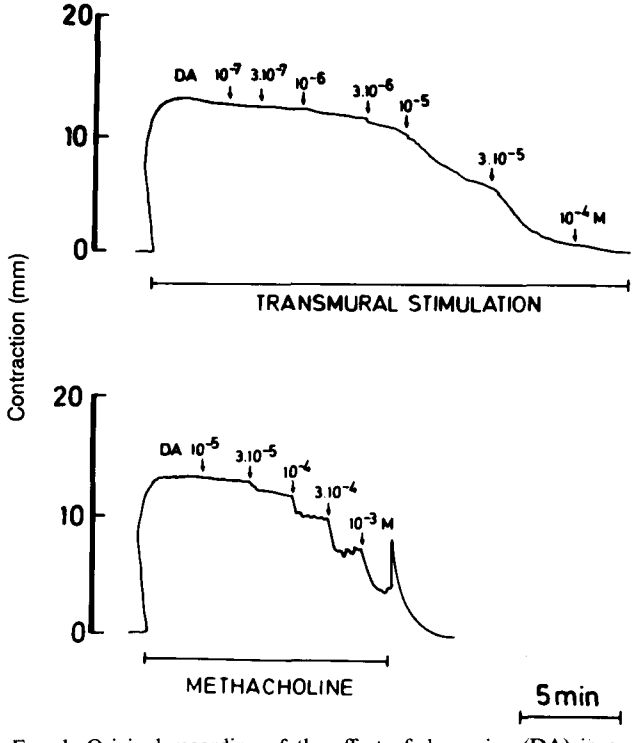

FIG. 1. Original recording of the effect of dopamine (DA) in a longitudinal muscle strip of the cat gastric fundus. Tone was raised by transmural stimulation (supramaximal voltage, 0·5 ms, 1 Hz, upper panel) or by addition of methacholine (3×10^{-8} M; lower panel).

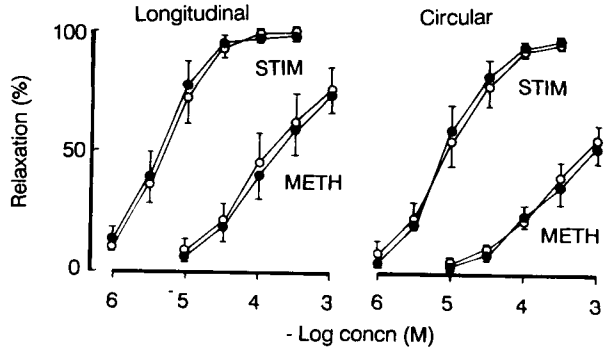

FIG. 2. Concentration-response curves for the relaxant effect of dopamine in longitudinal (left panel) and circular (right panel) muscle strips of the cat gastric fundus. The effect of the first (○) and second (●) administration of dopamine on transmural stimulation-(STIM) and methacholine-(METH) induced tone is shown. Results are means ± s.e.m., n = 6.

Effect of dopamine

Both in longitudinal and circular muscle strips, dopamine (10^{-6}–3×10^{-4} M) produced a concentration-dependent inhibition of the electrically-induced contraction; at the highest concentrations used, the inhibition was complete (Fig. 1). Dopamine also concentration-dependently relaxed the methacholine-contracted strips, but higher concentrations were needed and, even at a concentration of 10^{-3} M, dopamine did not completely inhibit the methacholine-induced contraction (76·0 ± 8·6% relaxation in longitudinal and 56·2 ± 5·7% in circular muscle strips; Fig. 2). Within the same strips the effect of dopamine was reproducible (Fig. 2). Tetrodotoxin (3×10^{-6} M) did not influence the effect of dopamine on methacholine-induced tone (n = 4 for both types of strips).

Influence of uptake blockers and α-, β- and dopamine receptor antagonists on the effect of dopamine

Changing the Tyrode solution to a solution also containing one of the uptake blockers or antagonists, did not change the amplitude of the contractions induced by electrical stimulation or by methacholine. In all control series, the effect of dopamine was reproducible.

For both cocaine (3×10^{-5} M) and hydrocortisone (3×10^{-5} M) the possible influence was examined in 6 strips of each type; the concentration-response curves for dopamine in the presence of the uptake blockers were not changed.

Phentolamine (10^{-6} M) antagonized the inhibitory effect of the higher concentrations of dopamine (10^{-5}–3×10^{-4} M) on electrically-induced contractions; the effect of the lower concentrations of dopamine was hardly influenced (Fig. 3). Phentolamine did not influence the effect of dopamine when tone was raised by methacholine. In contrast to phentolamine, domperidone (10^{-6} M) preferentially antagonized the inhibitory effect of the lower concentrations of dopamine on the electrically-induced tone. As for phentolamine, the inhibitory effect of dopamine on methacholine-induced tone was hardly influenced (Fig. 3). SCH 23390 (10^{-6} M) significantly reduced the relaxant effect of dopamine when tone was raised by transmural stimulation in longitudinal but not circular muscle strips. Propranolol (10^{-5} M) clearly antagonized the inhibitory effect of dopamine during methacholine-

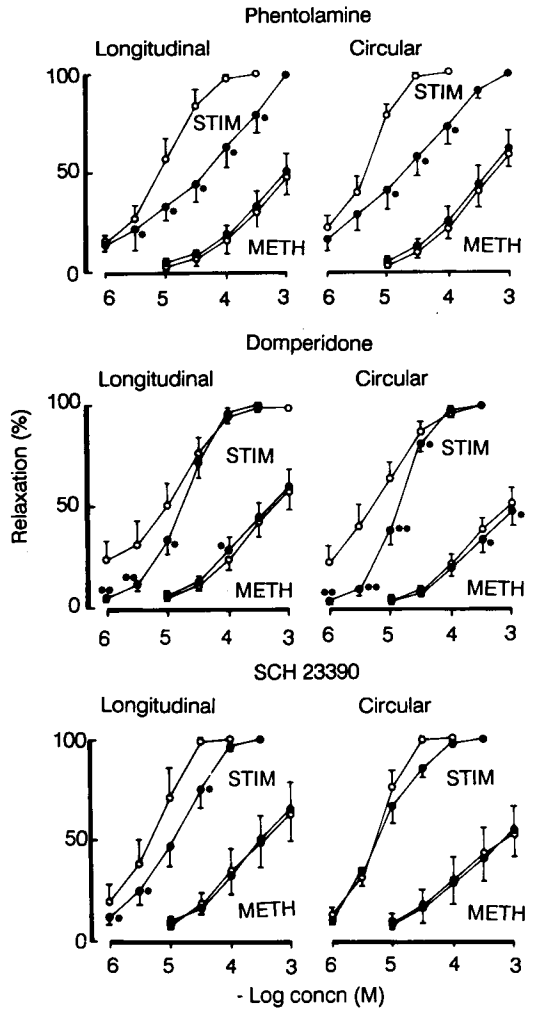

FIG. 3. Concentration-response curves for the relaxant effect of dopamine in longitudinal (left panel) and circular (right panel) muscle strips of the cat gastric fundus. The effect of dopamine on transmural stimulation-(STIM) and methacholine-(METH) induced tone is shown in the absence (○) and in the presence (●) of phentolamine (10^{-6} M, n = 6), domperidone (10^{-6} M, n = 11-12) and SCH 23390 (10^{-6} M, n = 6-7). Means ± s.e.m. are given. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the value in the absence of antagonist.

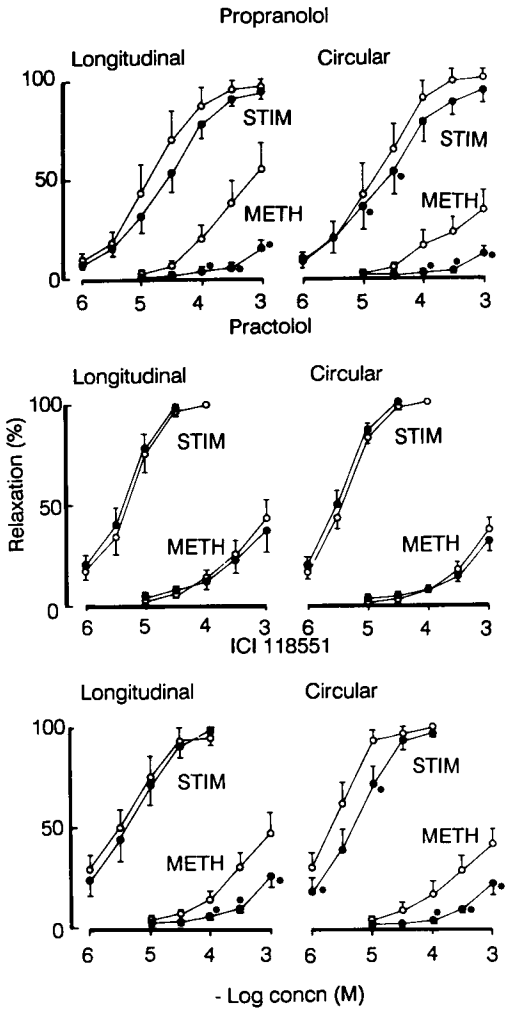

FIG. 4. Concentration-response curves for the relaxant effect of dopamine in longitudinal (left panel) and circular (right panel) muscle strips of the cat gastric fundus. The effect of dopamine on transmural stimulation-(STIM) and methacholine-(METH) induced tone is shown in the absence (○) and in the presence (●) of propranolol (10^{-5} M, n = 6), practolol (10^{-5} M, n = 7) and ICI 118551 (10^{-5} M, n = 7). Means ± s.e.m. are given. $^{*}P < 0.05$ compared with the value in the absence of the antagonist.

induced contractions (Fig. 4). In both types of strips, the inhibitory effect of dopamine was almost completely antagonized up to a concentration of 3×10^{-4} M. The inhibition by dopamine of the stimulation-induced contractions was to a small extent decreased by propranolol, although the reduction only reached significance in circular muscle strips for 10^{-5} and 3×10^{-5} M dopamine. Practolol (10^{-5} M) did not influence the effect of dopamine. The influence of ICI 118551 (10^{-5} M) on the relaxant effect of dopamine was similar to that of propranolol i.e. the inhibition of methacholine-induced tone by dopamine was greatly reduced. ICI 118551 reduced the inhibitory effect of dopamine on electrically-induced tone only in circular muscle strips (Fig. 4).

Table 1. Mean slopes and mean x-intercept values with 95% confidence limits from Schild plots for the α-adrenoceptor antagonists phentolamine and rauwolscine against dopamine in longitudinal and circular muscle strips of the cat gastric fundus (n = 8).

	Longitudinal		Circular	
	Slope	x-intercept	Slope	x-intercept
Phentolamine	0·57 (0·40–0·75)	7·95 (7·55–8·35)	0·88 (0·57–1·19)	7·66 (7·27–8·05)
Rauwolscine	0·89 (0·40–1·38)	9·08 (8·69–9·46)	0·95 (0·53–1·37)	9·11 (8·79–9·43)

Influence of the dopamine receptor antagonist domperidone and α-adrenoceptor antagonists on the effect of dopamine during electrically-induced contractions

In preliminary experiments, it was observed that the relaxant effect of dopamine during electrically-induced contractions was reproducible when studied four times consecutively. This result was confirmed in the control strips for the

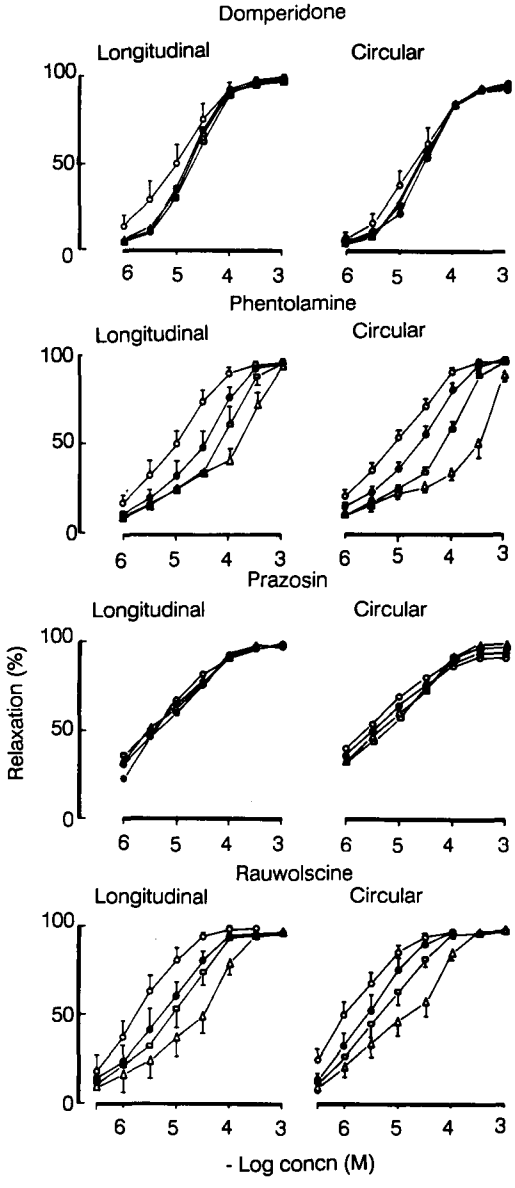

FIG. 5. Concentration-response curves for the relaxant effect of dopamine on transmural stimulation-induced tone in longitudinal (left panel) and circular (right panel) muscle strips of the cat gastric fundus. The effect of dopamine is shown in the absence (○) and presence of domperidone (●, 3×10^{-8}; □, $1{\cdot}8 \times 10^{-7}$; △, 10^{-6} M; n = 8), phentolamine (●, 3×10^{-8}; □, $1{\cdot}8 \times 10^{-7}$; △, 10^{-6} M; n = 8), prazosin (●, 10^{-8}; □, 10^{-7}; △, 10^{-6} M; n = 4) and rauwolscine (●, 10^{-9}; □, 3×10^{-9}; △, 10^{-8} M; n = 8). Means ± s.e.m. are given except when not possible for clarity.

different series of experiments. The addition of the different concentrations of each of the antagonists studied to the Tyrode solution did not influence the electrically-induced contraction amplitude. In the longitudinal fundus strips, the lower part of the concentration-response curve for dopamine was shifted to the right by 3×10^{-8} M domperidone; however, no further shift was produced by higher concentrations of domperidone (Fig. 5). In the circular fundus strips, a similar trend was observed although the shift to the right was less pronounced. The influence of the three α-adrenoceptor antagonists on the effect of dopamine is also shown in Fig. 5. In both types of strips, phentolamine shifted the concentration-response curve for dopamine to the right in a concentration-dependent manner; the shift to the right was clearly less pronounced for the lower part of the curve. Prazosin did not influence the effect of dopamine at all. Rauwolscine had a similar influence to phentolamine. For phentolamine and rauwolscine, Schild plots were constructed; the mean slopes and mean x-intercept values are given in Table 1.

Discussion

We have previously investigated the inhibitory effect of dopamine in the rat and dog gastric fundus. In the rat, the effect of dopamine is largely indirect through uptake of dopamine in sympathetic nerve endings and liberation of endogenous noradrenaline; postjunctional β-adrenoceptors on the smooth muscle cells and prejunctional α-adrenoceptors on the intramural cholinergic neurons are then activated (Lefebvre et al 1983). In the dog, dopamine acts largely directly via interaction with α-adrenoceptors on the intramural cholinergic neurons (Lefebvre et al 1984b). The results suggest that in the circular as well as in the longitudinal muscle layer of the cat gastric fundus, dopamine acts largely directly (as in the dog) but via both postjunctional β-adrenoceptors and prejunctional α-adrenoceptors (as in the rat).

Dopamine did not relax the cat gastric fundus strips when tone was not raised. This is probably due to the low basal tone of the preparation as we previously also observed the necessity of increasing tone to obtain non-adrenergic non-cholinergic relaxations upon transmural stimulation (Lefebvre et al 1986). Tone was thus raised by transmural electrical stimulation and by addition of methacholine. The electrically-induced contractions were stabilized and potentiated by the cholinesterase inhibitor eserine, used in the same concentration as in the rat and dog gastric fundus (Lefebvre et al 1983, 1984b). All further experiments were therefore performed in the presence of eserine. The contractions induced by electrical stimulation were blocked by tetrodotoxin but not by the ganglion blocking agent hexamethonium. As we have previously shown that the contractions are also blocked by atropine (Lefebvre et al 1986), these results illustrate that the electrically-induced contractions are due to activation of postganglionic cholinergic neurons. Contractions induced by the cholinergic agonist methacholine were blocked by atropine but not influenced by hexamethonium, indicating that methacholine induces a direct smooth muscle cell contraction by stimulation of postjunctional muscarinic receptors. When a similar degree of contraction was induced by transmural stimulation and methacholine, the relaxant effect of dopamine on electrically-induced tone was clearly more pronounced then on methacholine-induced tone. This illustrates that the inhibitory action of dopamine on the electrically induced contractions is, at least partially, due to prejunctional inhibition of cholinergic transmission. The inhibitory action of dopamine was not influenced by the neuronal uptake blocker cocaine (3×10^{-5} M (Weitzell et al 1979)); uptake of dopamine into nerve endings is thus not important. Extraneuronal uptake is also not important as hydrocortisone (3×10^{-5} M (Luchelli-Fortis & Langer 1975)) did not influence the inhibitory effect of dopamine.

The relaxant effect of dopamine, observed on methacholine-induced tone, is due to a direct interaction of dopamine with postjunctional receptors on the smooth muscle cells as it was not influenced by tetrodotoxin. The receptors involved are postjunctional β-adrenoceptors, as of all antagonists tested, only the non-selective β-adrenoceptor antagonist propranolol and the β_2-selective adrenoceptor antagonist ICI 118551 (Bilski et al 1983) blocked the postjunctional effect of dopamine. The β_1-selective adrenoceptor antagonist practolol had no effect. Also in the rat gastric fundus, dopamine interacts with postjunctional β-adrenoceptors, but no subtype selective antagonists were used (Lefebvre et al 1983). A later study in order to characterize the postjunctional β-adrenoceptors suggested that postjunctional β_1- and β_2-adrenoceptors are present (Lefebvre et al 1984a). In the cat colon, the inhibitory action of β-adrenoceptor agonists was also explained by an interaction with β_1- and β_2-adrenoceptors; while the effect of β_2-stimulation was localized at the smooth muscle cell level, it was suggested that β_1-stimulation may be related to inhibition of cholinergic neurotransmission (Ek & Lundgren 1982). No evidence for the latter mechanism was found in the cat gastric fundus, as both propranolol and ICI 118551 antagonized the inhibitory effect of dopamine on electrically-induced tone only to a minor extent. One might indeed expect that the postjunctional inhibitory effect of dopamine is also active during electrically-induced tone and contributes to the inhibition observed. We have no explanation why ICI 118551 did not antagonize the inhibition by dopamine on electrically-induced contractions in the longitudinal muscle strips. Atypical β-adrenoceptors, similar to the β_3-adrenoceptors of rat adipocytes, have been described in gastrointestinal tissues (McLaughlin & MacDonald 1990; Van Der Vliet et al 1990). Although it was not the aim of the present study to characterize the β-adrenoceptors in the cat gastric fundus, it is unlikely that dopamine interacts with atypical β-adrenoceptors in the cat gastric fundus. Indeed, in the rat colon, the inhibitory effect of phenylethanolaminotetralines, which selectively stimulate atypical β-adrenoceptors (Manara & Bianchetti 1990), is antagonized by propranolol but not by ICI 118551 (Croci et al 1988), while the inhibitory effect of dopamine in the cat gastric fundus is antagonized by both.

Inhibitory α-adrenoceptors on the intramural cholinergic neurons are involved in the prejunctional effect of dopamine, since the α-adrenoceptor antagonist phentolamine clearly antagonized this effect without influence on the inhibition of methacholine-induced tone. Interaction of catecholamines with prejunctional α-adrenoceptors on intramural cholinergic neurons is well established in the gastrointestinal tract (for references see Lefebvre et al 1983). However, phentolamine did not clearly reduce the effect of the lower concentrations of dopamine, while the D_2-receptor antagonist domperidone (Kohli et al 1983) did. Surprisingly, in longitudinal muscle strips, the D_1-receptor antagonist SCH 23390 (Goldberg et al 1984) also antagonized the prejunctional effect of dopamine. It is unlikely that this is due to an interaction of dopamine with prejunctional D_1-receptors as peripheral prejunctional dopamine receptors, both on noradrenergic (Willems et al 1985) and cholinergic (Drew & Hilditch 1984) nerves, belong to the D_2-class. Although it was reported that SCH 23390 does not influence the effect of antagonists at α-, β-, cholinergic, histamine or 5-HT receptors (Goldberg et al 1984), it was later shown to have antagonist as well as agonist activity at 5-HT receptors (Ohlstein & Berkowitz 1985; Skarsfeldt & Larsen 1988). Some non-specific antagonist activity at α-adrenoceptors might explain the observation in the cat gastric fundus, although not the difference between the longitudinal and circular muscle strips.

To further investigate the receptors involved in the prejunctional effect of dopamine in appropriate conditions, experiments were performed in the presence of propranolol to block the β-adrenoceptors and in the presence of cocaine and hydrocortisone to exclude all interference from uptake even if our results had shown that these agents did not influence the inhibition of dopamine. Phentolamine antagonized the prejunctional inhibitory effect of dopamine in a concentration-dependent way and this was mimicked by the α_2-adrenoceptor antagonist rauwolscine (Starke 1981) while the α_1-adrenoceptor antagonist prazosin (Starke 1981) had no effect. Although the antagonism of the lower concentrations of dopamine was again less clear, Schild plot analysis yielded a slope not different from unity except for the antagonism of dopamine by phentolamine in the longitudinal muscle strips. This suggests competitive antagonism at one receptor site. The pA_2 values for rauwolscine are in the range of those reported for its interaction with α_2-adrenoceptors (Michel & Whiting 1981; Alabaster et al 1985) and much higher than those reported for its interaction with α_1-adrenoceptors (Docherty & Starke 1981; Digges & Summers 1983). Together with the non-effect of prazosin, this allows the conclusion that dopamine acts at prejunctional α_2-adrenoceptors in the cat gastric fundus. However, the antagonist influence of domperidone on the lower concentrations of dopamine was confirmed. Although the non-concentration-dependency of this antagonism is difficult to explain, the result suggests a possible interaction of the lower concentration of dopamine with receptors other than α_2-adrenoceptors. We recently investigated the relaxant effect of the D_2-selective agonist quinpirole in the guinea-pig stomach; although the relaxant effect was mainly due to an interaction with α_2-adrenoceptors, the involvement of D_2-receptors could similarly not be fully excluded (Guenaneche et al 1991). The importance of the second type of receptor may vary to some extent from series to series. This might explain why a slope significantly lower than unity was obtained for the antagonism of dopamine by phentolamine in the longitudinal muscle strips.

It is concluded that the inhibitory effect of dopamine in the circular and longitudinal muscle layer of the cat gastric fundus is due to a postjunctional effect at muscular β_2-adrenoceptors, and to a prejunctional effect, mainly at α_2-adrenoceptors on intramural cholinergic neurones.

Acknowledgements

R. A. Lefebvre is a Senior Research Associate of the National Fund for Scientific Research (Belgium); he is indebted to Dr H. De Smet and Dr F. De Beurme for their help in part of the experiments. The study was financially supported by Grant No. 3.0012.86 of the Fund for Medical Scientific Research (Belgium).

References

Abrahamsson, H., Jansson, G., Martinson, J. (1973) Vagal relaxation of the stomach induced by apomorphine in the cat. Acta Physiol. Scand. 88: 296–302

Alabaster, V. A., Keir, R. F., Peters, C. J. (1985) Comparison of activity of alpha-adrenoceptor agonists and antagonists in dog and rabbit saphenous vein. Naunyn Schmiedebergs Arch. Pharmacol. 330: 33–36

Arunlakshana, O., Schild, H. O. (1959) Some quantitative uses of drug antagonists. Br. J. Pharmacol. 14: 48–58

Bilski, A. J., Halliday, S. E., Fitzgerald, J. D., Wale, J. L. (1983) The pharmacology of a β_2-selective adrenoceptor antagonist (ICI 118,551). J. Cardiovasc. Pharmacol. 5: 430–437

Blancquaert, J. P., Lefebvre, R. A., Willems, J. L. (1985) Influence of peripheral and central administration of apomorphine and morphine on intragastric pressure in the dog. Eur. J. Pharmacol. 107: 133–140

Croci, T., Cecchi, R., Tarantino, A., Aureggi, G., Bianchetti, A., Boigegrain, R., Manara, L. (1988) Inhibition of rat colon motility by stimulation of atypical beta-adrenoceptors with new gut-specific agents. Pharmacol. Res. Comm. 20: 147–151

Digges, K. G., Summers, R. J. (1983) Effects of yohimbine stereoisomers on contractions of rat aortic strips produced by agonists with different selectivity for α_1- and α_2-adrenoceptors. Eur. J. Pharmacol. 96: 95–99

Docherty, J. R., Starke, K. (1981) Postsynaptic α-adrenoceptor subtypes in rabbit blood vessels and rat anococcygeus muscle studied in vitro. J. Cardiovasc. Pharmacol. 3: 854–866

Drew, G. M., Hilditch, A. (1984) Prejunctional dopamine receptors modulate twitch responses to parasympathetic nerve stimulation in the rabbit isolated rectococcygeus muscle. Br. J. Pharmacol. 83: 871–881

Ek, B., Lundgren, B. (1982) Characterization of the β-adrenergic inhibition of motility in cat colon strips. Eur. J. Pharmacol. 77: 25–31

Goldberg, L. I., Glock, D., Kohli, J. D., Barnett, A. (1984) Separation of peripheral dopamine receptors by a selective DA_1 antagonist, SCH 23390. Hypertension 6: I25–I30

Goldberg, L. I., Volkman, P. M., Kohli, J. D. (1978) A comparison of the vascular dopamine receptor with other dopamine receptors. Ann. Rev. Pharmacol. Toxicol. 18: 57–79

Guenaneche, F., Schuurkes, J. A. J., Lefebvre, R. A. (1991) Influence of fenoldopam and quinpirole in the guinea-pig stomach. J. Auton. Pharmacol. 11: 221–235

Jo, Y. H., Sim, S. S., Choi, H., Kim, M. S. (1989) Effect of dopamine on electrical activity of isolated stomach muscle in cats. Dig. Dis. Sci. 34: 548–552

Kohli, J. D., Glock, D., Goldberg, L. I. (1983) Selective DA_2 versus DA_1 antagonist activity of domperidone in the periphery. Eur. J. Pharmacol. 89: 137–141

Lefebvre, R. A. (1990) Effects of dopamine on the digestive system. In: Amenta, F. (ed.) Peripheral Dopamine Pathophysiology. CRC Press, Boca Raton, pp 117–148

Lefebvre, R. A., Blancquaert, J. P., Willems, J. L., Bogaert, M. G. (1983) In vitro study of the inhibitory effects of dopamine on the rat gastric fundus. Naunyn Schmiedebergs Arch. Pharmacol. 322: 228–236

Lefebvre, R. A., Bogaert, M. G., De Schaepdrijver, A. F. (1986) In-vitro study of the enkephalinergic hypothesis for non-adrenergic, non-cholinergic innervation in the cat stomach. J. Pharm. Pharmacol. 38: 35–39

Lefebvre, R. A., Verplanken, P. A., Bogaert, M. G. (1984a) Pharmacological characterization of the postjunctional β-adrenoceptors in the rat gastric fundus. Eur. J. Pharmacol. 106: 1–9

Lefebvre, R. A., Willems, J. L., Bogaert, M. G. (1984b) Inhibitory effect of dopamine on canine gastric fundus. Naunyn Schmiedebergs Arch. Pharmacol. 326: 22–28

Luchelli-Fortis, M. A., Langer, S. Z. (1975) Selective inhibition by hydrocortisone of ^{3}H-normetanephrine formation during ^{3}H-transmitter release elicited by nerve stimulation in the isolated nerve-muscle preparation of the cat nictitating membrane. Ibid. 287: 261–275

Manara, L., Bianchetti, A. (1990) The phenylethanolaminotetralines: new selective agonists for atypical β-adrenoceptors. Trends Pharmacol. Sci. 11: 229–230

McLaughlin, D. P., MacDonald, A. (1990) Evidence for the existence of atypical β-adrenoceptors (β_3-adrenoceptors) mediating relaxation in the rat distal colon in vitro. Br. J. Pharmacol. 101: 569–574

Meyer, J. H. (1987) Motility of the stomach and gastroduodenal junction. In: Johnson, L. R. (ed.) Physiology of the Gastrointestinal Tract. 2nd edn, Raven Press, New York, pp 613–629

Michel, A. D., Whiting, R. L. (1981) 2-(2-Imidazolmethyl)-1,4-benzodioxans, a series of selective α-adrenoceptor antagonists. Br. J. Pharmacol. 74: 255P–256P

Ohlstein, E. H., Berkowitz, B. A. (1985) SCH 23390 and SK&F 83566 are antagonists at vascular dopamine and serotonin receptors. Eur. J. Pharmacol. 108: 205–208

Skarsfeldt, T., Larsen, J. J. (1988) SCH 23390—a selective dopamine D-1 receptor antagonist with putative 5-HT_1 receptor agonistic activity. Ibid. 148: 389–395

Starke, K. (1981) α-Adrenoceptor subclassification. Rev. Physiol. Biochem. Pharmacol. 88: 199–236

Stefanini, E., Clement-Cormier, Y. (1981) Detection of dopamine receptors in the area postrema. Eur. J. Pharmacol. 74: 257–260

Van Der Vliet, A., Rademaker, B., Bast, A. (1990) A beta adrenoceptor with atypical characteristics is involved in the relaxation of the rat small intestine. J. Pharmacol. Exp. Ther. 255: 218–226

Weitzell, R., Tanaka, T., Starke, K. (1979) Pre- and postsynaptic effects of yohimbine stereoisomers on noradrenergic transmission in the pulmonary artery of the rabbit. Naunyn Schmiedebergs Arch. Pharmacol. 308: 127–136

Willems, J. L., Buylaert, W. A., Lefebvre, R. A., Bogaert, M. G. (1985) Neuronal dopamine receptors on autonomic ganglia and sympathetic nerves and dopamine receptors in the gastrointestinal system. Pharmacol. Rev. 37: 165–216