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Catecholamine-induced relaxation and contraction of the lower oesophageal and pyloric sphincters of guinea-pig stomach: modification by domperidone

H. A. SAHYOUN, B. COSTALL AND R. J. NAYLOR*

Postgraduate School of Studies in Pharmacology, University of Bradford, Bradford BD7 1DP, U.K.

Catecholamine control of circular smooth muscle activity of the lower oesophageal (LOS) and pyloric sphincters (PS) of the guinea-pig was studied using α- and β-adrenoceptor agonists and antagonists. In both sphincters dopamine (DA) and noradrenaline (NA) caused relaxation followed by contraction of the circular smooth muscle, although the ability of NA to contract the PS was weak and inconsistent. Isoprenaline relaxed both sphincter preparations but, whilst phenylephrine contracted the muscle of the PS, it caused a biphasic relaxation-contraction of the LOS. The use of the α- and β-adrenoceptor antagonists, phentolamine and propranolol, indicated that contractions of both sphincters by NA and DA involved an α-type adrenoceptor whilst relaxation was mediated via a β-adrenoceptor (PS) or via both α- and β-adrenoceptors (LOS). Use of the α_1 and α_2 antagonists, prazosin and yohimbine, indicated that the α-adrenoceptor type involved with both the contractions and relaxation was α_1. Both domperidone and haloperidol antagonized the contractile responses of both tissues to DA (and partly the relaxation of the LOS) but were similarly effective against the contractions induced by NA and phenylephrine; an effect on α_1-adrenoceptors was therefore concluded. In selectively antagonizing the contractile effects of DA in the PS, domperidone enhanced DA's ability to relax this sphincter.

Certain neuroleptic agents with a potent ability to block cerebral dopamine (DA) receptors are also effective in facilitating gastric emptying, and such effects of domperidone and metoclopramide have proven clinical usefulness (Pinder et al 1976; Reyntjens et al 1978). However, the precise mechanism of action of domperidone and related agents on the gastrointestinal system is not known, and an interpretive analogy between such a peripheral effect and cerebral DA receptor blockade may be misleading. Thus, Ennis & Cox (1980) have shown that domperidone has significant α_1-adrenoceptor blocking action in the guinea-pig aorta, and we have shown a similar mechanism of action on circular smooth muscle of the stomach (Costall et al 1981; Sahyoun et al 1982; see also Schuurkes & Van Nueten 1981). Whilst relating such data to a facilitation of gastric emptying, it is appreciated that the overall action of domperidone on the stomach must also critically depend on sphincter activity. Hence, in the present study, we investigate the ability of domperidone to modify catecholamine-induced contraction and/or relaxation of the circular smooth muscle of the lower oesophageal (O) and pyloric (P) sphincters.

* Correspondence.

MATERIALS AND METHODS

Male Dunkin-Hartley guinea-pigs (350–450 g), which had been without food overnight, were killed by cervical trans-section. The stomach was removed with approximately 2 cm of oesophagus and duodenum and placed in Krebs-Henseleit solution for dissection of the LOS and PS. Strips were taken from the gastroesophageal (approximately 10 mm long, 5 mm wide) and gastroduodenal (approximately 15 mm long, 5 mm wide) junctions in a plane suitable to record tension changes in the circular muscle layer. Additionally, the mucosal layer was removed from the PS. Tissues were bathed in 15 ml oxygenated (95% O_2, 5% CO_2) Krebs-Henseleit solution containing 100 mg litre^{-1} ascorbic acid at 37 °C. One gram tension was applied to the tissues which were allowed to equilibrate for 30–45 min before the addition of drugs. Tension changes were detected by Grass tension transducers and displayed on a multichannel Grass recorder: sample traces obtained to DA, noradrenaline (NA), phenylephrine and isoprenaline are shown in Fig. 1. To allow a comparison of the absolute changes in tension between tissues and agonists, the maximum changes in tension to be recorded using the four agonists are shown in Fig. 2. In addition, tension changes were

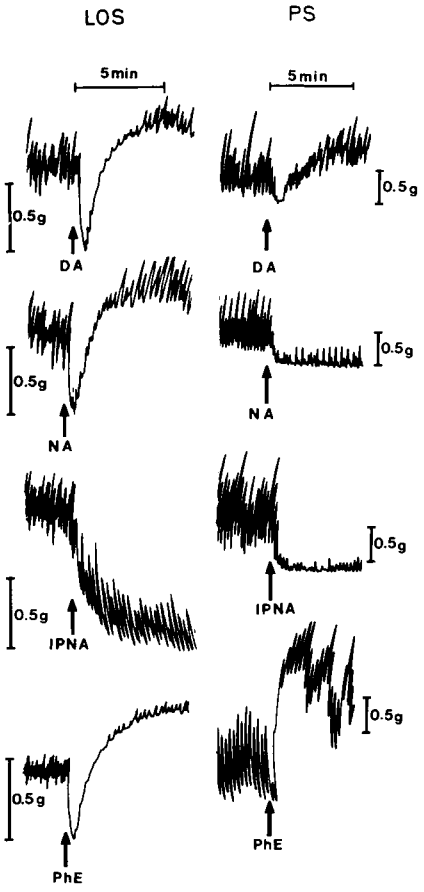

FIG. 1. Example traces of the responses of the LOS and PS to administration of DA ($1{\cdot}4 \times 10^{-4}$ M), NA ($2{\cdot}0 \times 10^{-6}$ M), isoprenaline (IPNA) ($6{\cdot}2 \times 10^{-7}$ M) and phenylephrine (PhE) ($8{\cdot}0 \times 10^{-6}$ M).

concomitantly monitored using an integrator (Illingworth & Naylor 1980) coupled to a CBM 3032 computer; this allowed a precise measure and record of the area of contraction and/or relaxation. To allow an easier comparison between treatments, figures were constructed to show changes as a % of control values (see Figure legends for precise description) and the significance of differences calculated from these using a Mann-Whitney 'U' test: s.e.m.s were calculated from integrated data and are given in the figure legends.

The contact time for DA, NA, phenylephrine and isoprenaline was 5 min. This time was dictated by the biphasic nature of some of the responses obtained: at 5 min the complete spectrum of response was apparent and stable. There was no evidence that desensitisation occurred in the agonist studies. Before the start of any experiment, the normal, repeatable response of tissues to contract-relax was established using DA, phenylephrine and isoprenaline. Subsequently each different agonist–antagonist interaction was assessed in a fresh tissue. Antagonists were allowed a 20 min incubation period before the addition of agonists: this pretreatment time was selected to ensure adequate receptor blockade, for example, for propranolol to inhibit the isoprenaline responses and phentolamine to inhibit the phenylephrine responses.

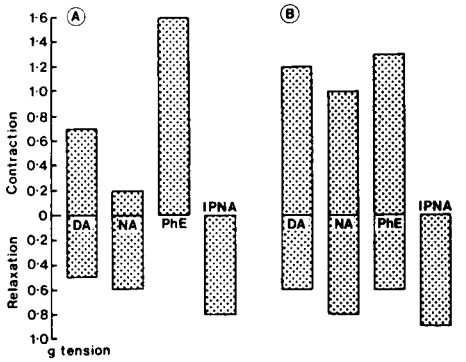

FIG. 2. Maximum tension changes (g) caused by DA, NA, phenylephrine and isoprenaline at their maximally effective concentrations (see Figs 3 and 6) on circular smooth muscle strips taken from the PS (A) and LOS (B) of the guinea-pig stomach. n = 6. s.e.m.s <11%. The maximum 'response' is a product of the maximum tension change and the duration of this change, thus response 'sizes' are determined in subsequent figures by integration of the 'area' of contraction or relaxation.

Domperidone (Janssen) and phentolamine mesylate (Rogitine, Ciba) were used in the parenteral forms prepared by the manufacturers; (±)-propranolol hydrochloride (ICI), NA hydrogen tartrate (Hoechst), DA hydrochloride (Koch Light), isoprenaline sulphate (Riker), phenylephrine hydrochloride (BDH), yohimbine hydrochloride (Sigma) and prazosin hydrochloride (Pfizer) were prepared in distilled water, and haloperidol (Janssen) from a solution prepared in 1% lactic acid.

RESULTS

Actions of DA, NA, phenylephrine and isoprenaline on the PS: modification by domperidone

DA (10^{-5}–10^{-3} M), NA (10^{-7}–10^{-5} M) and isoprenaline (10^{-7}–5×10^{-6} M) caused concentration-dependent relaxations of the circular smooth muscle of the PS. The DA response was followed by a marked contraction in the range 2×10^{-6}–$3{\cdot}5 \times 10^{-5}$ M; at higher concentrations the contractile responses decreased. Contractions to NA were weak

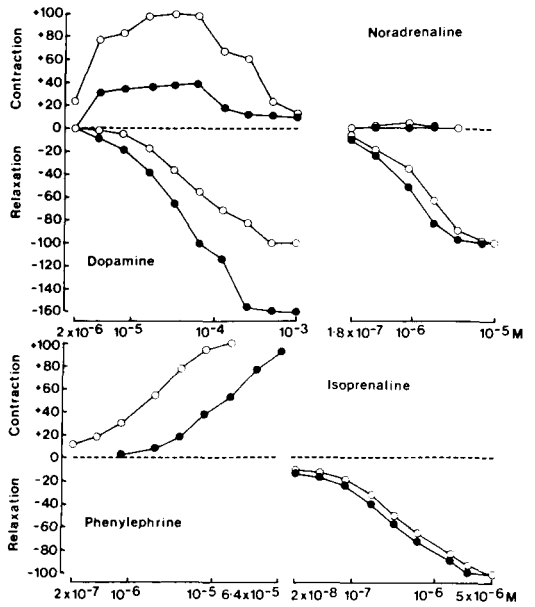

FIG. 3. Relationships between concentration and response for DA, NA, phenylephrine and isoprenaline (○—○), and the antagonism by 10^{-5} M domperidone (●—●), to contract (+ values) and relax (− values) circular smooth muscle of the PS. The size of response was determined by integration of the area of response: in order to compare sizes of contraction and relaxation responses, the size of the maximum relaxation response to each agonist was termed 100% and the 'sizes' of all other relaxation and contraction responses determined as a % of this maximum. n = 6 s.e.m.s <12%.

and inconsistent (Fig. 3) but phenylephrine (10^{-7}–10^{-5} M) caused contractions exclusively. Domperidone, 10^{-7} M, failed to affect the contraction or relaxation to any agonist, although 10^{-6} M reduced the contraction responses with 10^{-5} M further reducing DA and NA contractile potential to unmask the relaxation (DA); the contractions to phenylephrine were antagonized in a competitive manner. However, the isoprenaline-induced relaxation responses were not affected by any concentration of domperidone (Fig. 3).

Characterizing the catecholamine receptors involved in smooth muscle tension changes of the PS

Concentrations of propranolol (5×10^{-7} M) and phentolamine (10^{-6} M) were selected as those causing significant reductions in responses to submaximal concentrations of isoprenaline ($6{\cdot}2 \times 10^{-7}$ M) and phenylephrine (8×10^{-6} M) respectively. Challenging submaximal concentrations of NA (2×10^{-6} M) and DA ($1{\cdot}4 \times 10^{-4}$ M) with these selected antagonist concentrations showed propranolol to markedly reduce (approx. 80%) the relaxation responses to DA and NA, but not the contractions, whilst phentolamine reduced the contractions (approx. 70–90%) and enhanced the relaxation potentials of DA and NA. Haloperidol (10^{-6} M) exerted a similar activity spectrum. Propranolol abolished the relaxation to DA and NA resulting from phentolamine's action (Fig. 4, to allow immediate comparison, this figure includes the relevant data for domperidone).

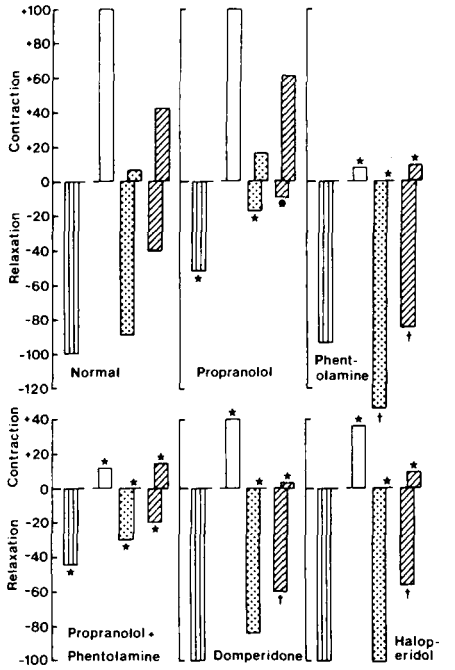

FIG. 4. Abilities of submaximal concentrations of isoprenaline ($6{\cdot}2 \times 10^{-7}$ M, striped columns), phenylephrine ($8{\cdot}0 \times 10^{-6}$ M, open columns), NA ($2{\cdot}0 \times 10^{-6}$ M, dotted columns) and DA ($1{\cdot}4 \times 10^{-4}$ M, hatched columns) to cause relaxations and/or contractions of circular smooth muscle of the PS of guinea-pig in the absence of any other treatment (normal) or in the presence of propranolol (5×10^{-7} M), phentolamine (10^{-6} M), propranolol (5×10^{-7} M) plus phentolamine (10^{-6} M), domperidone (10^{-5} M) or haloperidol (10^{-6} M). The + values on the ordinate indicate contraction, the − values relaxation. The size of response was determined by integration and is presented as a % of the maximum obtained with isoprenaline (relaxation) or phenylephrine (contraction). n = 6. s.e.m.s <11%. * indicates a significant reduction in response, † a significant increase (P <0·05, Mann-Whitney 'U' test, comparisons to normal).

In a more detailed characterization of the 'α-adrenoceptor' mechanisms, prazosin (10^{-9}–10^{-7} M) was found to antagonize the DA and phenylephrine contractions in a concentration-dependent manner, and to enhance the DA relaxation. Prazosin, at all concentrations (10^{-9}–10^{-7} M), failed to modify the

relaxation response to isoprenaline (Fig. 5A). Yohimbine failed to modify DA or phenylephrine relaxation and/or contractions when used in concentrations of 10^{-9}–10^{-6} M (results not shown).

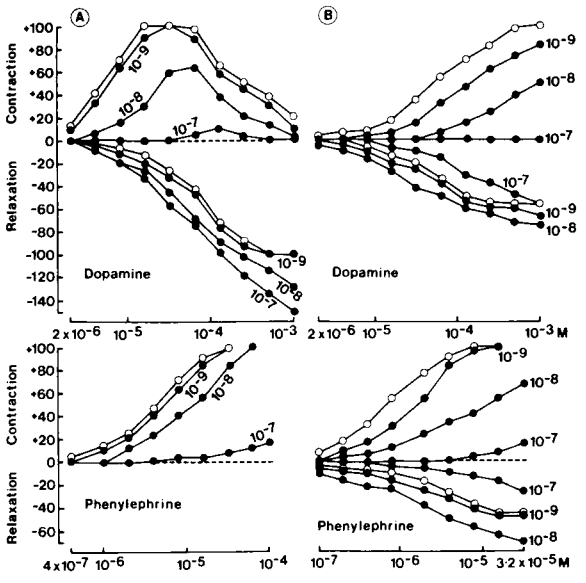

FIG. 5. Relationships between concentration and response for DA and phenylephrine in A. the PS and B. the LOS. DA or phenylephrine alone (○—○) or in the presence of prazosin (●—●) at the M concentrations indicated. The + values on the ordinate indicate contraction, the − values relaxation. The size of response was determined by integration. The maximum size of contraction to DA or phenylephrine alone was taken as 100%, and the size of all other responses, contraction or relaxation, expressed as a % of this. n = 6. s.e.m.s <12%.

Actions of DA, NA, phenylephrine and isoprenaline on the LOS: modification by domperidone

DA (10^{-5}–10^{-3} M), NA (10^{-7}–10^{-5} M) and phenylephrine (10^{-7}–10^{-4} M) caused relaxation followed by contraction of the circular smooth muscle of the LOS, whilst isoprenaline (10^{-8}–10^{-6} M) caused relaxation only (Fig. 6). Domperidone, 10^{-7} M, failed to modify any relaxation or contraction response, 10^{-6} M markedly reduced the contractions without modification of the relaxation responses, whilst 10^{-5} M domperidone markedly reduced both contractions and relaxations to DA and phenylephrine, and the contractions to NA. The isoprenaline response was unaffected by domperidone (10^{-7}–10^{-5} M) (Fig. 6).

Characterizing the catecholamine receptors involved in smooth muscle tension changes of the LOS

Concentrations of propranolol (5×10^{-7} M) and phentolamine (10^{-6} M) were selected as those causing

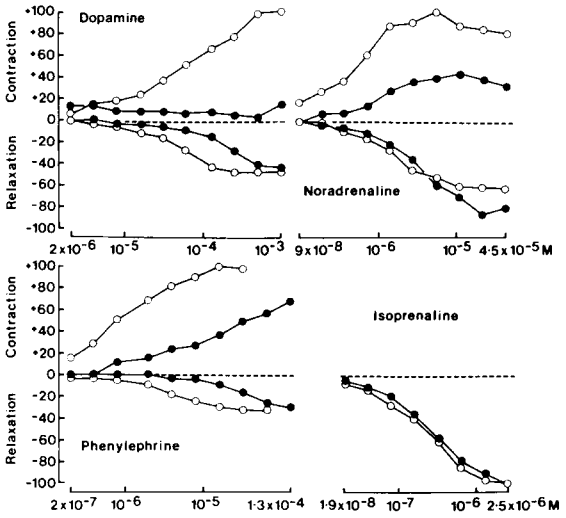

FIG. 6. Relationships between concentration and response for DA, NA, phenylephrine and isoprenaline (○—○) and the antagonism by 10^{-5} M domperidone (●—●) to contract (+ values) and relax (− values) circular smooth muscle of the LOS. The size of response was determined by integration of the area of response: in order to compare size of contraction and relaxation responses the maximum contraction (DA, NA, phenylephrine) or relaxation (isoprenaline) was termed 100%, and the sizes of all other contraction and relaxation responses determined as % of the appropriate maximum. n = 6. s.e.m.s <11%.

approximate 80% reductions in the responses to submaximal concentrations of isoprenaline ($6{\cdot}2 \times 10^{-7}$ M) and phenylephrine (8×10^{-6} M) respectively. The selected concentration of propranolol reduced the NA and DA relaxations by 40–50%, although contraction responses to the catecholamines or phenylephrine were not modified. In contrast, the selected concentration of phentolamine more effectively antagonized the contraction responses (by 100, 90 and 80% for NA, DA and phenylephrine) than the relaxation responses (by 35, 60 and 40% for NA, DA and phenylephrine). The isoprenaline response was unaffected by phentolamine (10^{-8}–10^{-6} M). The contraction and/or relaxation to isoprenaline, phenylephrine, NA and DA was virtually eliminated by combined phentolamine/propranolol treatment. Haloperidol (10^{-6} M) reduced the contractions to phenylephrine, NA and DA by approximately 80%, and also reduced the relaxations to phenylephrine and DA—a spectrum of action identical to that of domperidone (included in Fig. 7 for immediate comparison of data).

In the more detailed characterization of the α-adrenoceptor involved in the relaxation–contraction responses to DA and phenylephrine within the

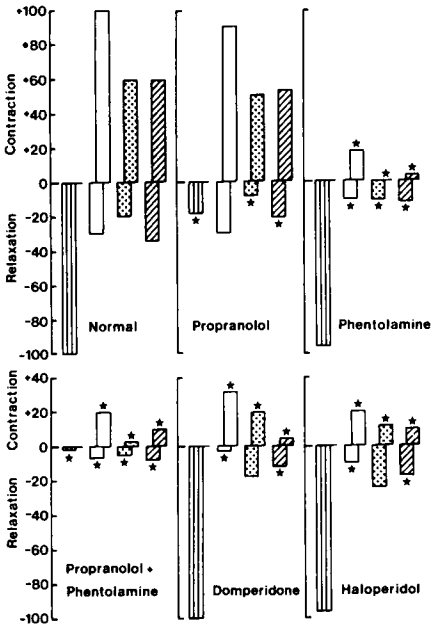

FIG. 7. Abilities of submaximal concentrations of isoprenaline ($6{\cdot}2 \times 10^{17}$ M, striped columns), phenylephrine ($8{\cdot}0 \times 10^{-6}$ M, open columns), NA ($2{\cdot}0 \times 10^{-6}$ M, dotted columns) and DA ($1{\cdot}4 \times 10^{-4}$ M, hatched columns) to cause relaxations and/or contractions of circular smooth muscle of the LOS of the guinea-pig in the absence of any (5×10^{-7} M), phentolamine (10^{-6} M), propranolol (5×10^{-7} M) plus phentolamine (10^{-6} M), domperidone (10^{-5}) or haloperidol (10^{-6} M). The + values on the ordinate indicate contraction, and − values relaxation. The size of response is determined by integration and is presented as a % of the maximum obtained with isoprenaline (relaxation) or phenylephrine (contraction). n = 6. s.e.m.s <12%. * indicates a significant reduction in response ($P < 0{\cdot}05$, Mann-Whitney 'U' test, comparisons to normal).

LOS, yohimbine (10^{-8}–10^{-6} M) was shown to be ineffective in modifying the contraction or relaxation to either compound. Prazosin, however, in concentrations as low as 10^{-9} M, caused significant antagonism of the contractile responses and only at the higher concentrations of 10^{-7} M were the relaxations to phenylephrine and DA reduced (Fig. 5B).

So that an immediate comparison can be made of the respective potencies and selectivities of action of propranolol, phentolamine, prazosin, yohimbine, haloperidol and domperidone, on smooth muscle of the LOS and PS in antagonizing the isoprenaline-, phenylephrine-, NA- and DA-induced relaxations and/or contractions, IC50 values are given in Table 1.

The effect of reserpine pretreatment on PS and LOS responses to DA, NA, phenylephrine and isoprenaline

PS and LOS strips were taken from normal and reserpine treated (5 mg kg^{-1} i.p., 24 h, a pretreatment shown to markedly reduce the action of tyramine, unpublished data) guinea-pigs and their responsiveness tested concurrently. There were no significant differences in the spectra of contraction–relaxation responses to NA, DA, phenylephrine and isoprenaline between the two groups.

DISCUSSION

In analysing the actions of NA and DA it is important to note that DA acted on the sphincters independently of NA, thus, the DA responses of the

Table 1. IC50 (M)*** values for antagonism of the contraction and/or relaxation responses of circular smooth muscle of (A) the PS and (B) the LOS to adrenergic agonists.

Adrenergic agonist	Concentration (M)	Response R or C*	IC50 (M) Propranolol	Phentolamine	Domperidone	Haloperidol	Prazosin
(A) *PS*							
IPNA	$6{\cdot}2 \times 10^{-7}$	R	4×10^{-7}	—	—	—	—
PhE	$8{\cdot}0 \times 10^{-6}$	C	—	9×10^{8}	8×10^{-6}	6×10^{-7}	2×10^{-8}
NA	$2{\cdot}0 \times 10^{-6}$	R	2×10^{-7}	—	—	—	—
NA	$2{\cdot}0 \times 10^{-6}$	C	—	**	**	**	**
DA	$1{\cdot}4 \times 10^{-4}$	R	2×10^{-7}	—	—	—	—
DA	$1{\cdot}4 \times 10^{-4}$	C	—	2×10^{-7}	7×10^{-6}	7×10^{-7}	8×10^{-9}
(B) *LOS*							
IPNA	$6{\cdot}2 \times 10^{-7}$	R	2×10^{-7}	—	—	—	—
PhE	$8{\cdot}0 \times 10^{-6}$	R	—	2×10^{-6}	5×10^{-6}	8×10^{-7}	1×10^{-7}
PhE	$8{\cdot}0 \times 10^{-6}$	C	—	2×10^{-7}	7×10^{-6}	1×10^{-7}	7×10^{-9}
NA	$2{\cdot}0 \times 10^{-6}$	R	5×10^{-7}	2×10^{-6}	—	—	3×10^{-7}
NA	$2{\cdot}0 \times 10^{-6}$	C	—	2×10^{-7}	3×10^{-6}	3×10^{-7}	6×10^{-9}
DA	$1{\cdot}4 \times 10^{-6}$	R	7×10^{-7}	8×10^{-7}	8×10^{-6}	1×10^{-6}	2×10^{-7}
DA	$1{\cdot}4 \times 10^{-6}$	C	—	2×10^{-7}	3×10^{-6}	3×10^{-7}	7×10^{-9}

— no antagonism at 5×10^{-7} M propranolol, 10^{-6} M phentolamine, 10^{-5} M domperidone, 10^{-6} M haloperidol, 10^{-7} M prazosin; *relaxation (R) or contraction (C); **contractile response too small to allow the demonstration of a concentration-related antagonism.

***Concentration of antagonist required to reduce the response of the agonist by 50%.

sphincters were not significantly modified by reserpine pretreatment and they could differ both quantitatively and qualitatively from those of NA. The action of DA on the circular smooth muscle of the PS was to cause relaxation followed by contraction: NA had a similar biphasic effect although the contraction phase was inconsistent and relatively less marked. The contraction phases of the responses to both DA and NA were sensitive to antagonism by phentolamine but not by propranolol, whilst the relaxation phases were specifically inhibited by propranolol. Since phenylephrine caused only a contraction (phentolamine sensitive) and isoprenaline only a relaxation (propranolol sensitive), we concluded from these initial experiments that the DA- and NA-induced contractions and relaxations of the PS are mediated via α- and β-adrenoceptors respectively. DA had an equal activity on both types of receptor whilst NA acted predominantly on the β-adrenoceptor. These results are at variance with the general belief that DA is always less potent than NA at α-adrenoceptors.

A more precise analysis of the nature of the contraction mediating α-adrenoceptors using prazosin and yohimbine has indicated that the contractile response to DA and phenylephrine was sensitive to prazosin and resistant to yohimbine. Whilst it proved impractical to assess antagonistic potencies in terms of pA_2 values (the biphasic nature of the agonist responses and/or the 'non-competitive' shifts in the response curves confound such determinations—see Furchgott et al 1973), this does not detract from the observations that in many tissues phenylephrine is a highly selective α_1-agonist and that prazosin and yohimbine are selective α_1- and α_2-antagonists respectively (Drew 1977). We conclude that the highly selective antagonism by prazosin of the contractile response in the PS of the guinea-pig suggests an α_1-type adrenoceptor. The essential observation of the present study is that domperidone selectively antagonizes the contractile effects of DA in the PS with a consequent enhancement of its ability to cause relaxation (β-stimulation). Haloperidol was shown to have a similar effect. The second important observation is that domperidone and haloperidol were also effective at blocking NA and phenylephrine contractions. Notwithstanding that both haloperidol and domperidone have a high specificity in blocking DA receptors in the cerebral system, we would conclude that data from all the above agonist/antagonist interactions concur to suggest a DA-domperidone action at α_1-receptors within the PS.

In the LOS, as in the PS, both DA and NA caused biphasic relaxation-contraction, but these were modified in a more complex manner by the adrenoceptor antagonists: the contractile effects were completely antagonized by phentolamine but the relaxations were partly reduced by phentolamine, partly by propranolol, with only a combined phentolamine–propranolol treatment causing a complete abolition. Similarly to observations with the PS, isoprenaline caused only a propranolol-sensitive relaxation of the LOS, but phenylephrine caused a biphasic relaxation–contraction response for which both components were phentolamine-sensitive. Thus, within the LOS, α-type adrenoceptors mediate the NA- and DA-induced contractions of the circular smooth muscle whilst both α- and β-adrenoceptors mediate the relaxation. Using longitudinal muscle strips taken from the guinea-pig gastroesophageal junction, Cox & Ennis (1980) have similarly concluded that a mixture of α- and β-adrenoceptor antagonists is required to completely inhibit DA-induced relaxations.

A further characterization of the α-type adrenoceptors mediating both relaxation and contraction using both prazosin and yohimbine showed that yohimbine was ineffective in modifying either the DA or phenylephrine relaxation or contraction. In contrast, prazosin inhibited both the contraction and relaxation with the contraction phase proving the most sensitive. The α-adrenoceptor type involved in both the relaxation and contraction in the LOS is therefore suggested to be of the α_1-type. Again using the longitudinal muscle strips, Cox & Ennis (1980) have shown that the contractile response to phenylephrine is sensitive to α_1-antagonists.

Possibly it should be mentioned here that the interpretation of the complexities of catecholamine control of the LOS is enhanced by species differences. Thus, in the rat the phenylephrine response is specifically antagonized by α-adrenoceptor antagonists (Takayanagi & Kasuya 1977) and in the opossum the DA response is insensitive to both α- and β-adrenoceptor blocking agents, but is neuroleptic sensitive (De Carle & Christensen 1976; Rattan & Goyal 1976; Mukhopadhyay & Weisbrodt 1977).

In the present study domperidone was found to inhibit the contraction phases of the responses to NA, DA and phenylephrine, which could be indicative of an ability to antagonize at α_1-adrenoceptors. However, it would not necessarily follow that domperidone should normally act to facilitate relaxation of the LOS since domperidone was also effective

in reducing the relaxation caused by DA (the inability of domperidone to antagonize the NA relaxation is probably reflective of a β-adrenoceptor action not influenced by domperidone). Thus, the possibility that domperidone may antagonize both a relaxation and a contraction response makes it difficult to predict the final motor response. The most important conclusion to be drawn from the studies on the functioning of the LOS is that domperidone may act as an α_1-antagonist, a conclusion which is in agreement with the findings of Cox & Ennis (1980) that domperidone antagonizes at α_1-receptors in the longitudinal smooth muscle of the LOS of the guinea-pig.

In conclusion, on the basis of our present and previous studies (Costall et al 1981), we would suggest that DA does exert some actions on the stomach and its sphincters which are independent of NA and which can be antagonized by domperidone acting through an α-adrenoceptor blockade.

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