J. Pharm. Pharmacol. 1990, 42: 752–757
Received March 21, 1990

Pre- and Post-junctional α-Adrenoceptor-mediated Responses in the Rat Gastric Fundus In-vitro

A. MACDONALD, J. KELLY† AND P. W. DETTMAR*

*Department of Biological Sciences, Glasgow College, Cowcaddens Road, Glasgow, G4 0BA and *Department of Pharmacology, Reckitt & Colman Pharmaceutical Division, Dansom Lane, Hull HU8 7DS, UK*

Abstract—The effects of α_1- and α_2-adrenoceptor agonists on smooth muscle tone and on cholinergic excitatory and non-adrenergic, non-cholinergic inhibitory responses to field stimulation have been investigated in the rat gastric fundus in-vitro. None of the α-adrenoceptor agonists tested, noradrenaline, phenylephrine, cirazoline, guanoxabenz or UK-14,304 showed any contractile effects at concentrations up to 30 μM. In preparations where tone was raised by barium (0·5–2 mM), the mixed α_1- and α_2-adrenoceptor agonist noradrenaline (0·01–10 μM), and the selective α_1-adrenoceptor agonists cirazoline (0·01–10 μM) and phenylephrine (0·01–10 μM) produced concentration-dependent relaxations which were antagonized by the α_1-adrenoceptor antagonist prazosin (0·01–1·0 μM). The selective α_2-adrenoceptor agonists UK-14,304 (0·03–30 μM) and guanoxabenz (0·03–30 μM), had no relaxant effects in raised tone. UK-14,304 (0·03–1·0 μM) produced a concentration-dependent inhibition of cholinergic nerve-induced responses which was antagonized by the α_2-adrenoceptor antagonist idazoxan (0·03–1·0 μM) but not by prazosin (0·03–1·0 μM). Noradrenaline (0·03–1·0 μM) also produced an inhibition of cholinergic nerve-induced responses which was antagonized by idazoxan (0·03–1·0 μM). A small component of the noradrenaline inhibitory effects was antagonized by prazosin (10%). Cirazoline (0·03–1·0 μM) produced a small inhibition of cholinergic nerve-induced responses which was antagonized by prazosin (0·03–1·0 μM). The prazosin-sensitive components of the inhibitory effects of noradrenaline and cirazoline occurred at concentrations which also produced post-junctional relaxation. UK-14,304 (0·03–1·0 μM) also attenuated non-adrenergic, non-cholinergic (NANC) inhibitory nerve-induced responses and this effect was antagonized by idazoxan (0·03–1·0 μM). The effects of α_1-adrenoceptor agonists on NANC nerve-induced responses proved difficult to assess since these agonists caused post-junctional relaxation which itself reduced the size of the inhibitory nerve-induced responses. It is concluded that α-adrenoceptor mediated responses in the rat gastric fundus in-vitro consist of post-junctional α_1-adrenoceptor-mediated relaxation of the smooth muscle and pre-junctional α_2-adrenoceptor-mediated inhibition of both cholinergic excitatory and non-adrenergic, non-cholinergic inhibitory nerve-induced responses.

Stimulation of α-adrenoceptors in non-sphincteric gastrointestinal muscle generally produces relaxation (a) by a direct action on post-junctional α-adrenoceptors present on smooth muscle cells and (b) by an indirect action on pre-junctional α-adrenoceptors situated on intrinsic cholinergic neurons (Burnstock & Wong 1981; Daniell 1982). Examination of the types of α-adrenoceptor has generally shown post-junctional α-adrenoceptors to be of the α_1-subtype, while those located pre-junctionally are of the α_2-subtype (e.g. Wikberg 1977).

In the rat gastric fundus, the presence of post-junctional inhibitory α_1-adrenoceptors has been demonstrated (Lefebvre et al 1983; Verplanken et al 1984; Kelly & MacDonald 1990) although an excitatory α-adrenoceptor mediated response has also been reported (Ogle & Wong 1971). Pre-junctional α_2-adrenoceptors on cholinergic neurons have also been demonstrated in the rat isolated gastric fundus, although it has been suggested that they are atypical, having characteristics of both α_1- and α_2-adrenoceptor subtypes (McClelland & Sanger 1982; Lefebvre et al 1983; Verplanken et al 1984). The present study was carried out to examine these α-adrenoceptor mediated responses in the rat gastric fundus using selective α_1- and α_2-adrenoceptor agonists and antagonists. As α_2-adrenoceptors in the gastrointestinal tract have also been reported to be present pre-junctionally on non-adrenergic, non-cholinergic nerves (Fontaine et al 1984) and post-junctionally on smooth muscle mediating contraction (Sahyoun et al 1982) or relaxation (Bauer 1982; Bauer & Kuriyama 1982), their presence at these sites in the rat gastric fundus was also investigated. Preliminary accounts of this work have previously been reported (Dettmar et al 1984, 1985a, b, 1986).

Methods

Male Sprague Dawley rats, 150–300 g, were killed by a blow to the head and cervical dislocation. The gastric fundus was removed and strips prepared by the method of Vane (1957). Tissues were suspended between silver/silver chloride "ring and hook" electrodes in 30 mL organ baths containing Krebs medium of the following composition (mM): NaCl, 119; KCl, 4·7; $CaCl_2$, 2·5; $MgSO_4$, 1·0; $NaHCO_3$, 25·0; KH_2PO_4, 1·2; D-glucose, 11·1. The solution was maintained at 37°C and gassed continuously with 5% CO_2 in oxygen. Each muscle was placed under an initial resting tension of 1 g and allowed to equilibrate for 1 h before any further experimental procedures. Muscle tension was recorded with Bioscience Type UF1 isometric transducers and displayed on Wash-

† Present address: Biosciences Research Centre, SmithKline Beecham Pharmaceuticals, Research Division, Great Burgh, Yew Tree Bottom Road, Epsom KT18 5XQ, UK.

Correspondence to: A. MacDonald, Department of Biological Sciences, Glasgow College, Cowcaddens Road, Glasgow G4 0BA, UK.

ington oscillographs. Electrical field stimulation (EFS) was applied via the electrodes using a Harvard Research Stimulator and Cycle Timer, with a 1 ms pulse width and supramaximal voltage (150 V).

Propranolol (2 μM) was present throughout to prevent effects mediated via β-adrenoceptors.

In experiments involving catecholamines, the Krebs medium also contained the following: cocaine (3 μM) to block neuronal uptake; hydrocortisone (30 μM) to block extraneuronal uptake; ethylenediaminetetra-acetic acid (30 μM) and L-ascorbic acid (30 μM) to block oxidation.

In experiments to investigate the effects of drugs on cholinergic nerve-induced responses, EFS was applied at 0·5 Hz for 24 s. The Krebs solution also contained neostigmine (1 μM) to inhibit acetylcholinesterase and give more reproducible contractions to EFS. Under these conditions, contractile responses to EFS were abolished by either atropine (1 μM) or tetrodotoxin (1 μM) and were unaffected by hexamethonium (30 μM), suggesting that they were due to stimulation of post-ganglionic intrinsic cholinergic neurons. In experiments investigating the pre-junctional effects of α-adrenoceptor agonists, the antagonist contact time was 15 min.

To examine relaxant responses of the fundus, tone was induced by the addition of barium chloride (0·5–2 mM) to the baths in a concentration which produced a stable, plateau contraction. In all experiments using barium, atropine (2 μM) was present to prevent any contractile effects of barium mediated via the stimulation of cholinergic neurons (Gershon 1967). Under these conditions, tetrodotoxin (3 μM) had no effect on barium-induced tone and therefore α-adrenoceptor-mediated relaxations were not due to pre-junctional inhibition of excitatory nerves. In experiments investigating the post-junctional effects of α-adrenoceptor agonists the antagonist contact time was 30 min.

In experiments involving inhibitory nerve-induced responses, tone was raised as described above and EFS was applied at 0·5 Hz for 10 s. To examine non-adrenergic, non-cholinergic nerve-induced responses, guanethidine (5 μM) was added to the Krebs medium to prevent the release of noradrenaline. Under such conditions, the relaxant responses to EFS were abolished by tetrodotoxin (1 μM) and were unaffected by hexamethonium (30 μM), suggesting that they were due to stimulation of postganglionic non-adrenergic, non-cholinergic (NANC) neurons. In experiments to investigate the pre-junctional effects of α-adrenoceptor agonists, the antagonist contact time was 15 min.

All values are expressed as the mean $\pm$ standard error of the mean. The significance of differences was determined using paired and unpaired t-tests.

Drugs used

The following drugs were used: atropine monosulphate (Sigma); barium chloride (Fisons); carbamylcholine chloride (carbachol, BDH); cirazoline hydrochloride (Synthelabo); cocaine hydrochloride (Ross & McFarlane); corynanthine hydrochloride (Sigma); guanethidine monosulphate (Ciba); guanoxabenz hydrochloride (Roussel Uclaf); hydrocortisone (Sigma); 5-hydroxytryptamine creatinine sulphate (Koch-Light); idazoxan hydrochloride (Reckitt & Colman) neostigmine methyl sulphate (Sigma); (−)-noradrenaline bitartrate (Sigma); (−)-phenylephrine hydrochloride (Sigma); prazosin hydrochloride (synthesized by Dept of Medicinal Chemistry, Reckitt & Colman); (±)-propranolol hydrochloride (Sigma); tetrodotoxin (Sigma); tyramine hydrochloride (Sigma); and UK-14,304 (5-bromo-6-[2-imidazolin-2-yl-amino-]-quinoxaline bitartrate, synthesized by Dept of Medicinal Chemistry, Reckitt & Colman).

Hydrocortisone was dissolved in absolute ethanol before addition to the Krebs solution. All other drugs were dissolved in distilled water.

Results

Post-junctional effects of α-adrenoceptor agonists

None of the α-adrenoceptor agonists tested, noradrenaline, phenylephrine, cirazoline, guanoxabenz or UK-14,304, displayed any contractile effects at concentrations up to 30 μM. The fundus often responded to washing by a non-sustained contraction but these contractions also occurred in the absence of drugs and their size was unaltered by any previous addition of any of the α-adrenoceptor agonists studied or by the addition of prazosin (1 μM) or idazoxan (1 μM) after an α-adrenoceptor agonist. The size of the "washout" contractions appeared to depend only on the length of time since the previous wash, increasing with increasing time between washes.

In preparations where tone was raised by barium, noradrenaline (0·01–3 μM), cirazoline (0·01–3 μM), and phenylephrine (0·01–3 μM) produced concentration-dependent relaxations (e.g. Fig. 1). Similar relaxant effects were obtained in preparations where tone was raised by either carbachol (0·3 μM) or 5-hydroxytryptamine (0·03–0·3 μM). The relaxant effects were antagonized by prazosin (0·01–1 μM) (e.g. Figs 1, 4a) and corynanthine (1–2 μM) but were unaffected by idazoxan (0·01–0·1 μM). In contrast to the effects of α_1-adrenoceptor agonists, UK-14,304 (1 μM) had no relaxant effect in raised tone (Fig. 1). This lack of effect was confirmed in additional experiments with higher concentrations of UK-14,304 (30 μM) and with guanoxabenz (30 μM).

Effects of α-adrenoceptor agonists on cholinergic nerve-induced responses

UK-14,304 (0·03–1 μM) produced a concentration-dependent inhibition of cholinergic nerve-induced responses which was partially reversed by idazoxan (0·1 μM) but unaffected by prazosin (0·1 μM; Fig. 2).

Noradrenaline (0·03–1·0 μM) also produced a concentration-dependent inhibition of cholinergic nerve-induced responses (Fig. 3). Noradrenaline was more potent than UK-14,304 and the maximum inhibition produced was greater, with the responses reduced to around 10% of the control values.

Idazoxan (0·03–1 μM) partially reversed the inhibition but responses were only returned to around 50% of the control values. Further additions of prazosin (1·0 μM) after idazoxan (1·0 μM) produced a small, but significant additional reversal of the noradrenaline-induced inhibition to around 60% of the control values (Fig. 3a). The relative contributions of the prazosin-sensitive and idazoxan-sensitive components of the noradrenaline-induced inhibition were similar when the antagonists were administered in the reverse order: prazosin (0·03–1 μM) produced a small reversal of the noradrenaline-

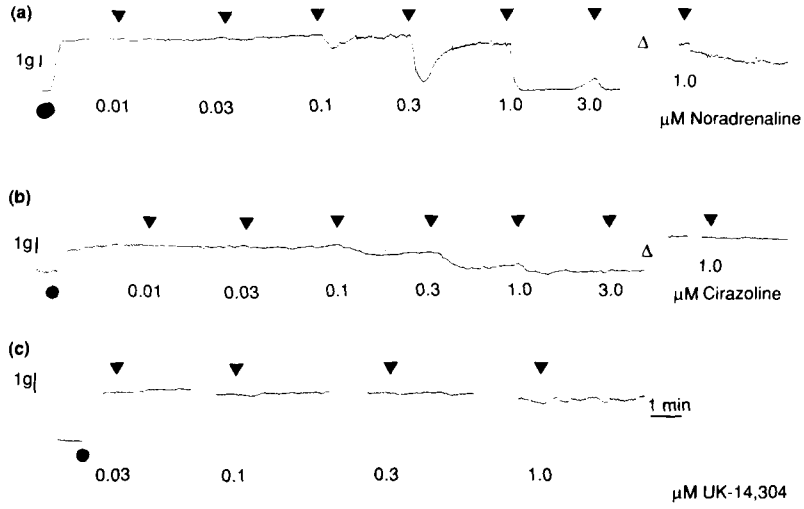

FIG. 1. Representative tracing showing the effects of noradrenaline, cirazoline and UK-14,304 on raised tone in the rat gastric fundus. Barium chloride (1 mM) was added at the filled circle. Cumulative additions of each agonist are indicated by the arrows. In (a) and (b) at the open triangle, tissues were washed and left in contact with prazosin (1 μM) for 30 min before raising the tone with barium and addition of the agonists (shown at arrows).

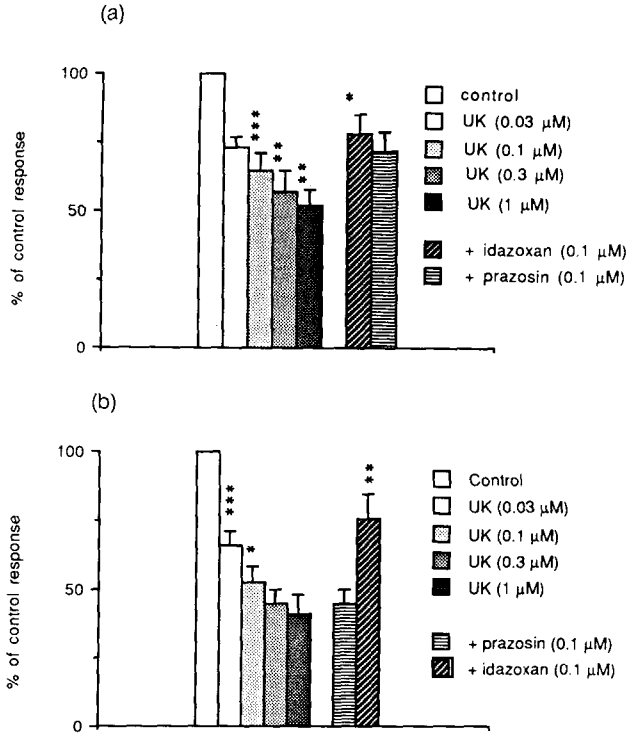

FIG. 2. (a) Effect of UK-14,304 on cholinergic nerve-induced responses in the rat gastric fundus. Columns show the effects of cumulative additions of UK-14,304 (UK) followed by the addition of idazoxan then prazosin. (b) As above except UK-14,304 is followed by the addition of prazosin first, then idazoxan. Significant differences from previous treatment are shown $*P<0.05$, $**P<0.01$, $***P<0.001$, paired t-test, n = 6.

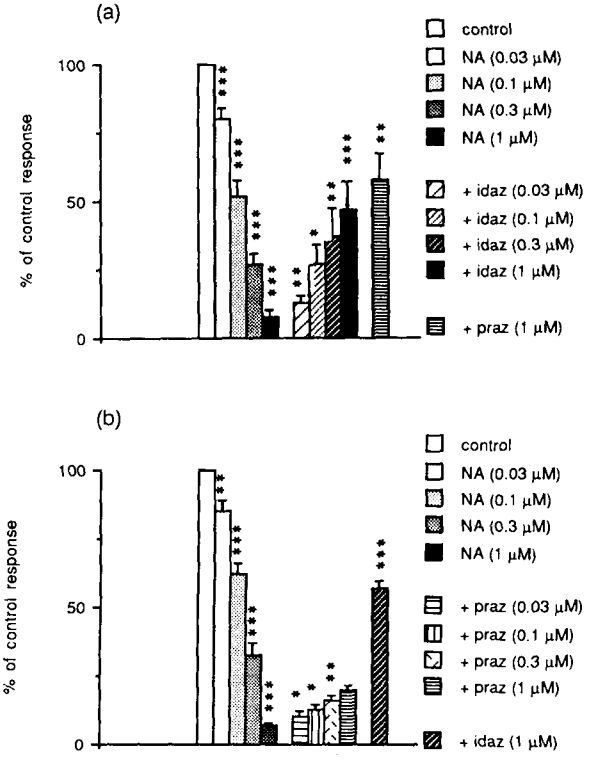

FIG 3. (a) The effects of noradrenaline on cholinergic nerve-induced responses in the rat gastric fundus. Columns show the effects of cumulative addition of noradrenaline (NA) followed by cumulative addition of idazoxan (idaz) and then prazosin (praz). (b) As above except that noradrenaline followed first by prazosin, then by idazoxan. Significant differences from previous treatment are shown $*P<0.05$, $**P<0.01$, $***P<0.001$, paired t-test, n = 8.

induced inhibition (from 8 to 20% of control responses) and the further addition of idazoxan (1·0 μM) increased the responses to around 60% of the control values (Fig. 3b).

Cirazoline (0·03–1 μM) produced only a small inhibition of cholinergic nerve-induced responses which was partly prevented by prazosin (1·0 μM; Fig. 4b) although the difference was statistically significant only at the highest (1 μM) concentration of cirazoline ($P<0.01$, Student's t-test).

Pre- and post-junctional inhibitory effects of α_1-adrenoceptor agonists

The effects of noradrenaline and cirazoline against choliner-

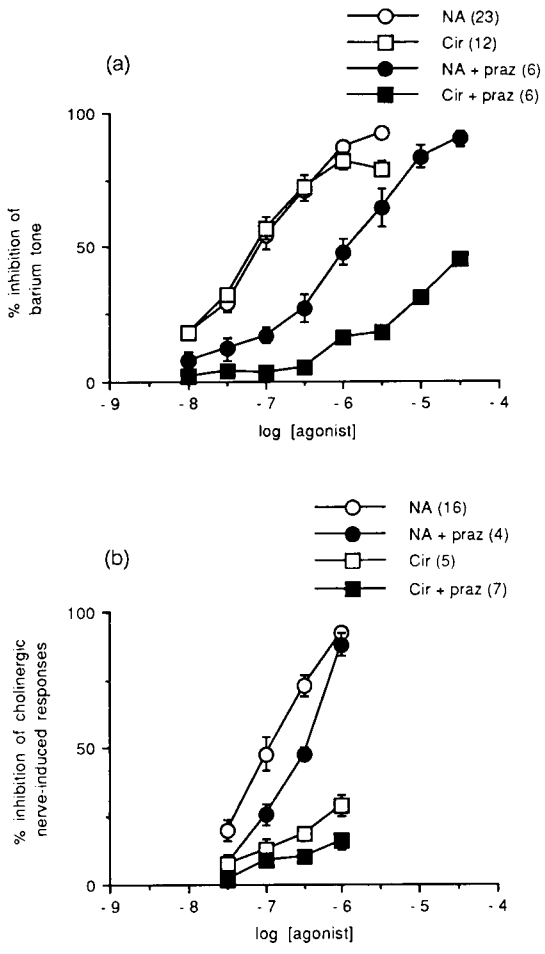

FIG. 4. Effects of noradrenaline (NA) and cirazoline (Cir) on (a) barium chloride-induced tone and (b) cholinergic nerve-induced responses. Open symbols represent the effects in the absence and closed symbols in the presence of prazosin (praz, 1 μM). Numbers of experiments are indicated in brackets.

gic nerve-induced responses and against barium chloride-induced tone are shown for comparison in Fig. 4. The small, prazosin-sensitive component of the inhibition of nerve-induced responses occurred at concentrations of the agonists that also showed marked post-junctional effects against barium chloride-induced tone. Thus no separation of the α_1-inhibitory effects against cholinergic nerve-induced responses and barium chloride-induced tone was seen. The sensitivity of the fundus to post-junctional α_1-adrenoceptor-mediated inhibition was similar in barium-, carbachol- and 5-hydroxytryptamine-induced tone.

Effects of α-adrenoceptor agonists on non-adrenergic, non-cholinergic, (NANC) nerve-induced responses

UK-14,304 (0·03–1 μM) produced a concentration-dependent inhibition of non-adrenergic, non-cholinergic nerve-induced responses which was partially reversed by idazoxan (0·1 μM) but unaffected by prazosin (0·1 μM) (Fig. 5).

The effects of α_1-adrenoceptor agonists on non-adrenergic, non-cholinergic nerve-induced responses proved difficult to assess since these agonists also produce post-junctional relaxation (see above). Since tone is necessary to demonstrate the inhibitory nerve-induced responses, the post-junctional α_1-adrenoceptor-mediated loss of tone made it impossible to assess any pre-junctional effects of the α_1-adrenoceptor agonists.

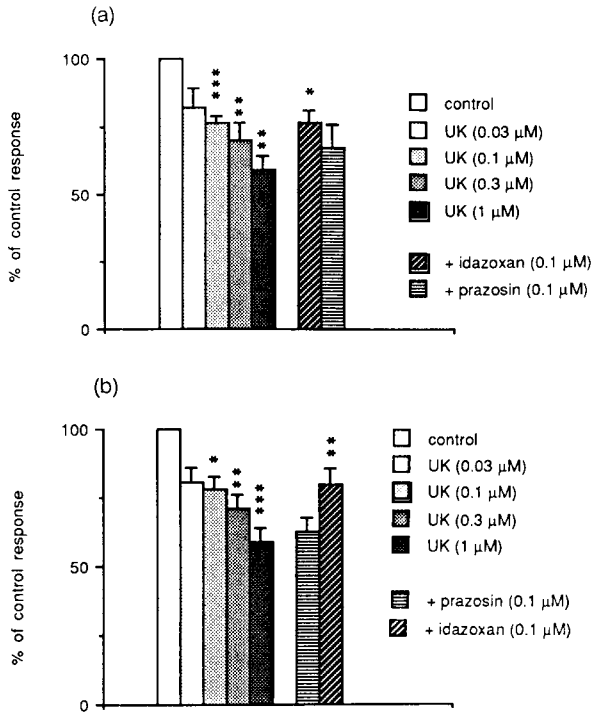

FIG. 5. (a) Effect of UK-14,304 on non-adrenergic, non-cholinergic nerve-induced responses in the rat gastric fundus. Columns show effects of cumulative addition of UK-14,304 (UK) followed by idazoxan and then prazosin. (b) As above except that UK-14,304 was followed by prazosin first and then idazoxan. Significant differences are shown * $P<0.05$, ** $P<0.01$, *** $P<0.001$, paired t-test, n = 5–6. For the UK-14,304 treatment groups these refer to differences from control value. For the idazoxan and prazosin treatments differences refer to the preceding treatment.

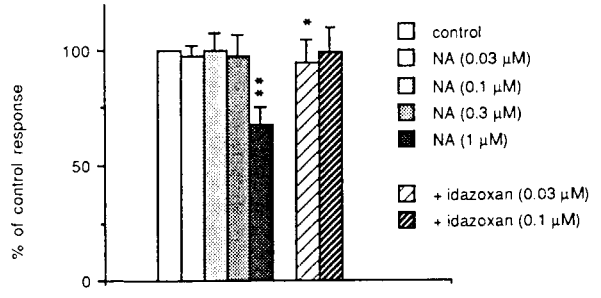

FIG. 6. Effect of noradrenaline on non-adrenergic, non-cholinergic nerve-induced responses in the rat gastric fundus. Columns show effects of cumulative addition of noradrenaline (NA) followed by idazoxan. Significant differences from previous treatment are shown * $P<0.05$, ** $P<0.01$, *** $P<0.001$, paired t-test, n = 5.

The effects of noradrenaline were therefore studied in the presence of prazosin (1 μM) to block any post-junctional α_1-adrenoceptor-mediated reductions in tone. Noradrenaline (1 μM) inhibited the non-adrenergic, non-cholinergic nerve-induced responses and this inhibition was reversed by idazoxan (0·03–0·1 μM) (Fig. 6).

Effects of endogenous noradrenaline

Tyramine (1–300 μM) had no effect on the cholinergic nerve-

induced responses (n = 8). To investigate endogenous feedback inhibition during nerve-stimulation, the effects of idazoxan alone (0·03–3 μM) in the absence of guanethidine was tested. No significant effects of idazoxan on cholinergic nerve-induced responses or inhibitory nerve-induced responses over a wide range of frequencies (1–50 Hz, constant train length 10 s, n = 8) were observed.

Discussion

The present results confirm and extend the previous findings of inhibitory post-junctional α_1-adrenoceptors in the rat gastric fundus (Lefebvre et al 1983; Verplanken et al 1984; Dettmar et al 1984, 1985b, 1986). However, the antagonism of the effects of noradrenaline by prazosin was less effective than that of cirazoline (Fig. 1) and less than would be expected if noradrenaline was acting only at α_1-adrenoceptors. This is probably due to an additional action of noradrenaline at atypical adrenoceptors and is dealt with in more detail elsewhere (Kelly & MacDonald 1990).

There was no evidence for any excitatory post-junctional α-adrenoceptor-mediated "washout" response as reported by Ogle & Wong (1971). Those authors reported that after the α_1-adrenoceptor agonist phenylephrine, there were washout contractions which could be blocked by phentolamine. However, in the present studies any "washout" contractions observed after α-adrenoceptor agonists were unaffected by the α_1- and α_2-adrenoceptor antagonists prazosin and idazoxan, respectively. Indeed any washout contractions observed were only dependent on the length of time since the previous wash and were not significantly altered by the presence of any of the α-adrenoceptor agonists studied including phenylephrine.

We also found no evidence for post-junctional α_2-adrenoceptors, either excitatory as reported in guinea-pig gastric smooth muscle (Sahyoun et al 1982), or inhibitory as reported in the guinea-pig ileum (Bauer 1982; Bauer & Kuriyama 1982). This suggests that the presence of post-junctional α_2-adrenoceptors may vary according to species and area of the gastrointestinal tract. The physiological role of post-junctional α_2-adrenoceptors, excitatory or inhibitory, in the gut is not known.

Contractions of the rat gastric fundus elicited by electrical field stimulation were inhibited by the α_2-adrenoceptor agonist UK-14,304, an effect which was antagonized by idazoxan but not by prazosin. This confirms the presence of pre-junctional inhibitory α_2-adrenoceptors on cholinergic neurons (McClelland & Sanger 1982; Lefebvre et al 1983; Verplanken et al 1984). Noradrenaline, a mixed α_1- and α_2-adrenoceptor agonist, also produced a marked inhibition of cholinergic nerve-induced contractions. This inhibition was partly antagonized by idazoxan but also, to a lesser extent, by prazosin. The α_1-adrenoceptor agonist cirazoline produced a small but significant inhibition of responses which was antagonized by prazosin but not by idazoxan. These effects may be evidence for a pre-junctional α_1-adrenoceptor on cholinergic neurons in this preparation as suggested previously (McClelland & Sanger 1982; Lefebvre et al 1983; Verplanken et al 1984). However, in the present study, the prazosin-sensitive component of the inhibition by noradrenaline and by cirazoline occurred only at concentrations of the agonists which also had marked activity at post-junctional inhibitory α_1-adrenoceptors. This is in contrast to the results of Verplanken et al (1984), who found post-junctional effects only at concentrations higher than those necessary to inhibit nerve-induced contractions and higher than the concentrations at which we were able to demonstrate post-junctional inhibitory effects. The difference is not due to the agent used to raise tone in the measurement of post-junctional effects, since in the present study the sensitivity to noradrenaline was similar in barium-, carbachol- and 5-hydroxytryptamine-induced tone. Satisfactory resolution of this may depend on the measurement of the acetylcholine output, but in the meantime we would conclude that the inhibition of cholinergic nerve-induced responses by α_1-adrenoceptor agonists in our experiments can be explained by the stimulation of post-junctional inhibitory α_1-adrenoceptors.

Tyramine had no effect on the cholinergic nerve-induced responses and likewise idazoxan itself had no effect over a wide range of frequencies. Thus we were unable to demonstrate any effects of endogenously-released noradrenaline on the pre-junctional α_2-adrenoceptors of cholinergic neurons in this preparation. This may seem odd since it is generally believed that the main effect of sympathetic stimulation in the gastrointestinal tract is to reduce cholinergic nerve activity via pre-junctional α_2-adrenoceptors and that only at high frequencies of stimulation are the post-junctional adrenoceptors on the smooth muscle activated (Furness & Costa 1974). This difficulty may be resolved if the anatomical location of the α_2-adrenoceptors is taken into consideration. In the present study the α_2-adrenoceptors demonstrated are situated on post-ganglionic cholinergic nerves presumably on the nerve terminals in the longitudinal muscle layer and thus are not particularly accessible to noradrenaline released from sympathetic neurons which are present in the myenteric plexus but not in the smooth muscle layer (Costa & Gabella 1971). During sympathetic stimulation in-vivo however, noradrenaline released from sympathetic neurons in the myenteric plexus may activate α_2-adrenoceptors situated pre-junctionally on pre-ganglionic cholinergic nerves or on cholinergic interneurons (Gillespie & Khoyi 1977). Thus the present study has demonstrated the presence of pre-junctional α_2-adrenoceptors on cholinergic nerve endings in the rat gastric fundus which are not activated by neuronally released noradrenaline under the experimental conditions used. It may be that they are stimulated by circulating catecholamines.

The presence of prejunctional inhibitory α_2-adrenoceptors on non-adrenergic, non-cholinergic intrinsic neurons was also demonstrated. This is in contrast to the finding of Lefebvre & Bogaert (1986), who found the α_2-agonist clonidine to have no effect on NANC responses in the rat gastric fundus. The difference may be due to the different stimulation parameters; in the present study the NANC responses were obtained at 0·5 Hz for 20 s whereas Lefebvre & Bogaert (1986) used a higher frequency (5 Hz) for longer (45 s). Inhibitory pre-junctional α_2-adrenoceptors have also been previously demonstrated on NANC neurons in the mouse colon (Fontaine et al 1984) and in guinea-pig airways (Grundstrom et al 1984; Grundstrom & Andersson 1985). The physiological role of pre-junctional α_2-adrenoceptors

situated on NANC nerves in the gastrointestinal tract is not known although their activation may abolish inhibitory neurogenic tone (Fontaine et al 1984). Their activation may also be expected to affect gut reflexes since the NANC nerves are involved in such reflexes as receptive relaxation of the stomach and the descending inhibition of peristalsis (Gillespie 1982). In the present study we were unable to demonstrate any effects of endogenous noradrenaline and thus it seems that the α_2-adrenoceptors may be present on the nerve terminals of NANC nerves inaccessible to noradrenaline released from sympathetic neurons in the myenteric plexus, but possibly activated by circulating catecholamines.

We were unable to test for the presence of pre-junctional α_2-adrenoceptors on noradrenergic nerves since we were unable to selectively remove the inhibitory NANC component of the inhibitory response to electrical field stimulation. We would have expected these receptors to be activated by endogenous noradrenaline but were unable to demonstrate this.

In conclusion, α-adrenoceptor-mediated responses in the rat gastric fundus in-vitro consist of post-junctional α_1-adrenoceptor-mediated relaxation of the longitudinal smooth muscle and pre-junctional α_2-adrenoceptor-mediated inhibition of both cholinergic excitatory and non-adrenergic, non-cholinergic inhibitory nerve-induced responses.

References

Bauer, V. (1982) Distribution and types of adrenoceptors in the guinea-pig ileum: the action of α- and β-blocking agents. Br. J. Pharmacol. 76: 569–578

Bauer, V., Kuriyama, H. (1982) Homogeneous and non-homogeneous distribution of inhibitory and excitatory adrenoceptors in the longitudinal muscle of the guinea-pig ileum. Ibid. 76: 603–611

Burnstock, G., Wong, H. (1981) Systemic pharmacology of adrenergic agonists and antagonists: effects on the digestive system. In: Szerekes, L. (ed.) Adrenergic Activators and Inhibitors 54 (2), Springer-Verlag, Berlin pp 129–159

Costa, M., Gabella, G. (1971) Adrenergic innervation of the gastrointestinal tract. Zellforschung. 122: 357–377

Daniell, E. E. (1982) Pharmacology of adrenergic, cholinergic and drugs acting on other receptors in gastrointestinal muscle. In: Bertaccini, G. (ed.) Handbook of Experimental Pharmacology, 59 (2), Springer-Verlag, Berlin, pp 249–322

Dettmar, P. W., Kelly, J., MacDonald, A. (1984) Characterisation of α-adrenoceptor mediated responses in the rat gastric fundus. Br. J. Pharmacol. 83: 390P

Dettmar, P. W., Kelly, J., MacDonald, A. (1985a) The effects of UK-14,304 on nerve-induced responses in the rat gastric fundus. Ibid. 86: 491P

Dettmar, P. W., Kelly, J., MacDonald, A. (1985b) α_1- and α_2-adrenoceptor-mediated effects of noradrenaline in the rat gastric fundus. Ibid. 86: 613P

Dettmar, P. W., Kelly, J., MacDonald, A. (1986) The effect of noradrenaline on non-adrenergic, non-cholinergic nerve-induced responses in the rat gastric fundus. Ibid. 89: 668P

Fontaine, J., Grivegnee, A., Reuse, J. (1984) Adrenoceptors and regulation of intestinal tone in the isolated colon of the mouse. Ibid. 81: 231–243

Furness, J. B., Costa, M. (1974) Review article: the adrenergic innervation of the gastrointestinal tract. Ebergnisse de Physiol (Reviews of Physiol.) 69: 1–52

Gershon, M. D. (1967) Effects of tetrodotoxin on innervated smooth muscle preparations. Br. J. Pharmacol. Chemother. 29: 259–279

Gillespie, J. S. (1982) Review: non-adrenergic, non-cholinergic inhibitory control of gastrointestinal motility. In Wienbeck, M. (ed.) Motility of the Digestive Tract, Raven Press, New York, pp 51–63

Gillespie, J. S., Khoyi, M. A. (1977) The site of and receptors responsible for the inhibition by sympathetic nerves of intestinal smooth muscle and its parasympathetic motor nerves. J. Physiol. 267: 767–789

Grundstrom, N., Andersson, R. G. G. (1985) In vivo demonstration of α_2-adrenoceptor mediated inhibition of the excitatory non-cholinergic neurotransmission in guinea-pig airways. Naunyn-Schmiedebergs Arch. Pharmacol. 328: 236–240

Grundstrom, N., Andersson, R. G. G., Wikberg, J. E. S. (1984) Inhibition of the excitatory non-adrenergic, non-cholinergic neurotransmission in the guinea-pig tracheobronchial tree mediated via α_2-adrenoceptors. Acta Pharmacol. Toxicol. 54: 8–14

Kelly, J., MacDonald, A. (1990) Relaxant effects of α-adrenoceptor agonists in the rat isolated gastric fundus. J. Pharm. Pharmacol. 42: 30–34

Lefebvre, R. A., Bogaert, M. G. (1986) Neither morphine nor clonidine influence the non-adrenergic, non-cholinergic inhibitory response in the rat gastric fundus. Ibid. 38: 621–622

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

McClelland, C. M., Sanger, G. (1982) Antagonism by metoclopramide of an inhibitory response to clonidine in the rat isolated stomach muscle. Br. J. Pharmacol. 77 (Suppl.): 484P

Ogle, C. W., Wong, C. Y. (1971) The inhibitory and excitatory properties of alpha-adrenoceptors in the rat stomach. Life Sci. 10: 153–159

Sahyoun, H. A., Costall, B., Naylor, R. J. (1982) Benzamide action at α_2-adrenoceptors modifies catecholamine-induced contraction and relaxation of circular smooth muscle from the guinea-pig stomach. Naunyn-Schmiedebergs Arch. Pharmacol. 319: 8–11

Vane, J. R. (1957) A sensitive method for the assay of 5-hydroxytryptamine. Br. J. Pharmacol. Chemother. 12: 344–349

Verplanken, P. A., Lefebvre, R. A., Bogaert, M. G. (1984) Pharmacological characterisation of alpha-adrenoceptors in the rat gastric fundus. J. Pharmacol. Exp. Ther. 231: 404–410

Wikberg, J. E. S. (1977) Localisation of adrenergic receptors in guinea-pig ileum and rabbit jejenum to cholinergic neurones and to smooth muscle cells. Acta Physiol. Scand. 99: 190–270