J. Physiol. (1987), **388**, *pp.* 25–39
With 7 text-figures
Printed in Great Britain

MODULATION OF THE VAGAL DRIVE TO THE INTRAMURAL CHOLINERGIC AND NON-CHOLINERGIC NEURONES IN THE FERRET STOMACH BY BACLOFEN

BY P. L. R. ANDREWS*, S. BINGHAM AND K. L. WOOD
From the Department of Physiology, St. George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE

(*Received 17 April 1986*)

SUMMARY

1. In the urethane-anaesthetized ferret vagotomy (cervical and abdominal) and hexamethonium both produced an increase in gastric corpus pressure after treatment with atropine and guanethidine, section of the greater splanchnic nerves and adrenalectomy.

2. The pressure increase was due to an interruption of a tonic vagal drive to the intramural non-adrenergic, non-cholinergic inhibitory neurones.

3. The $GABA_B$ receptor agonist baclofen (8 mg/kg s.c.) produced an increase in gastric pressure and enhanced the amplitude of the rhythmic contractions. Baclofen was without effect in vagotomized animals.

4. In the presence of atropine, guanethidine, adrenalectomy and section of the greater splanchnic nerves, baclofen produced only a slight enhancement of rhythmic contractions but the large increase in gastric pressure was still present. Under the above conditions the effects of baclofen on the whole stomach were virtually identical to those observed in the corpus region alone.

5. Baclofen was without effect on the magnitude of the corpus relaxation produced by submaximal vagal efferent stimulation in the presence of atropine.

6. These results demonstrate that the $GABA_B$ agonist baclofen, probably acting at a central site, enhanced rhythmic gastric activity by increasing the vagal drive to the intramural cholinergic neurones. Simultaneously gastric pressure was increased primarily by a reduction in the tonic vagal drive to the intramural non-adrenergic, non-cholinergic inhibitory neurones in the corpus region. The results of both the baclofen and vagotomy studies further demonstrate the importance of the vagal innervation of the non-adrenergic, non-cholinergic inhibitory neurones in the regulation of gastric pressure.

INTRODUCTION

The vagus nerve contains preganglionic efferent fibres which can stimulate or inhibit gastric motility by activation of the post-ganglionic cholinergic or non-adrenergic, non-cholinergic (n.a.n.c.) neurones respectively (Andrews & Scratcherd,

* Address for correspondence.

1980; Andrews & Lawes, 1985). It is usually assumed that an enhancement of gastric motility and emptying mediated by the vagus is due solely to activation of the intramural cholinergic nerves and no consideration is given to a role for the n.a.n.c. nerves. However, in a moderately distended stomach (e.g. after a meal) where the vagal drive to the n.a.n.c. nerves is assumed to be high to maintain the pressure at a low level, gastric pressure could be increased solely by a reduction in this inhibitory tone (Andrews, 1986). Whilst there is some evidence from human (Aune, 1969; Staadas, 1975; Minami & McCallum, 1984) and animal (Muren, 1956; Harper, Kidd & Scratcherd, 1959; Jahnberg, Martinson, Hulten & Fasth, 1975; Andrews & Lawes, 1982) studies that abdominal vagotomy causes an elevation in the gastric pressure response to a standard distension, direct evidence that this is due to removal of a vagal drive to the intramural n.a.n.c. inhibitory neurones is lacking. Therefore the first aim of this study was to investigate the effects of vagotomy on the pressure in the ferret gastric corpus, the area which plays the major role in determining the over-all intra-gastric pressure (Andrews & Lawes, 1982) and which in other species (e.g. dog) has been shown to be important in the emptying of liquids (Kelly, 1980).

Recent studies in the rat (Andrews & Wood, 1986) have demonstrated a vagally dependent increase in gastric motility after subcutaneous administration of baclofen (2–8 mg/kg), a GABA analogue which penetrates the blood–brain barrier (Faigle & Keberle, 1972) and is thought to exert its gastric stimulatory effect by an action on the ventromedial hypothalamus (Wood, Addae, Andrews & Stone, 1987). Pilot studies in the ferret (K. L. Wood, unpublished observations) demonstrated a similar vagally dependent stimulation of gastric motility but the relative contributions of the vagal input to the intramural cholinergic excitatory and n.a.n.c. inhibitory neurones was not determined. Therefore, the second aim of this study was to identify the relative contributions of these two systems to the response to baclofen and to compare its effects (if any) on the n.a.n.c. inhibitory system to those of vagotomy. In addition, by using a drug with known central effects it was hoped that an insight would be gained into the central neuropharmacology of the vagal outflow.

A preliminary account of part of this work has been presented to the Physiological Society (Andrews, Bingham & Wood, 1986).

METHODS

Animals and surgery

Eighty ferrets of either variety and sex weighing between 680 and 1400 g were used. They were deprived of food overnight but allowed water *ad libitum*. Following anaesthesia with urethane (1·5 g/kg I.P., 50%, w/v, in 154 mM-NaCl) the trachea and external jugular vein were cannulated. Pressure was monitored either in the whole stomach or in the corpus region alone surgically prepared as previously described (Andrews & Scratcherd, 1980) and inflated with 20 ml 154 mM-NaCl. Rectal temperature was monitored and maintained at 39 °C by a heating blanket (Palmer Bioscience).

Vagotomy study

The greater splanchnic nerves were sectioned and the adrenal glands either ligated or surgically removed in all animals. Following 1 h basal recording of corpus pressure guanethidine was administered (5 mg/kg I.V.) and 30 min later atropine (1 mg/kg I.V.) was given. After a further 30 min the vagi were ligitated and cut at either the cervical or abdominal level. In the case of abdominal vagotomy the cervical vagi were subsequently sectioned and the peripheral cut end of

the cervical vagus stimulated (20 V, 0·5 ms; 10 Hz, 10 s) to ensure the completeness of the lesion. In another group after guanethidine and atropine administration hexamethonium was given. Following the highest dose of hexamethonium (20 mg/kg I.A.) the cervical vagi were sectioned.

Because it has been reported that oesophageal distension can reflexly produce gastric relaxation (Abrahamsson & Jansson, 1969), corpus pressure was monitored in one group via a cannula inserted into the isolated corpus via the pylorus and antrum. The oesophagus was ligated in the region of the lower oesophageal sphincter taking care to exclude the vagi.

Baclofen study

In the studies that investigated the effects of baclofen on the vagal input to the n.a.n.c. system the greater splanchnic nerves were sectioned, the adrenal glands ligated, and guanethidine and atropine administered as described above. Where appropriate the abdominal vagi were sectioned as they coursed over the subdiaphragmatic portion of the oesophagus.

Drugs

The following drugs were used at the doses indicated in the text: atropine suphate (BDH), guanethidine (Ismelin, CIBA), hexamethonium (Sigma) and baclofen (Lioresal, CIBA). They were all dissolved in 154 mM-NaCl and administered subcutaneously (femoral triangle) intravenously (jugular vein), or intra-arterially (aorta, see Andrews & Lawes (1985) for method) as indicated. The doses of atropine and guanethidine used have previously been shown to abolish the vagal excitatory and splanchnic inhibitory gastric motility responses respectively and to have durations of action exceeding the periods of observation in the present experiments (Andrews & Lawes, 1982, 1985).

Analysis

The following parameters of gastric motility were measured: gastric or corpus tone, the difference in pressure between the atmospheric 'zero' and the prevailing pressure upon which rhythmic contractions were superimposed; contraction amplitude, the pressure difference between the tone level and the peak pressure attained during rhythmic contractions; line length, the total length of the inkline drawn by the chart recorder in arbitrary units (a.u.) and used as an index of gastric motility (Grundy & Scratcherd, 1984). In the vagotomy study the time taken for the pressure to plateau was taken as the time between the vagotomy and the first point at which the corpus tone achieved the pressure at which it remained stable. Time was measured from the original records using a paper speed of 30 mm/min.

Statistics

Results are presented as mean ± S.E. (n animals) and statistical significance was tested using a paired or unpaired sample t-test and P value are indicated in the legends or text.

RESULTS

The effect of vagotomy and hexamethonium on corpus pressure and motility

There was no significant difference in the corpus pressures after the various drug treatments between the groups with the corpus intubated via the oesophagus (+o.t.) and the group without an oesophageal tube (−o.t.) and therefore the pre-vagotomy pressure values from these groups were combined. Guanethidine had no effect on the corpus pressure whilst atropine caused a small ($1{\cdot}0 + 0{\cdot}2$ cmH_2O, $n = 17$) but significant ($P < 0{\cdot}0001$) decrease in pressure and virtually abolished and rhythmic contractions (Fig. 1*A*).

Vagotomy. Immediately following vagotomy corpus pressure increased. The magnitude of the plateau pressure achieved following vagotomy was neither influenced by the presence of an oesophageal tube nor the site of the vagotomy (Fig. 1*A*). The time taken to reach the plateau pressure was also unaffected by the lesion site (+o.t., 17 ± 1 min, $n = 8$; −o.t., 19 ± 1 min, $n = 5$). 1 h after vagotomy the pressures were

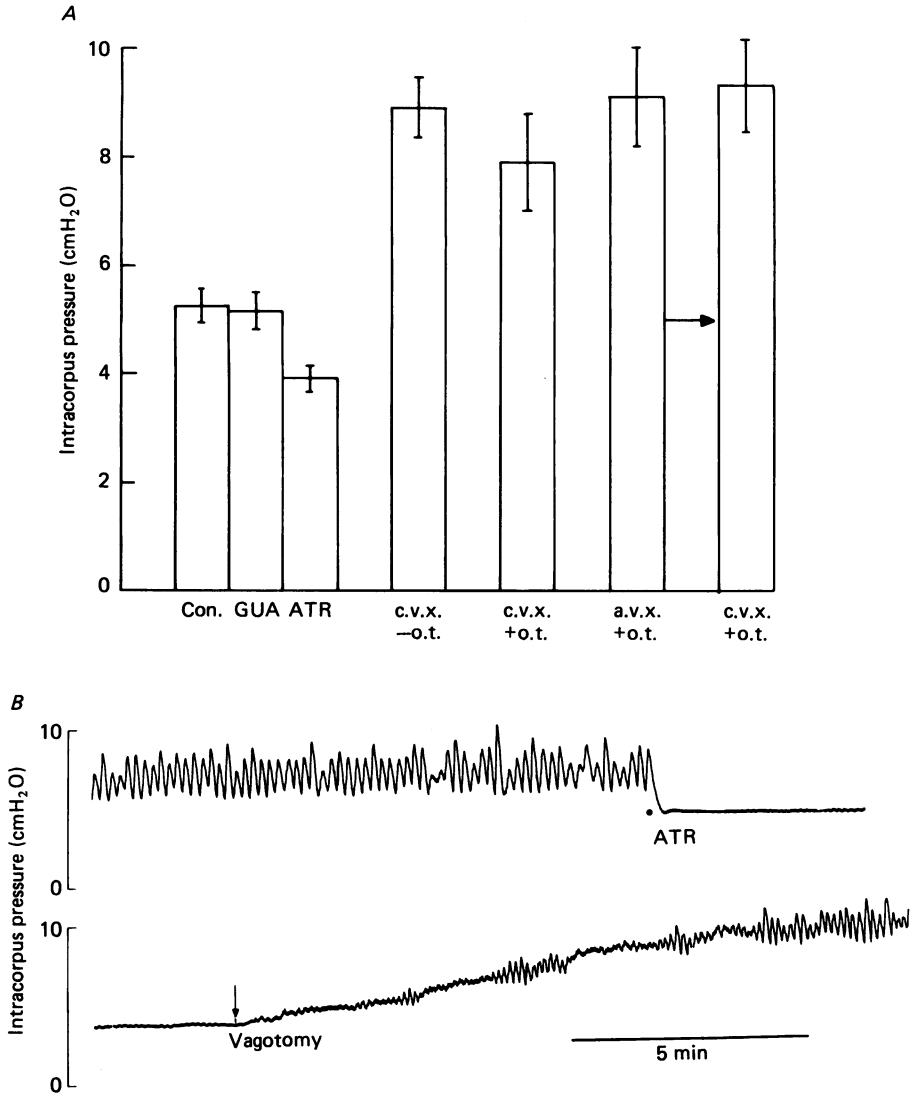

Fig. 1. *A*, the prevailing intracorpus pressure (20 ml 154 mM-NaCl) during the control period after recovery from surgery (con.), followed by guanethidine (GUA) and atropine (ATR) treatment. This was followed by cervical vagotomy (c.v.x.) in groups with (+o.t., $n = 8$ animals) and without (−o.t., $n = 5$ animals) an oesophageal tube. In a separate group with oesophageal tube (+o.t.) abdominal vagotomy (a.v.x., $n = 4$ animals) was followed by cervical vagotomy. Cervical vagotomy significantly increased the corpus pressure when compared to the pressures before atropine (+o.t., $P < 0{\cdot}0001$; −o.t., $P < 0{\cdot}03$) or after atropine (+o.t., $P < 0{\cdot}0001$; $P < 0{\cdot}007$). Abdominal vagotomy also had a significant effect on the corpus pressure when compared with the pressure prior to ($P < 0{\cdot}015$) and after atropine treatment ($P < 0{\cdot}009$). *B*, record of intracorpus pressure in a ferret with greater splanchnic nerves cut, adrenalectomized and treated with guanethidine. After atropine (ATR) treatment vagotomy (cervical) produced an immediate increase in the prevailing pressure and rythmic contractions became apparent. Note that the post-vagotomy plateau pressure had not been attained within the duration of this record.

not significantly different from the plateau values. In addition to producing an increase in corpus pressure, vagotomy in the presence of atropine also enhanced the amplitude of the rhythmic contractions in this region (Fig. 1*B*).

There was no significant difference in the magnitude of the corpus pressure increase in the three groups (cervical vagotomy +o.t., or −o.t., and abdominal vagotomy) and therefore the values of the actual increase in pressure for each group were pooled. This showed that vagotomy produced an increase in corpus pressure of $3{\cdot}5 \pm 0{\cdot}4$ cmH_2O when compared to the pressure prior to atropine and guanethidine and $4{\cdot}80 \pm 0{\cdot}35$ cmH_2O ($n = 17$ animals) when compared to that after the atropine administration.

Hexamethonium. In the presence of atropine and guanethidine with the vagi intact a dose of hexamethonium (20 mg/kg I.A.) which blocks the corpus response to vagal stimulation (Andrews & Lawes, 1985) produced an increase in corpus pressure of $5{\cdot}6 \pm 0{\cdot}9$ cmH_2O ($n = 4$ animals). This dose of hexamethonium was administered in three equal aliquots; the first produced an increase in pressure of $2{\cdot}2 \pm 0{\cdot}5$ cmH_2O, the second a further rise of $2{\cdot}6 \pm 0{\cdot}4$ cmH_2O and the third an additional small increase of $0{\cdot}80 \pm 0{\cdot}04$ cmH_2O. In addition to increasing corpus pressure hexamethonium also enhanced contraction amplitude. Following hexamethonium vagotomy was without further effect on corpus pressure.

The effects of baclofen on gastric and corpus pressure and motility

Baclofen doses of 8 mg/kg S.C. and 0·5 mg/kg I.V. were used as they produced a stimulation of gastric motility and acid secretion in the rat and dog (Goto & Debas, 1983, Goto, Hollinshead & Debas, 1984, Andrews & Wood, 1986).

Stomach. The effects of subcutaneous baclofen on several parameters of gastric motility are presented in Fig. 2 and an original record is show in Fig. 3. Baclofen caused an increase in gastric tone, mean contraction amplitude and gastric motility line length which had not declined to basal values within the 2·5 h observation period. As illustrated in Fig. 2, gastric tone was significantly different from the basal level within 10 min ($P < 0{\cdot}05$) after baclofen administration and peaked within the following 40 min ($P < 0{\cdot}005$). The mean increase in tone at this time was $2{\cdot}6 \pm 0{\cdot}8$ cmH_2O ($n = 6$). In contrast, although the stimulation of contraction amplitude and line length was apparent within the first 15 min after baclofen administration, peak values were attained after about 1 h ($P < 0{\cdot}05$). The stimulation of motility was prevented by prior vagotomy and could be curtailed by vagotomy during the course of the response.

Intravenous baclofen (0·5 mg/kg) produced an immediate increase in gastric tone which reached a peak value $1{\cdot}7 \pm 0{\cdot}4$ cmH_2O ($n = 6$, $P < 0{\cdot}01$) above the control pressure about 10 min after the injection. The tone then declined steadily to control values over the next 30 min. Whilst both the rhythmic contraction amplitude and line-length values showed small increases they failed to reach statistical significance.

The gastric response to subcutaneous baclofen was also studied in the presence of atropine (1 mg/kg I.V.), guanethidine (5 mg/kg I.V.), adrenalectomy and greater splanchnic nerve section. Under these conditions baclofen (8 mg/kg S.C.) produced a prompt increase in tone ($P < 0{\cdot}01$ at 5 min, $P < 0{\cdot}005$ at 30 min) and a small but significant increase in the level of rhythmic activity ($P < 0{\cdot}05$). In animals with a

bilateral abdominal vagotomy under the above conditions, baclofen produced a very small increase in gastric tone and contractile activity which was not significant and at no time comparable in magnitude to that seen in the vagally intact animals. The results from these experiments are summarized in Fig. 4 and an example of an individual response is shown in Fig. 5.

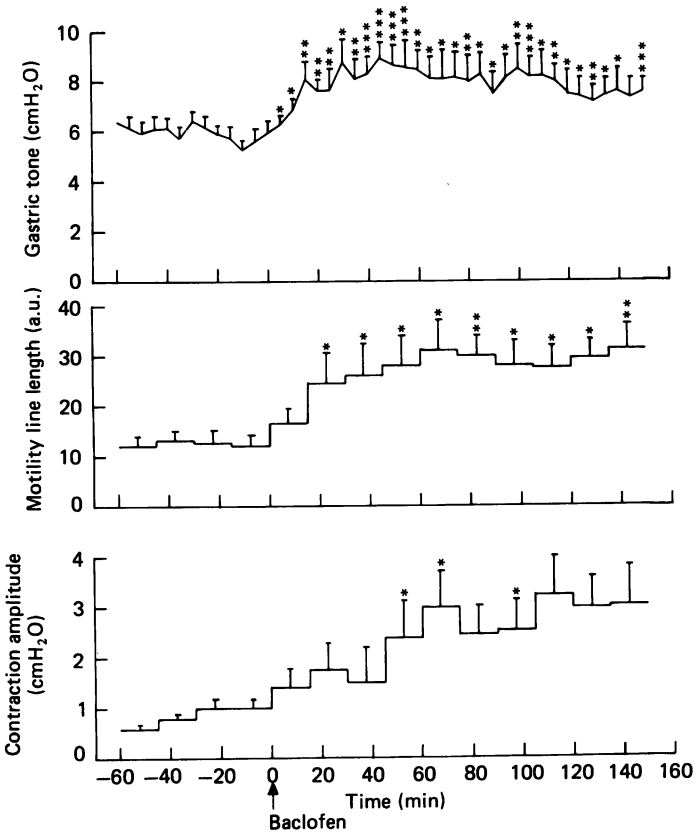

Fig. 2. The effect of baclofen (8 mg/kg s.c.) on the over-all gastric pressure (tone), motility line length (in arbitrary units, a.u.) and contraction amplitude. The latter parameters were measured over 15 min periods whereas tone was measured every 5 min. $n = 6$ animals, * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}005$.

Gastric corpus. The experiments on the whole stomach in the presence of atropine described on p. 29 and the vagotomy study indicated that vagal modulation of the n.a.n.c. neurone activity was probably involved in the over-all pressure increase in response to baclofen. As the gastric corpus is the region most involved in the regulation of gastric tone via the vagally driven n.a.n.c. nerves it was decided to investigate the effects of baclofen on the corpus alone.

In the presence of atropine, guanethidine, adrenalectomy and greater splanchnic nerve section, baclofen (8 mg/kg s.c.) produced a prompt onset (5 min) steady increase in corpus pressure which reached a plateau after 30–40 min ($P < 0{\cdot}005$) (Fig. 6). In addition there was a small but significant increase in contraction amplitude ($P < 0{\cdot}05$) and line length ($P = 0{\cdot}05$) (Figs. 6 and 7). The increase in pressure

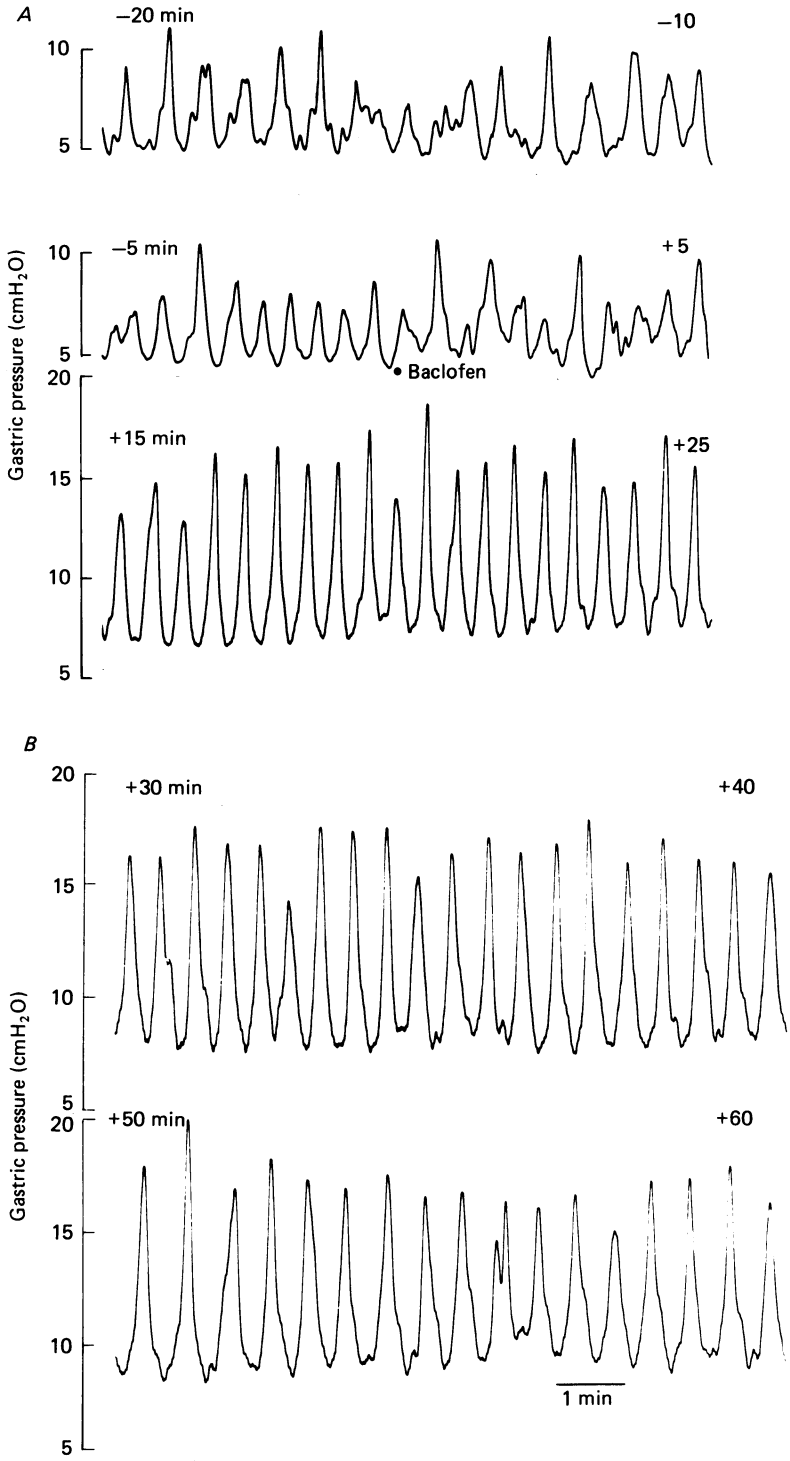

Fig. 3. The gastric motility response of an animal to baclofen (8 mg/kg s.c.). Note the elevation of tone and enhancement of contraction amplitude within 15 min of baclofen administration.

under these conditions in the corpus was similar in magnitude and time course to that observed in the whole stomach reported above (corpus pressure increase $3{\cdot}0 \pm 0{\cdot}4$ cmH_2O; whole-stomach increase $2{\cdot}6 \pm 0{\cdot}8$ cmH_2O, both at 30 min after baclofen).

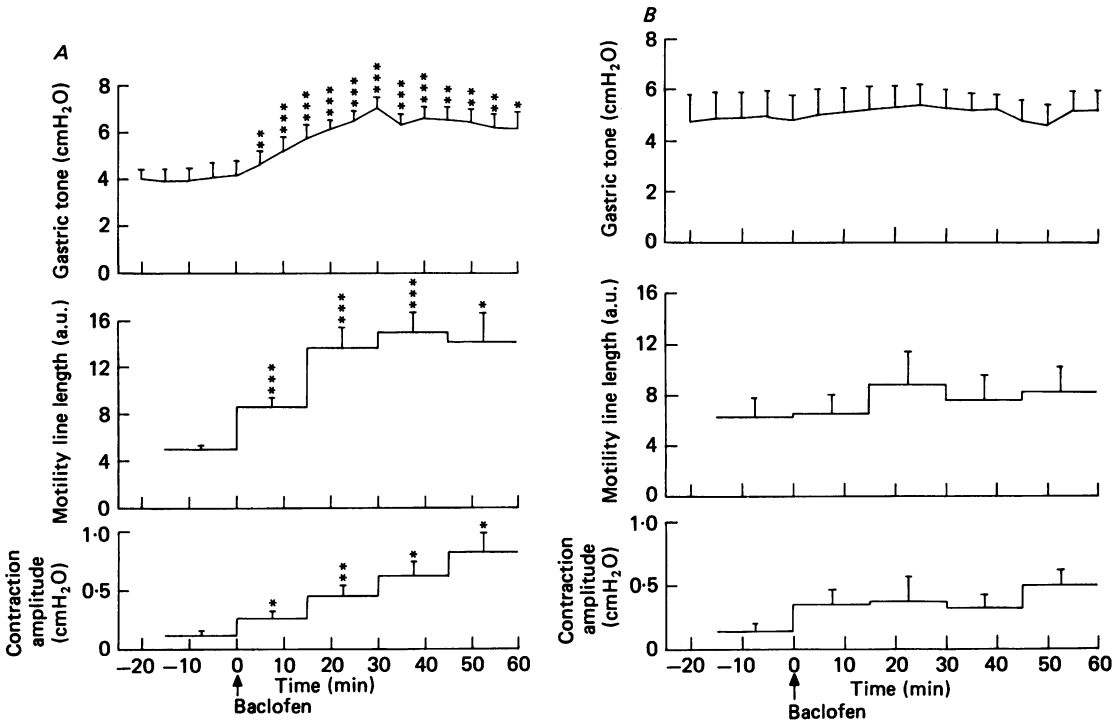

Fig 4. *A* shows the effect of baclofen (8 mg/mg s.c.) on gastric motility parameters in atropinized, guanethidine-treated, adrenalectomized ferrets, with greater splanchnic nerve section ($n = 6$ animals). A significant stimulation of all parameters was observed (* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$). Note that whilst the increase in tone is comparable to that in intact animals (Fig. 2) the enhancement of contraction amplitude is much reduced. *B*, conditions as in *A* but in addition the animals were vagotomized prior to baclofen administration. There was no significant increase in any of the parameters ($n = 5$ animals).

Once the corpus pressure had reached a plateau in response to baclofen a further increase (1–2 cmH_2O) could be produced in some animals by vagotomy but this effect was not systematically studied.

In animals vagotomized at the start of the experiment baclofen was without effect on corpus pressure.

Intravenous administration of baclofen (0·5 mg/kg) in the presence of atropine, guanethidine, adrenalectomy and greater splanchnic nerve section produced a transient increase in corpus pressure that reached a peak value of $1{\cdot}9 \pm 0{\cdot}6$ cmH_2O ($n = 6$, $P = 0{\cdot}02$) above basal after about 10 min. This increase is comparable to that observed in the whole stomach in response to I.V. baclofen ($1{\cdot}7 \pm 0{\cdot}4$ cmH_2O, see p. 29).

Baclofen and the vagally driven relaxation of the gastric corpus. To exclude the

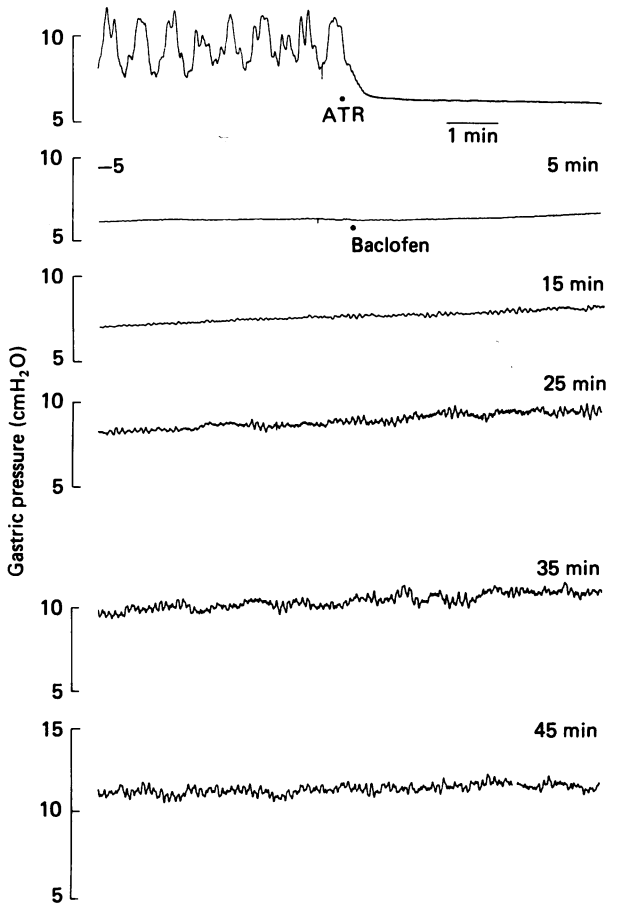

Fig. 5. The effect of baclofen (8 mg/kg s.c.) on gastric motility in an atropinized animal in the presence of greater splanchnic nerve section, adrenalectomy and guanethidine. Note that whilst there was a small enhancement of rhythmic contractile activity, the major effect of baclofen administration was an elevation of gastric tone that was particularly large in this animal.

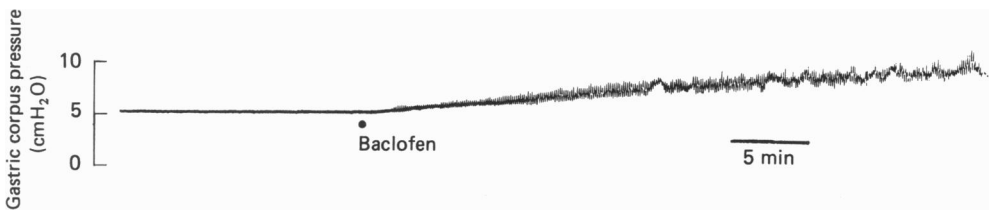

Fig. 6. The effect of baclofen (8 mg/kg s.c.) on gastric corpus motility in the presence of atropine, guanethidine, adrenalectomy and greater splanchnic nerve section. Note the progressive increase in tone and stimulation of rhythmic contractions.

possibility that the gastric tone increase in response to baclofen was primarily due to an effect on the n.a.n.c. nerves at a peripheral site the magnitude of the gastric corpus relaxation in response to submaximal vagal stimulation (5 Hz, 10 s; 20 V, 0·5 ms) was compared in animals before and after baclofen (8 mg/kg s.c.) administration. Baclofen was without significant effect on the magnitude of the vagally driven relaxation.

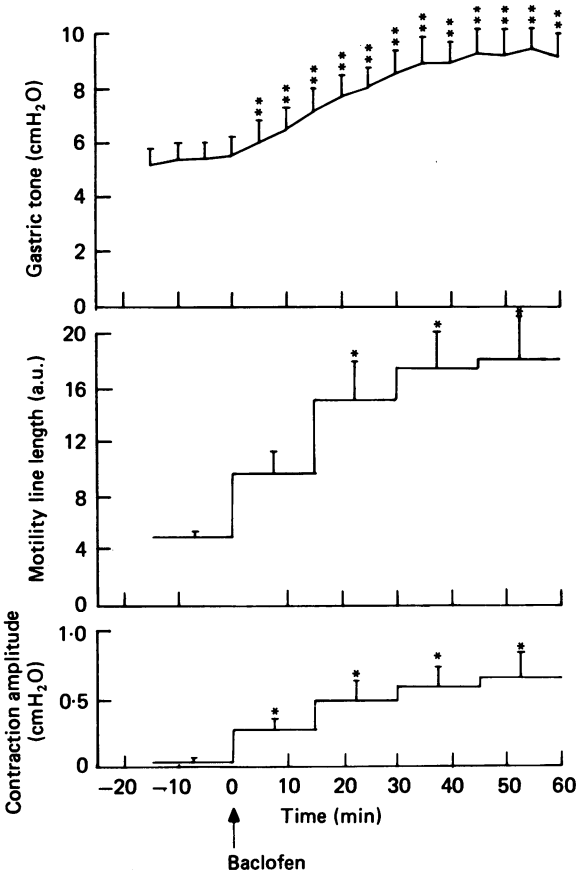

Fig. 7. The effect of baclofen (8 mg/kg s.c.) on various parameters of gastric corpus motility in atropinized, guanethidine-treated adrenalectomized animals with greater splanchnic nerve section ($n = 5$). Note the similarity to the response of the whole stomach under the same conditions (Fig.3*A*). * $P < 0{\cdot}05$, ** $P < 0{\cdot}005$.

DISCUSSION

The mechanism of the effects of baclofen and vagotomy on gastric motility

The results from this study demonstrate that baclofen produces an increase in gastric motility by two vagally dependent mechanisms which reflect changes in activity in both the vagal fibres driving the intramural cholinergic neurones and those driving the n.a.n.c. neurones.

In the whole stomach subcutaneous baclofen produced an increase in the over-all

gastric pressure (tone) and in the amplitude of the superimposed rhythmic contractions. Neither component of the response was observed in vagotomized animals. In the presence of atropine (and guanethidine, adrenalectomy and greater splanchnic nerve section) the tone increase was similar to the non-atropine-treated group but only a small increase in the amplitude of the rhythmic contractions was observed. In the presence of atropine baclofen produced an increase in corpus pressure of similar magnitude to that observed in the whole stomach indicating that the effects of baclofen on gastric pressure are mainly due to an effect on the corpus region. Taken together these results indicate that baclofen enhances the amplitude of rhythmic gastric contractions primarily by vagal driving of the intramural cholinergic nerves and that the increase in tone is mediated by a different mechanism involving mainly the corpus.

The results from the vagotomy study show that this lesion produces an increase in corpus pressure by interruption of a tonic vagal efferent drive to intramural n.a.n.c. inhibitory neurones. Using hexamethonium it was possible to produce a dose-related increase in corpus pressure by antagonism of the transmission between the vagal efferents and the intramural n.a.n.c. neurones. The tonic vagal efferent discharge is probably generated in response to the corpus distension and represents the vago-vagal gastro-gastric relaxation reflex described by Abrahamsson & Jansson (1973). The possibility that the presence of the oesophageal tube contributed to the relaxation of the corpus by activation of an oesophago-gastric reflex (Abrahamsson & Jansson, 1969) was discounted (see p. 27).

The similarity between the effects of vagotomy and baclofen on gastric corpus pressure in the presence of atropine strongly suggests a similar mechanism of action and this is discussed below.

In the presence of atropine, guanethidine, adrenalectomy and greater splanchnic nerve section baclofen produced a steady increase in corpus pressure and an increase in the amplitude of the rhythmic contractions but was without effect in vagotomized animals. The similarity between the magnitude of the pressure increase in the stomach and corpus produced by baclofen under similar conditions suggests that the pressure changes observed in the stomach were due mainly to an increase in corpus tone. It is of interest that in animals vagotomized after the corpus pressure had plateaued in response to baclofen there was a further increase in pressure indicating that baclofen at this dose reduces but does not abolish the vagal drive to the n.a.n.c. system. This idea is supported by a comparison of the corpus pressure increases in animals with vagotomy ($4{\cdot}8 \pm 0{\cdot}35$ cmH_2O), hexamethonium ($5{\cdot}6 \pm 0{\cdot}9$ cmH_2O) or baclofen ($3{\cdot}0 \pm 0{\cdot}4$ cmH_2O).

The results from the vagotomy and baclofen studies taken together suggest that baclofen produces its increase in gastric pressure by decreasing the tonic vagal drive to the intramural n.a.n.c. inhibitory neurones in the gastric corpus. This contrasts with the stimulation of rhythmic contractions by baclofen which also requires an intact vagus but is mostly atropine sensitive. This effect of baclofen is probably due to an enhanced vagal drive to the intramural cholinergic neurones in both the corpus and antrum.

In this study we have only used a single subcutaneous dose of balofen and it would be of interest to determine whether the differential vagal effects on the cholinergic

and n.a.n.c. systems could be separated using different doses or routes of administration. The observation that I.V. baclofen produced only a significant increase in the tone may provide some indication that the two systems can be activated separately. It is possible that this may represent two central sites of action with different sensitivities to baclofen.

The site of action of baclofen. Although results from other studies strongly indicate that the effects of baclofen on the stomach are due to a central site of action (Goto & Debas, 1983; Andrews & Wood, 1986; Wood *et al.* 1987) consideration should be given to possible peripheral effects. Indications that GABA may be involved in the peripheral control of gut function come from studies demonstrating GABA-like immunoreactivity in myenteric neurones (Saito & Tanaka, 1986) and the presence of glutamic acid decarboxylase in the gut (Tanaka, 1985). $GABA_B$ receptors have been implicated in the regulation of motility as *in vitro* some of the effects of GABA are insensitive to bicuculline and mimicked by baclofen (Giotti, Luzzi, Spagnesi & Zilletti, 1983*a*, *b*). Thus it is possible that baclofen could have produced its effects in the present study by modulation of the vagal drive at a peripheral site. The main indication that this is not the case is that baclofen had no effect on the magnitude of the corpus relaxation evoked by submaximal vagal stimulation.

Although the effects of baclofen on vagally evoked contractions were not investigated, *in vitro* studies have revealed that baclofen *antagonizes* cholinergic contractions of the gut by a pre-synaptic action (Giotti *et al.* 1983*a*, *b*). Therefore a stimulation of motility by a peripheral site of action appears unlikely. This antagonist effect of baclofen requires doses between 10^{-7} and 10^{-3} M (ibid) whereas intravenous doses of baclofen of 5 mg/kg which give rise to tissue concentrations of more than 10^{-7} M have pronounced long-lasting effects on synaptic transmission in the spinal cord (Fox, Knjevic, Morris, Puil & Werman, 1978). The present study used doses of 8 mg/kg S.C. and 0·5 mg/kg I.V. and based on the data from Fox *et al.* (1978) it is highly unlikely that these doses would have produced tissue concentrations sufficiently high to have peripheral effects.

Goto, Tache, Debas & Novin (1985) demonstrated that in the rat subcutaneous baclofen (4 mg/kg) evoked an increase in vagal efferent discharge within 5 min which plateaued in 20 min (cf. time course of motility responses). As their study used a multifibre preparation of the cervical vagus the data can only be used to illustrate that subcutaneous baclofen can influence the vagal outflow by an action at a central site. The above observations all suggest a central site of action for baclofen.

Unlike GABA, the GABA analogue baclofen penetrates the blood–brain barrier (Faigle & Keberle, 1972) and could therefore act either at the level of the brain-stem nuclei from which the gastric vagal efferents originate (Leslie, 1985) or at extramedullary sites which influence this outflow (e.g. cerebral cortex, Eliasson, 1952; Hurley-Gius & Neafsey, 1986; hypothalamus, Lissander, 1975; or cerebellum, Lissander & Martner, 1975). Whilst the present study in the ferret does not allow us to draw conclusions about the site of action of baclofen, an extramedullary site of action is suggested by the observations that baclofen (8 mg/kg S.C.) has no effect on gastric motility in the decerebrate rat (Andrews & Wood, 1986) and intrahypothalamic injections of baclofen produce a marked stimulation of gastric motility (Wood *et al.* 1987).

Baclofen is a particularly interesting compound because it appears to increase gastric motility by simultaneously increasing an excitatory vagal drive and decreasing an inhibitory one, a combination which is likely to occur under physiological conditions (Davison & Grundy, 1980; Andrews, 1986), and may act by modifying both vagal outflows at a common site. Although there is evidence to support an involvement off the hypothalamus in the gastric motility response to baclofen, it would be unwise to exclude a brain-stem site of action.

Whilst there is no direct evidence that systemic baclofen can influence the medullary vagal outflow to the gut, other medullary neurones (e.g. respiratory) are influenced by systemic baclofen (0·5–2 mg/kg I.V., Lalley 1986). Micro-injection of the $GABA_A$ receptor antagonist bicuculline into the nucleus ambiguus enhanced gastric antral and pyloric motility in the cat (Williford, Ormsbee, Norman, Harmon, Garvey, Dimicco & Gillis, 1981). Although the results from the present study may appear to be inconsistent with these micro-injection experiments it should be borne in mind that systemic baclofen could act at multiple central sites with different sensitivities (cf. 2-deoxy-*d*-glucose, Kadekaro, Timo-Iaria & Vicentini, 1977) and hence the motility changes observed may be the net effect of an action at several sites. Identification of the precise site at which baclofen acts to influence the gastric vagal efferents awaits a micro-injection study of several regions of the ferret brain.

In conclusion, this study has shown that a centrally acting $GABA_B$ receptor agonist can modify the vagal outflow to the gastric corpus which, with respect to motility, mimics a pattern which might be predicted to occur as the stomach empties. To our knowledge this paper provides the first report of a centrally acting compound which can influence the vagal outflow to the n.a.n.c. intramural nerves. Consideration should be given to the possibility that such pharmacological manipulations could be used to facilitate gastric emptying in patients in whom gastric stasis may be due to inappropriate activity in the vagal fibres during the n.a.n.c. nerves.

K.L.W. is an S.E.R.C., C.A.S.E. student. We are grateful to the S.E.R.C., Smith Kline and French and the Wellcome Trust for financing this research.

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