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Systemic baclofen stimulates gastric motility and secretion via a central action in the rat

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1 Intravenous (0.5 mg kg^{-1}) or subcutaneous (2–16 mg kg^{-1}) administration of the γ-aminobutyric acid (GABA) analogue baclofen resulted in a stimulation of gastric motility and secretion in the rat, anaesthetized with urethane.

2 The motility response to subcutaneous injection was dose-related.

3 This effect was abolished by vagotomy or atropine. There was no response to baclofen in decerebrate animals.

4 These results indicate that systemic baclofen, probably acting at a site rostral to the brainstem, stimulates gastric motility and acid secretion by a vagally-dependent mechanism.

Introduction

Electrical stimulation of a number of central nervous system structures has revealed the profound influence that the brain can exert on the gastrointestinal tract via the parasympathetic and sympathetic outflows. Whilst stimulation and complementary lesioning studies have identified some of the neuroanatomical pathways regulating autonomic outflow to the gut, little is known about their neuropharmacology. A variety of substances e.g. 5-hydroxytryptamine (5-HT, Bugajski *et al.*, 1977), cholecystokinin (CCK, Ishikawa *et al.*, 1985), thyrotrophin releasing hormone (TRH, Morley *et al.*, 1979) and calcitonin (Morley *et al.*, 1981) have been shown to influence gastrointestinal motility and secretion after intracerebroventricular injection and it has been suggested they may be involved in the CNS pathways regulating these functions. Modification of gut function after drug administration into specific brain regions also provides clues about the neurotransmitters involved at these sites (e.g. hypothalamus, Costall *et al.*, 1985).

Clinically, modification of gastric secretion and/or motility has usually been limited to the use of peripherally acting drugs (e.g. histamine H_2-and dopamine D_2-receptor antagonists). Many of the substances found to be active when given centrally have no effect when administered systemically as they do not cross the blood brain barrier (BBB). The use of systemically administered drugs which cross the BBB and act centrally to influence gastric autonomic outflow (e.g. the vagus) might provide a novel way of influencing gastric function.

The lipophilic γ-aminobutyric acid (GABA) analogue baclofen, which is used clinically as a muscle relaxant in spastic conditions, penetrates the BBB (Faigle & Keberle, 1972). Recent studies in rat, dog and man have shown that intravenously or subcutaneously administered baclofen stimulates gastric acid secretion via the vagus (Goto & Debas, 1983: Goto *et al.*, 1984; Pugh *et al.*, 1985). However, gastric motility was not monitored in these studies.

The aims of this study were to examine the effects of baclofen on gastric motility and to extend previous secretory studies by comparing the responses to intravenous and subcutaneous routes of adminstration in the rat. A dose range of 2–16 mg kg^{-1} was chosen to investigate the dose-response relationship of subcutaneous baclofen on gastric motility so that our results could be compared with the dose-response curve constructed for acid secretion by Goto & Debas (1983). An intravenous dose of 0.5 mg kg^{-1} was selected so that our data could be compared with those obtained for the dog (Goto *et al.*, 1984). Experiments were also performed to determine whether the biological activity was confined to one enantiomer of the racemic mixture as stereoselective actions have been reported in other systems (e.g. Olpe *et al.*, 1978; Kerwin & Pycock, 1978; Waldmeier & Maitre, 1978).

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Methods

Experiments were performed on 80 male Wistar rats in the weight range 190–250 g. They were deprived of food overnight but allowed water *ad libitum*. The animals were anaesthetized with urethane (1.2 g kg^{-1} i.p., 25% w/v in 154 mM NaCl) such that the withdrawal of the hindlimb in response to a strong pinch was abolished.

The trachea and external jugular vein were cannulated and the abdominal cavity opened via a midline incision. Animals in which gastric motility was monitored had the pylorus ligated and a wide bore tube inserted into the stomach via the mouth and secured with a ligature at the cervical level, care being taken to exclude the vagi. The stomach was inflated with 5 ml of warm 154 mM NaCl. Pressure was measured by a transducer (Palmer 8138) attached to the gastric cannula and the output displayed on chart recorders (Gould 2400, Bryans 28,000).

A modified Ghosh & Schild (1958) technique described by Parsons (1969) was used in animals in which hydrogen ion (H^+) secretion was measured. A small hole was made in the forestomach of a pylorus-ligated rat and any food residue present was washed out. A second incision was made near the pyloric sphincter, care being taken to avoid the gastroepiploic arteries and any nerve fibres visible. Perspex cannulae were inserted and tied into the stomach via these incisions. The stomach was perfused with warm 5% w/v glucose at 3 ml min^{-1}, the effluent perfusate passing over a pH electrode. Changes in pH were converted by an antilog unit (Parsons, 1969) to a function of H^+ activity and continuously recorded on a pen recorder (Servoscribe).

Rectal temperature was monitored and maintained at 37°C by an electric blanket and an overhead lamp. At least 30 min elapsed after surgery before experimentation began. Motility or acid secretion was monitored for 30 min before drug administration by either s.c. (femoral triangle) or i.v. (jugular vein) routes and followed for a further 120–150 min. Control animals received 154 mM NaCl injections at the corresponding schedule.

The role of the vagus in the response was assessed by sectioning the vagal trunks either in the abdomen or neck or by atropine treatment. Five animals were decerebrated under urethane anaesthesia by intercollicular section and suction and allowed to recover for at least 60 min before drug administration.

Drugs

In all experiments (±)-baclofen (Lioresal, CIBA) dissolved in 154 mM NaCl was administered either intravenously or subcutaneously as a bolus, the volume not exceeding 1 ml. The laevo (−)-and dextro (+)-enantiomers of baclofen were treated in the same way as the racemic mixture. In some experiments atropine sulphate (BDH) or atropine methyl nitrate (BDH) were given i.v. and i.p. respectively. Different animals were used for each drug injection.

Analysis

Acid Instantaneous H^+ secretion above the basal level was measured from the trace at regular intervals pre- and post-drug administration. The following parameters of the response were also measured when appropriate: maximum output — peak concentration of H^+ reached after baclofen administration; latency — interval between baclofen administration and onset of response; time to peak — interval between onset and peak of response; half decay time — time taken for H^+ output to fall to half maximum; duration — interval between onset of stimulated H^+ output and its return to the basal level.

Motility

Three components of the gastric motor response to baclofen were measured: (a) Tone: this is defined as the difference between atmospheric 'O' pressure and the mean level of prevailing pressure upon which the rhythmic contractions were superimposed. (b) Line length: total length of the inkline drawn on the chart recorder measured from original records using a T.D.S. bitpad and a C.E.D. alpha mini computer. This measurment has been used as an index of total gastric motility in other species (Grundy & Scratcherd, 1982). Results are expressed in arbitrary units (au). (c) Contraction amplitude: the amplitude of a contraction was taken as the difference between the tone and the maximum pressure achieved during the contraction. The mean contraction amplitude was calculated for consecutive 15 min periods.

Statistics

Results are expressed as mean ± s.e., number of animals (n) and significance tested by a paired sample t test and P values are stated at appropriate points in the text.

Results

The effect of baclofen on gastric acid secretion

(±)-Baclofen administered either by bolus intravenous injection (0.5 mg kg^{-1}) or subcutaneously (8 mg kg^{-1}) stimulated gastric H^+ secretion. The time course and duration of the responses were markedly different and will be described separately.

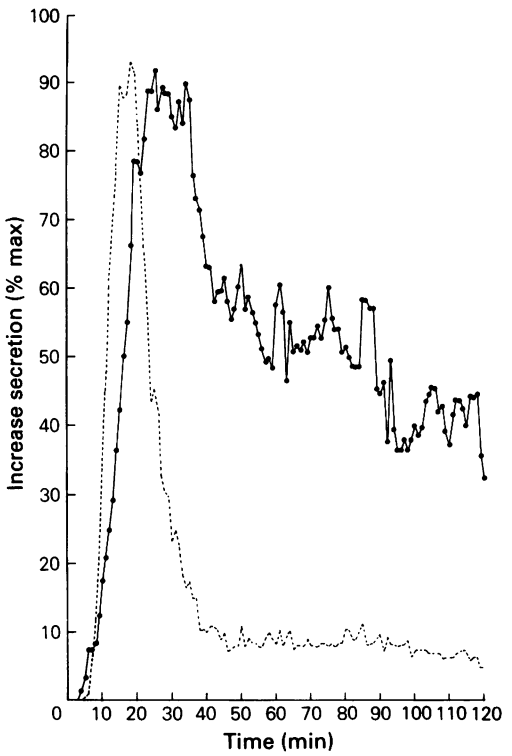

Figure 1 Increase in H^+ secretion produced by s.c. (8 mg kg^{-1}, $n = 3$,) and i.v. (0.5 mg kg^{-1}, $n = 4$,) baclofen given at time zero. Note the similar latencies but different patterns of response. Maximum s.c. output was $1496 \pm 822\,\mu$Eq l^{-1}. Maximum i.v. output was $149 \pm 72\,\mu$ Eq l^{-1}.

Subcutaneous administration A dose of 8 mg kg^{-1} s.c. produced a detectable increase in gastric H^+ secretion after a latency of 5.7 ± 1.5 min ($n = 4$). Peaking between 22–130 min (mean 24 min) after baclofen administration, the acid secretion declined to a plateau value above 40% of the peak output in 3 out of 4 animals. H^+ secretion was sustained and maintained above the basal level for the 2.5 h observation period, as can be seen in Figure 1. Whilst the pattern of response was similar for each animal, the magnitude of secretion was very variable (maximum output $1496 \pm 822\,\mu$Eq l^{-1}, $n = 4$).

Studies with the same dose (8 mg kg^{-1}, s.c.) of either dextro (+)-or laevo (−)-baclofen revealed that whilst (−)-baclofen stimulated H^+ secretion in a similar pattern to the racemic mixture, the magnitude of effect was smaller (maximum output $786 \pm 311\,\mu$Eq l^{-1}), and the (+)-enantiomer was without effect.

Intravenous administration Intravenous bolus injection of (+)-baclofen (0.5 mg kg^{-1}) stimulated H^+ secretion after a delay of 6.6 ± 0.9 min ($n = 4$). Secretion rapidly increased to reach a peak of $149 \pm 72\,\mu$Eq l^{-1} ($n = 4$) after 10.4 ± 1 min from which, in contrast to the subcutaneous response, it rapidly declined towards basal values with a half decay time of 7.5 ± 1.2 min (Figure 1).

The effects of baclofen on gastric motility

Subcutaneous administration Gastric tone often showed an immediate transient (2 min) decrease of 1 cmH_2O after a s.c. injection of baclofen or saline; tone returned to basal values after about 2 min.

Previous studies have shown a dose-response relationship between subcutaneous baclofen and gastric acid secretion (Goto & Debas, 1983) and this route was chosen to determine whether a similar dose-related motility response existed. Examples of responses are shown in Figure 2 and illustrate that the response consists primarily of an increase in the amplitude of individual contractions and an increase in tone. The dose-dependent change in these parameters together with line length are described below. Control s.c. injections of 1 ml 154 mM NaCl produced no consistent stimulation of gastric motility.

During this series of experiments it became apparent that the highest dose of baclofen (16 mg kg^{-1}, s.c.) was toxic; 2 out of 6 animals died

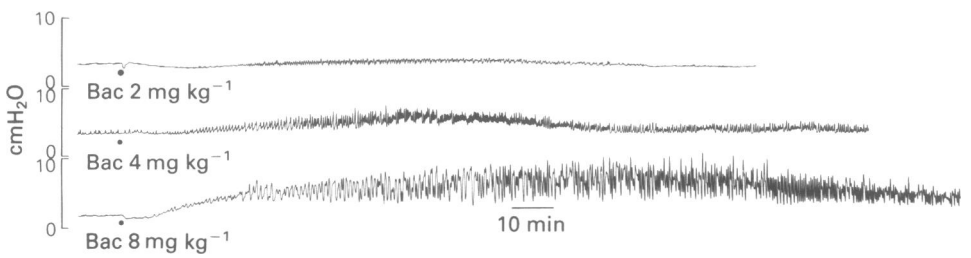

Figure 2 Record showing the motility response of the rat stomach to graded subcutaneous doses of baclofen (Bac, 2–8 mg kg^{-1}). Note that at the highest dose the response is sustained at a time when it is declining at the lower doses.

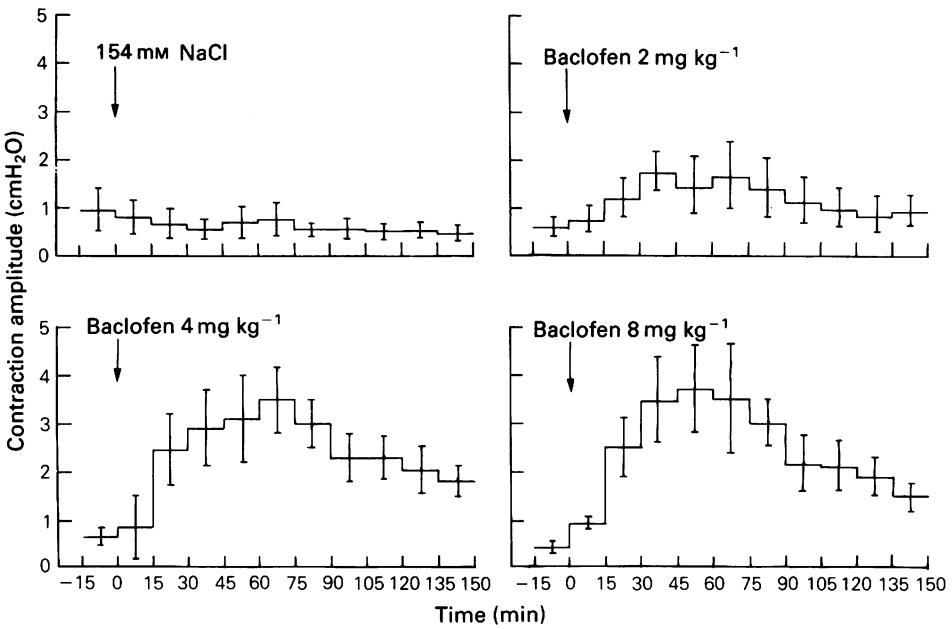

Figure 3 The effect of baclofen (2, 4 and 8 mg kg^{-1}, s.c.) on gastric contraction amplitude (mean values are shown with vertical lines indicating s.e., mean $n = 6$ per group).

within the first hour of administration of this dose and a further 2 within the next half hour. No deaths occurred at other doses.

Tone Baclofen (s.c.) produced a dose-dependent increase in gastric tone which peaked at approximately 1 h. The group basal tone was 5.2 ± 0.5 cmH_2O ($n = 22$). After 1 h it was 7.0 ± 0.9 cmH_2O ($n = 6$) for 2 mg kg^{-1}, 8.5 ± 1.8 cmH_2O ($n = 6$) for 4 mg kg^{-1}, 13.7 ± 4 ($n = 6$) for 8 mg kg^{-1} and 11.4 ± 2.2 cmH_2O ($n = 4$) for 16 mg kg^{-1}. These increases were significant ($P<0.05$) for all doses except 2 mg kg^{-1}.

Contraction amplitude At all doses of baclofen, contraction amplitude was enhanced within the first 15 min after drug injection (Figure 3). This increase achieved statistical significance ($P<0.05$) within 30 min and peaked during the 60–75 min period, although gastric tone was declining at this time. Mean contraction amplitude then declined towards basal values which had not been reached at the higher doses by the end of the 2.5 h observation period. Doses of 4 and 8 mg kg^{-1} produced effects of similar magnitude (peaks at 3.5 ± 0.9 and 3.6 ± 0.9 cmH_2O respectively, $n = 6$) which were larger than the responses to 2 and 16 mg kg^{-1}.

Line length This provides an index of the 'total activity' of the stomach and incorporates changes in contraction frequency which were observed to increase (e.g. see Figure 2) after baclofen administration but which were not systematically investigated. Subcutaneous baclofen produced a dose-dependent increase of line length, although this failed to achieve statistical significance at the lowest dose. Again a dose of 16 mg kg^{-1} was less effective than the 4 mg kg^{-1} dose.

As with the secretory response, the dextro, (+)-enantiomer of baclofen had no effect on gastric motility, whereas the laevo (−)-enantiomer produced motility effects similar in all respects to those produced by the racemic mixture when administered subcutaneously (8 mg kg^{-1}) (Figure 4).

Intravenous administration Baclofen (0.5 mg kg^{-1}, i.v.) at the dose which stimulated acid secretion, resulted in a stimulation of gastric motility primarily by increasing the contraction amplitude ($P<0.05$) and line length ($P<0.05$) (Figure 5). The effect of baclofen on all three motility parameters is quantified in Figure 5. Whilst mean tone did not increase, stimulation was observed in some animals. The magnitude of these effects was similar to that induced by a 2 mg kg^{-1}, s.c. dose.

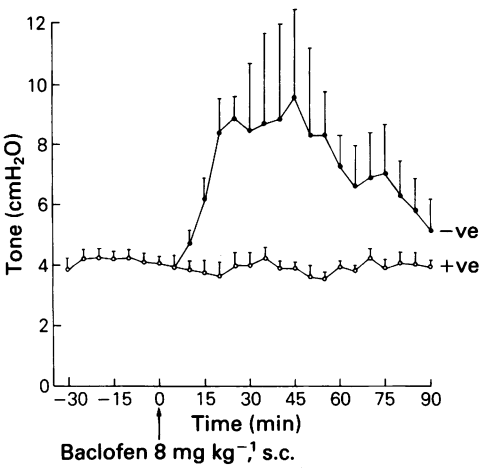

Figure 4 Comparison of the effects of baclofen enantiomers (8 mg kg^{-1}, s.c.) on gastric tone ($n = 4$ per group). (−)-Baclofen (●) produced an increase in gastric tone; (+)-baclofen (○) was without significant effect.

Comparison of time course of acid and motility responses

Whilst the H^+ response to a s.c. injection paralleled the motility response, the time course of the H^+ response to i.v. baclofen differed markedly from that of the motility response; H^+ secretion had returned to basal values when the motility response reached its peak.

Although the duration and magnitude of the motility response to these i.v. and s.c. doses was different, the pattern of response was similar.

The effect of atropine, vagotomy and decerebration on the response to baclofen

Bilateral cervical ($n = 10$) or abdominal vagotomy ($n = 4$) abolished the gastric secretory and motor

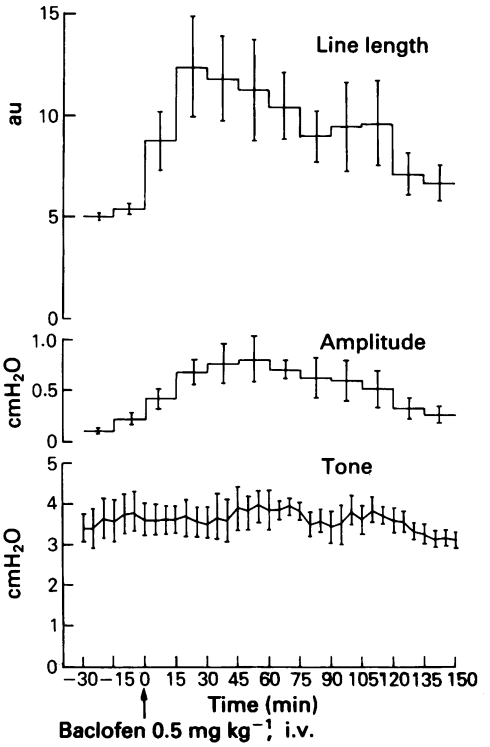

Figure 5 The differential effects of intravenous baclofen on parameters of gastric motility. A significant increase in contraction amplitude and line length occurred whilst tone was not elevated.

responses (Figure 6) to baclofen in the majority of animals although in 2 out of 8 there was a small increase in acid output.

Pretreatment with atropine sulphate (1 mg kg^{-1}, i.v. $n = 4$) or atropine methyl nitrate (20 mg kg^{-1}, i.p., or 1 mg kg^{-1}, i.v., $n = 5$) prevented the motility response

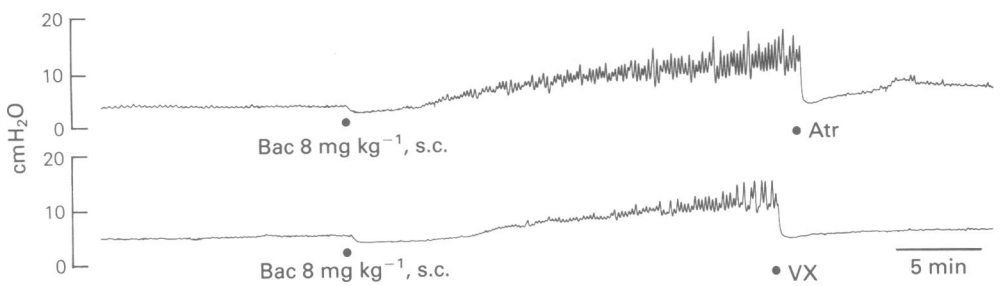

Figure 6 Record of the gastric motility response to subcutaneous baclofen (Bac, 8 mg kg^{-1}) showing the curtailing effect of bilateral cervical vagotomy (VX) and atropine methyl nitrate (1 mg kg^{-1}, i.v., Atr). Note that both procedures reduce the gastric tone and amplitude of contractions.

to baclofen or curtailed it if administered in the course of the response. (Figure 6). The acid response is also abolished by atropine sulphate (Goto & Debas 1983). Baclofen (8 mg kg^{-1} s.c.) did not stimulate gastric motility in 5 rats which had been decerebrated 60 min before drug administration; acid output was not monitored.

Discussion

The results from this study demonstrate that systemic baclofen produces a vagally-dependent stimulation of gastric motility, in addition to the previously described stimulation of gastric acid secretion.

Characteristics of the response

Baclofen (s.c.) caused a dose-related increase in gastric tone, contraction amplitude and accumulated activity (line length) over a similar dose-range which stimulated acid secretion (Goto & Debas, 1983). Although an increase in all the measured indices of gastric muscle activity occurred, it is not possible to predict whether baclofen would enhance gastric emptying rate since increasing motility does not always equate with enhanced emptying.

One of the striking features of the response was the rapidity of onset and lack of difference in the latency between the s.c. and i.v. routes indicating that baclofen was rapidly absorbed from s.c. sites. The latency of response was consistent with the rapid onset of enhanced vagal discharge induced by s.c. baclofen (4 mg kg^{-1}, s.c.) in the rat (Goto *et al.*, 1985). The secretory response was more transient than the motility response after i.v. baclofen whereas these parameters paralleled each other after s.c. administration. The reason for this is unclear, but it may indicate that the sites from which motor and secretory responses are evoked have different sensitivities to baclofen.

Site and mechanism of action

Abdominal or cervical vagotomy abolished or markedly reduced the secretory and motor responses to baclofen, suggesting that it acts at a central site to stimulate the vagal outflow to the stomach. A central site of action is supported by the observation that the discharge in multi-fibre recordings of vagal efferent activity was increased by baclofen (4 mg kg^{-1}, s.c.) in the urethane-anaesthetized rat (Goto *et al.*, 1985).

The enhancement of motility appears to be due mainly to vagal activation of the intramural postganglionic cholinergic excitatory nerves as the response was abolished or markedly reduced by vagotomy or atropine. However, the possibility that the response is also due in part to a decrease in the tonic activity of the vagal efferents supplying the intramural non-adrenergic, non-cholinergic (NANC) inhibitory nerves cannot be excluded (Andrews, 1986).

Electrical stimulation studies have shown that sites in the forebrain, hypothalamus and brainstem can all enhance gastric motility via the vagus (Eliasson, 1952; Grijalva *et al.*, 1980; Pagani *et al.*, 1985). Baclofen could influence motility at any one or all of these sites since it penetrates the BBB. Our preliminary studies have shown that the response is not present in decerebrate animals indicating that it is likely that the primary site of action of baclofen is rostral to the brainstem.

The precise pharmacological mechanism(s) by which baclofen stimulates gastric motility and secretion is unclear. This study revealed that the biological activity of racemic baclofen resides with the (−)-enantiomer. Interestingly, the (−)-enantiomer was less active than would have been expected had the dose of racemate been doubled, a phenomenon which has been observed in other systems (Olpe *et al.*, 1978).

The stereospecificity of action supports the contention that baclofen is interacting with $GABA_B$ receptores for (−)-baclofen has over 100 times the affinity for these receptors than (+)-baclofen (Bowery *et al.*, 1985). Baclofen may act by modulating release of transmitters, e.g. 5-HT (Bowery *et al.*, 1980), excitatory amino acids (Potashner, 1978). Thus, the observed response may be the result of a net change in the activity of central pathways regulating vagal efferent discharge produced by modulation of a variety of neurotransmitter systems at a number of sites.

In conclusion, we have demonstrated that systemically administered baclofen can stimulate gastric acid secretion and motility via a vagal pathway. The ability of baclofen to stimulate gastric function via the vagus had led to the suggestion (Goto *et al.*, 1984) that it could be used as a test for vagotomy in man, as an alternative to the 'insulin test' (Lythgoe, 1961). Our results provide support for this idea and in addition, indicate the potential that systemically administered drugs which cross the BBB have for stimulating gastric motility. This approach to overcoming gastric emptying problems, such as those observed in diabetic gastroparesis (e.g. Horowitz *et al.*, 1985) or postoperatively may be more fruitful than designing more gastrokinetic drugs which act only at peripheral sites.

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