Effects of partial truncal vagotomy on intragastric pressure responses to vagal stimulation and gastric distension in ferrets

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SUMMARY Changes in intragastric pressure after dorsal truncal vagotomy, investigated by stimulation of the surviving vagal branches and by step inflation of the stomach, were divided into an early phase lasting five days, and a late phase continuing for at least three months. During the early phase the amplitude of vagal evoked contraction was diminished but the resting pressure and the response to gastric inflation were increased. After the fifth day vagal evoked contractions doubled in amplitude but the resting pressure and the response to step inflation of the stomach returned to control levels. Ventral vagotomy did not produce any substantial changes. Alterations to gastric and body weight, or to the relation between resting pressure and evoked contraction and relaxation were excluded as causes of the enhanced vagal effectiveness. Sprouting of axons into denervated territory occurred too late to explain the changes, but an increase in synaptic density within the innervated territory has not been ruled out.

Changes in the innervation of gastric smooth muscle after partial vagotomy merit investigation because many of the complications of vagotomy relate to alterations in motility. Selective or truncal vagotomy with drainage causes more complications related to motility than highly selective vagotomy.¹⁻⁴ Recurrence rates of ulceration after highly selective vagotomy rise considerably, however, with length of follow up⁵⁻⁶ which implies that there is an element of plasticity involved in secretomotor innervation. Surgery for peptic ulceration is therefore a compromise between avoiding recurrent ulceration and risking disorders of motility.

Changes in motility after various forms of vagotomy include alteration in the rate of gastric emptying,⁷ reduction of phase III of cyclic motor activity^{8,9} and irregularity of pacemaker potentials.¹⁰ The effects of vagotomy on motility alter with time¹⁰⁻¹³ and many

of the effects are particularly evident in the first few postoperative months. The present investigation was designed to characterise plasticity in motor innervation, particularly with respect to which vagal trunk is involved, the time course of such changes and the possible underlying mechanisms.

The recovery of vagal evoked contractions of the ferret stomach after partial truncal vagotomy may involve changes in the target organ, increased effectiveness of the surviving extrinsic innervation, or both. Resting pressure partly determines the amplitude of vagal evoked contractions.¹⁴ This may explain why larger stomachs are associated with greater evoked contractions¹⁵ which, in turn, may explain the correlation of body weight with the amplitude of evoked contractions.¹⁶ If vagotomy altered any of these factors then the amplitude of evoked contractions could have increased as a consequence of changes in the target organ alone, rather than in the surviving vagal branches. Thus if vagotomy caused an increase in gastric weight or an increase in resting gastric pressure, then an increase in vagal evoked contraction could be explained without recourse to neuronal plasticity. For the purposes of this paper, neuronal plasticity is defined as any longterm adap-

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tive change in a nerve which, in the present context, compensates for loss of function.

Differential loss of relaxatory influences¹⁵ and the redundancy known to exist in the vagal innervation of the stomach¹⁷ are additional potential mechanisms which have to be excluded before functional recovery can be attributed to plasticity in the vagus. A previous study¹⁷ indicated that sectioning the left cervical vagus induced an increase in responses evoked by the surviving right vagus, but not *vice versa*, suggesting the possibility that the left vagus is more potent than the right. Their apparent equivalence may be the result of smooth muscle limitations at suprathreshold levels of stimulation.¹⁴ This possibility was investigated.

In the ferret,¹⁸⁻²⁰ the dorsal trunk is distributed to the dorsal surface of the corpus and both surfaces of the antrum. The ventral trunk reaches only the ventral surface of the stomach, principally the corpus. The number of efferent axons is the same in the dorsal and ventral trunks and there are also equal numbers of efferents in the left and right cervical nerves. Equal numbers of neurones in the dorsal motor nuclei project to the stomach,²¹ but more in the left nucleus project to the corporoantral junction where contractions begin.

The aims of the present investigation were: (i) to determine the time course of recovery of evoked gastric contractions after partial vagotomy; (ii) to investigate any changes in the intrinsic motor responses of the stomach; (iii) to examine the possibility that changes in body weight, gastric weight, or resting intragastric pressure might contribute to the increase in vagal evoked contractions; (iv) to investigate possible changes in vagal evoked relaxation, and in particular to determine whether a selective loss of inhibition explained enhancement of contraction.

Gastric emptying and rhythmic contractions are complex phenomena which depend on a number of factors, any of which might have been altered in opposing directions by vagotomy. For this reason the less complicated contractions evoked by gastric inflation and vagal stimulation were investigated in this study.

Methods

ANIMALS

Seventy seven ferrets of either sex weighing 415–1600 g were used. Animals for vagotomy were anaesthetised with pentobarbitone (60 mg/kg ip). The dorsal or the ventral abdominal trunk of the vagus was ligated below the diaphragm with two silk ligatures 1 cm apart. The intervening nerve was removed and later examined histologically. The abdominal wound was closed in layers and the animals were allowed to

recover. The postoperative diet was water on the first day, milk on the second, and meat with fluid thereafter.

Animals were randomly allocated to one survival group, the groups being allowed to survive for 3, 5, 7, 21, 28 or 84 days. At the end of the survival period the animals were anaesthetised with urethane (1.5 g/kg 50% w/v in 154 mM-NaCl ip). A tracheostomy was done in all animals. The right external jugular vein was cannulated for the administration of drugs. The pylorus was occluded by a ligature. The stomach was intubated *via* the oesophagus with a firm plastic tube 5 mm external diameter, inside which was a second tube 2 mm external diameter. The outer tube was used to inflate the stomach rapidly with 20 ml 154 mM-saline at 38°C. Intragastric pressure was monitored *via* the inner tube connected to a pressure transducer (Bioscience model 8138), the output from which was displayed on a chart recorder (Bryans 28000).

The cervical vagi were divided and the peripheral cut ends were stimulated (Devices Isolated Stimulator timed by a Digitimer D4030) using parameters giving maximal responses²² (10 Hz, 10 s trains, 0.5 ms pulses, voltages as in the results) delivered *via* bipolar silver electrodes immersed in liquid paraffin at 39°C. Care was taken to shield the electrodes with plastic covers.

The sections of tissue removed at vagotomy were examined histologically and were shown to be neural. At the end of the experiment, the cervical vagi were stimulated after division of the surviving vagal trunk. In no case was there any evoked contraction, confirming that the previously vagotomised trunk had been totally divided as far as motor axons were concerned.

In all cases the pressure was measured with the transducer placed at the same height as the supine animals' vertebral column, or a correction was applied to give the equivalent pressure.

STATISTICAL ANALYSIS

The data were subjected to factor analysis, regression analysis, and paired (within a group of animals) or unpaired (between groups of animals) *t* tests. Results are expressed as means $\pm$ SE of the mean.

Results

VAGAL EVOKED CONTRACTIONS

Dorsal vagotomy

Stimulation of the cervical vagi (20 V, 10 Hz, 0.5 ms pulses, 10 s duration) caused a brief contraction of the stomach followed by a relaxation lasting several minutes.

The results of stimulating the left and/or right

Table 1 Vagal evoked contractions after dorsal vagotomy

Source of variance	Sum of squares	df	Mean square	F	P
Nerves	38.1	2	19.0	1.0	ns
Days	2213.8	6	369.0	20.1	<0.001
Nerve × day	62.2	12	5.2	0.3	ns
Within group	1931.4	105	18.4		
Total	4245.5				

Five animals per group. Nerves: left, right or both cervical evoked responses; day: postoperative survival for 0, 3, 5, 7, 21 or 28 days; nerve × day: interaction between nerves and postoperative survival; within group: variance within each experimental group.

cervical vagi were subjected to factor analysis (Table 1), excluding the group which survived 84 days because it had only four members. Time had a highly significant effect on the amplitude of evoked response, but it did not matter which nerve was stimulated – that is, stimulation of the left, right or both cervical nerves evoked the same amplitudes of response. Because the identity of the stimulated nerve made no difference, subsequent analysis was confined to left cervical evoked responses.

Responses evoked at different intervals after vagotomy were compared with each other using an unpaired *t* test. In the control group of six ferrets stimulation of the left cervical vagus evoked contractions of 2.39 ± 0.25 kPa (24.4 ± 2.5 cmH₂O, Fig. 1). After division of the dorsal trunk (day 1 response evoked *via* the ventral trunk) the amplitude fell to 1.22 ± 0.39 kPa (12.4 ± 4.0 cmH₂O, $p < 0.005$), similar to the level obtained by stimulating the ventral trunk

Fig. 1 Gastric contractions evoked by stimulation of the left cervical vagus after dorsal vagotomy. On the first postoperative day contractions were reduced to the amplitude of those evoked by stimulating the surviving ventral trunk. By the fifth postoperative day, however, they had increased to prevagotomy values, equal to those previously evoked by stimulating the dorsal trunk. ($10 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$)

Table 2 Vagal evoked contractions after ventral vagotomy

Source of variance	Sum of squares	df	Mean square	F	P
Nerves	6.7	2	3.3	0.3	ns
Day	181.5	5	36.3	3.1	<0.05
Nerve × day	46.2	10	4.6	0.4	ns
Within group	849.5	72	12.0		
Total	1083.9				

Four animals per group. Nerves: left, right or both cervical evoked responses; day: postoperative survival for 0, 3, 5, 7, 21 or 28 days; nerve × day: interaction between nerves and postoperative survival; within group: variance within each experimental group.

before dorsal vagotomy. The amplitude on the third day (1.35 ± 0.25 kPa, 13.8 ± 2.5 cmH₂O) was lower than the control response ($p < 0.02$) and was not significantly different from the day 1 response. By the fifth day, however, the amplitude (2.01 ± 0.23 kPa, 20.5 ± 2.3 cmH₂O) had returned to control levels and had increased significantly above day 1 levels ($p < 0.01$); on all subsequent days the responses remained significantly above the day 1 levels ($p < 0.005$). As a check to ensure that the recovery was sustained, the responses on day 84 were compared with the greatest responses (day 21) and found not to be significantly different.

Thus dorsal vagotomy halved the amplitude of the response evoked by stimulation of the cervical vagus, and the response remained low for three days. By the fifth day responses showed a substantial enhancement to prevagotomy levels, where they remained for at least three months.

Ventral vagotomy

The responses to stimulation of the left cervical vagus in control animals and at various times after ventral vagotomy are shown in Figure 2. Factor analysis (Table 2) indicated that there was no significant difference in the responses to stimulation of the left,

Fig. 2 Gastric contractions evoked by stimulation of the left cervical vagus after ventral truncal vagotomy. There was little change immediately after ventral vagotomy, and minimal increases above the immediate postvagotomy levels were found after 21 and 84 days. ($10 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$)

right or both cervical nerves. Thus the maximal contributions of the left and right cervical vagi to the dorsal trunk were equal.

The control amplitude of contraction (2.24 ± 0.19 kPa, 22.9 ± 1.9 cmH₂O) was not significantly different from any of the amplitudes after vagotomy. The responses immediately after vagotomy (day 1 responses evoked *via* the dorsal trunk, 1.87 ± 0.11 kPa, 19.1 ± 1.1 cmH₂O) were significantly lower than the responses on day 21 (2.33 ± 0.12 kPa, 23.8 ± 1.2 cmH₂O, $p < 0.025$) and on day 84 (2.26 ± 0.14 kPa, 23.1 ± 1.4 cmH₂O, $p < 0.05$) but these differences were small and unlikely to be of great physiological importance. This shows that surgery *per se*, even of the ventral trunk, does not cause changes of the magnitude seen after dorsal vagotomy. Because there were no substantial changes after ventral vagotomy, the ventral groups were not examined further.

Body and gastric weights

To confirm that the allocation of ferrets to different survival groups had been randomly allocated successfully, the body weights of the ferrets which had received dorsal vagotomies were subjected to analysis of variance. Allocation to different survival times had no significant effect ($F = 0.963$, $df = 6$ and 21) indicating the the groups were comparable.

Analysis of variance of the stomach weights of the animals which had received a dorsal vagotomy indicated that there was no significant difference between the groups ($F = 1.669$, $df = 6$ and 21).

Comparison of cervical vagi

The cervical vagi were stimulated at various intensities, from near threshold (4 V) to maximal levels (16 V). The responses to stimulation of either cervical vagus were equal at 8, 12, and 16 V. At 4 V, however, the left vagus evoked responses 50–100% greater than those obtained from the right ($p < 0.02$).

RESPONSES TO STEP INFLATION

Responses to inflation of the stomach after division of both the cervical vagi must reflect intrinsic reflexes or myogenic contraction of the smooth muscle. Changes in either of these non-vagal mechanisms were tested collectively by giving a step inflation of the stomach. Inflation of the stomach with 20 ml warm saline in under 2 s caused an immediate increase in pressure which fell to a plateau within five minutes.

The peak pressure was measured in control ferrets and at various times after dorsal vagotomy (Fig. 3). All groups had a bilateral cervical vagotomy an hour before step inflation of the stomach. After dorsal vagotomy peak pressures rose by more than 30% of the control values (2.18 ± 0.17 kPa, 22.2 ± 1.7 cmH₂O

Fig. 3 Peak pressures in response to 20 ml step inflation after dorsal vagotomy. For the first three days there was an increase in the pressure obtained, but by the fifth day the peak pressure had returned to control levels. These changes are the inverse of those affecting vagal evoked contractions (Fig. 1). ($10 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$)

v 1.63 ± 0.11 kPa, 16.6 ± 1.1 cmH₂O, $p < 0.01$). On day 3 the peak pressures were still significantly raised (2.35 ± 0.25 kPa, 24.0 ± 2.6 cmH₂O, $p < 0.025$). By the fifth day, however, the peak pressures were no longer significantly above control levels, and on subsequent days they returned to the control values.

Enhanced contraction was temporary, therefore, disappearing at the same time (day 5) as the surviving ventral trunk became more effective.

RESTING INTRAGASTRIC PRESSURE

The resting pressure was measured 30 minutes after inflation of the stomach with 20 ml warm saline (Fig. 4). After dorsal vagotomy the resting pressure in-

Fig. 4 Resting pressures with an intragastric volume of 20 ml after dorsal vagotomy. Resting pressure was significantly raised for the first three days after dorsal vagotomy, but it returned to control levels after five days. There was no significant reduction below control levels. ($10 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$)

creased, reaching its highest level three days later (0.76 ± 0.02 kPa, 7.8 ± 0.2 cmH₂O), when it was significantly higher than control levels (0.61 ± 0.04 kPa, 6.2 ± 0.4 cmH₂O, $p < 0.005$). The resting pressure then fell, and by the fifth day it was no longer significantly raised. The pressure on day 3 was significantly higher than on day 7 and on all later days ($p < 0.05$).

Thus dorsal vagotomy had a similar effect on resting pressure as on peak pressure: the increase in resting pressures lasted only until the surviving ventral branch became more effective in evoking gastric contractions (Fig. 1 v Fig. 4). There was no evidence that the resting pressure fell below control levels.

EVOKED CONTRACTIONS AND RESTING PRESSURE

Within hours of vagotomy¹⁴ the regression of evoked contractions (Y) on resting pressure (X) was:

$$Y = 2.61 - 1.74 \times X, n = 64, p < 0.001 \text{ (kPa)}$$

$$Y = 26.67 - 1.74 \times X, n = 64, p < 0.001 \text{ (cmH}_2\text{O)}$$

Evoked contractions in 10 of 12 (83%) of the ferrets in the 0–3 day groups were less than 1.5 cmH₂O above the pressure predicted by this equation, whereas 21 of 28 (75%) of the evoked contractions in the 5–84 day groups were more than 0.15 kPa (1.5 cmH₂O) above the predicted pressure ($\chi^2 = 11.697$, $df = 1$, $p < 0.001$). In short, for a given resting pressure, a greater evoked contraction was obtained after day 5 than before. This is further evidence that

Fig. 5 Relation of vagal evoked relaxation to resting pressure more than one day after dorsal vagotomy (continuous line). For comparison the regression line obtained on the day of vagotomy is included (broken line). There is no evidence of reduced relaxation at a given pressure in the vagotomised group. ($10 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$)

changes in resting pressure did not account for the differences in evoked contractions before and after the fourth day.

VAGAL EVOKED RELAXATION

It might be postulated that an increase in vagal evoked contraction was the result of a selective loss of vagal inhibition, leaving excitatory effects unchallenged. Immediately after 10 s of vagal stimulation there is a contraction followed by a period of relaxation, the latter being an indication of vagally dependent inhibitory processes.²³

Vagal evoked relaxation takes over 10 min to recover even after brief periods of stimulation, so only the first relaxatory response was analysed in each ferret. The relaxation obtained 1–84 days after dorsal vagotomy is plotted *versus* resting pressure in Figure 5. As the resting pressure increased the degree of relaxation also increased. The regression equation was:

$$Y = 0.08 - 0.40 \times X, n = 40, p < 0.001 \text{ (kPa)}$$

$$Y = 0.77 - 0.40 \times X, n = 40, p < 0.001 \text{ (cmH}_2\text{O)}$$

where Y is the degree of relaxation and X is the resting pressure. For comparison the regression line obtained from a control group (one hour after vagotomy) in a previous experiment is also shown in Figure 5. It is evident that the slopes of the two lines are very similar. The degree of relaxation obtained after dorsal vagotomy was marginally greater than in the control group.

Thus there is no evidence for a selective loss of inhibition after dorsal vagotomy nor for an alteration of the relation between vagal evoked relaxation and resting pressure.

Discussion

Two processes appear to affect vagal evoked gastric contractions after partial truncal vagotomy: an early process enhances the contraction of the stomach in response to a step inflation or a static intragastric volume, while a later process coming into effect as the first process wanes, enhances the effectiveness of surviving vagal branches. Enhancement of vagal evoked contractions was not explained by changes in the weights of ferrets or of their stomachs, by a decrease in resting pressure, nor by a differential loss of vagal inhibition.

EARLY CHANGES

Either an increased ability of muscle to contract or an enhanced excitability of the intrinsic reflexes were indicated by the increases in resting and inflation evoked pressure. The changes in peak (Fig. 3) and vagal evoked (Fig. 1) pressures were striking mirror images of each other, suggesting that the increased

effectiveness of the surviving nerve might have been a signal for the disappearance of peripheral compensation, analogous to the loss of extrajunctional receptors after reinnervation of skeletal muscle.²⁴ Changes in the muscle or the intrinsic reflexes did not, therefore, account for the eventual increase in effectiveness of the surviving vagal branches.

These early changes develop at the same time as the hypergastrinaemia which follows vagotomy in dogs²⁵ and man.²⁶ Although gastrin is known to affect the gastric pacemaker and the generation of action potentials,^{27,28} no link with the early changes in the present experiments has been established.

LATER CHANGES

With the exclusion of non-vagal factors and of differential loss of vagal inhibition, the increase in effectiveness of the surviving vagal branches must be caused by changes in the branches themselves or in the distribution of their activity. Possible mechanisms include neuronal sprouting, which could increase the area occupied by preganglionic neurones; increased synaptic density without change in territory; or redistribution of postganglionic neurones.

Autoradiographic studies,¹⁹ done in conjunction with the present study, showed that territorial gains by sprouting did occur, but too late (Al-Muhtaseb, personal communication) and in the wrong trunk to account for the changes in contractility recorded in the present work, although they may be related to later changes in secretion.

While sprouting into neighbouring territory was too late, an early increase in synaptic density within the original territory of the surviving branches is not excluded. Increases in synaptic density²⁹ and the formation of functional synapses³⁰⁻³² occur early enough to account for the enhanced effectiveness of the ventral vagus found on the fifth postoperative day, although there is no positive evidence of this.

An alternative explanation of the results is that after dorsal vagotomy, postganglionic neurones spread into the denervated territory, distributing activity from the ventral vagus.³³

FACTORS GOVERNING THE PHYSIOLOGICAL CHANGES

The fact that dorsal vagotomy caused a substantial increase in the effectiveness of the ventral trunk and not *vice versa* requires explanation, as does the previous finding¹⁷ that left, but not right, cervical vagotomy caused a similar increase.

Differences between branches of the vagus

There has been disagreement over whether the left cervical vagus has gastric effects greater than, or equal to, those of the right in dogs, cats, rabbits,³⁴

rats,³⁵ cats³⁶ and ferrets.²¹ These discrepancies may be resolved by the present finding in the ferret that whereas the cervical vagi evoked equal responses at all suprathreshold levels of stimulation (when smooth muscle imposed a ceiling), at threshold levels the left cervical vagus evoked greater contractions. Those who found a greater potency of the left vagus may have been using lower intensities of stimulation. Sectioning the dorsal trunk or left cervical nerve would cause a greater loss of excitatory activity at low (presumably more physiological) intensities of stimulation than sectioning the ventral trunk or right cervical nerves. Loss of activity is a stimulus to sprouting.^{30,32,37}

The difference in the ability of the ventral and dorsal trunks to evoke gastric contractions relates to the difference in the distribution of these nerves in the ferret.¹⁸⁻²⁰ Nerve evoked gastric activity spreads from one part of the stomach to another only when there is a neural connection present.³⁸

Degeneration as a stimulus

Degenerating nerves induce growth of neurites in neighbouring axons.^{29-31,39} Degeneration of afferents,³⁹ or loss of an inhibitory factor⁴⁰ also induce sprouting in efferent nerves. The dorsal trunk has considerably more afferents than the ventral¹⁸ and this may explain why sectioning the dorsal trunk caused a substantial increase in ventral evoked responses but not *vice versa*. A similar argument has been applied to left *versus* right cervical vagotomy in ferrets.¹⁷

Functional overlap and peripheral ceilings

In intact ferrets stimulation of the dorsal vagus gives a response as great as that obtained from stimulation of both abdominal vagi together,¹⁷ suggesting that the peripheral mechanism imposes a ceiling on the amplitude of evoked contraction¹⁴ which the normal dorsal trunk is capable of reaching independently. Thus plastic changes in the dorsal vagus after ventral vagotomy would not be expected to exceed the ceiling. The normal ventral vagus, on the other hand, cannot usually evoke a maximal contraction. Plasticity occurring in the ventral vagus, therefore, may allow this branch fuller access to the peripheral mechanism and permit visible changes in evoked contraction.

Changes in motility in the first few postoperative days after partial vagotomy involve compensatory mechanisms confined to smooth muscle or its intrinsic plexuses. By the fifth postoperative day, however, surviving branches of the vagus become more effective and the non-vagal compensatory mechanisms disappear. Sprouting of axons into neighbouring territory occurs at three months, too

late to account for the enhanced effectiveness of the surviving vagus. An increase in synaptic density within the original territory must therefore be considered as an explanation. The extent to which these changes apply to man remains to be determined. If early changes in synaptic density do occur, then methods which prevent this^{41,42} may be able to contribute to the reduction of recurrent ulceration, alongside developments in surgical technique which combine the advantages of truncal and parietal cell vagotomy.⁴³

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