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THE CENTRAL CONTROL OF THE LUMBAR SYMPATHETIC PATHWAY TO THE LARGE INTESTINE OF THE CAT

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SUMMARY

1. The origin of the lumbar sympathetic inhibitory outflow to the large intestine was studied by recording simultaneously changes in colonic motility and efferent firing in the lumbar colonic nerves (l.c.n.) following lesions at various levels of the neuraxis.

2. Multiunit recordings from the l.c.n. usually consisted of irregular grouped discharges which were unrelated to spontaneous colonic contractions or to respiratory or cardiac cycles. The firing was depressed by the administration of ganglionic blocking agents or by decentralization of the inferior mesenteric ganglion, indicating that it was post-ganglionic and primarily central in origin.

3. In the majority of experiments colonic motility and l.c.n. firing were not altered by transection of the cervical (C2–C3) or thoracic (T10–T13) spinal cord. However, in these acute spinal animals destruction of the lumbar ventral roots or the lumbar spinal cord markedly enhanced colonic motility and depressed l.c.n. firing. These findings indicate supraspinal mechanisms are not essential for the generation of the lumbar inhibitory outflow to the colon.

4. Transection of the l.c.n. enhanced colonic motility in animals with an intact neuraxis, in acute spinal animals and in animals where the thoracolumbar sympathetic outflow was blocked. It is concluded that peripheral ganglionic as well as spinal pathways can sustain an inhibitory input to the colon.

5. L.c.n. firing was enhanced by stretching or pinching the proximal colon or small intestine or by electrical stimulation of intestinal afferent fibres (Aδ and C fibres) in the l.c.n. and mesenteric branches of the splanchnic nerves. The reflexes occurred via spinal pathways and were blocked by transection of the lumbar dorsal roots. Spontaneous firing in the l.c.n. was also generated by isolated segments of the lumbar spinal cord; however, this firing occurred independently of traditional reflex pathways since it was unaffected by transection of the lumbar dorsal roots. It is concluded that the spontaneous firing must be generated via ventral root afferent pathways or via endogenous oscillator circuits in the lumbar spinal cord.

INTRODUCTION

Interruption of the lumbar sympathetic pathways to the colon enhances colonic motility in experimental animals (Learmonth & Markowitz, 1929; Garry, 1933). This observation suggests that sympathetic nerves exert a tonic inhibitory influence on

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the colon. While the origin of this inhibitory activity has not been definitely established, there is various evidence indicating that it might be initiated via reflexes in (1) peripheral ganglia (Kuntz & Saccomanno, 1944; Szurszewski & Weems, 1976), (2) the spinal cord (Garry, 1933), or (3) supraspinal centres (Hulten, 1969).

The present investigation was undertaken to examine the role of central nervous system in generating the lumbar sympathetic inhibitory input to the colon of the cat. By monitoring, simultaneously, sympathetic efferent firing and colonic motility before and after lesions at various levels of the neuraxis, we obtained evidence that a major part of the efferent inhibitory outflow arose in the lumbar spinal cord and was not dependent on the integrity of supraspinal pathways or afferent input entering the lumbosacral dorsal roots.

Preliminary reports of these observations have been published (Krier & de Groat, 1977; de Groat & Krier, 1977).

METHODS

Experiments were performed on sixty-seven cats of either sex anaesthetized with chloralose (50–70 mg/kg, I.V.) or sodium pentobarbitone (25–30 mg/kg, I.V.) after induction with halothane. Five cats were anaesthetized with urethane (1–1·2 g/kg, I.P.). Following tracheal intubation the colon and its neural connexions with the inferior mesenteric ganglion (i.m.g.) were exposed through a mid line abdominal incision. Post-ganglionic axons from the i.m.g. travel to the colon via the lumbar colonic (l.c.n.) and hypogastric nerves (h.g.n.), while the preganglionic input to the i.m.g. is carried in the inferior splanchnic nerves (Langley & Anderson 1895, Harris, 1943). Usually a number of lumbar colonic nerves (l.c.n.) (four to six) could be identified forming a network around the inferior mesenteric artery. In the majority of experiments two l.c.n. were sectioned at a point 2–3 cm distal to the i.m.g. and prepared for recording efferent activity. The remainder of the fibres were left intact. In some experiments electrodes were placed on intact or sectioned l.c.n. to stimulate afferent axons. Mesenteric nerves which accompany the superior mesenteric artery were isolated at points 2–3 cm peripheral to the coeliac ganglion. Electrodes were placed on these nerves to activate visceral afferent fibres. Renal nerves containing sympathetic post-ganglionic efferent fibres to the kidney were dissected from the adventitia of the left renal artery. These fibres were used to monitor sympathetic vasomotor outflow. In some animals the carotid sinus and the aortic depressor nerves were isolated bilaterally so that they could be stimulated during the course of the experiment. In many preparations a laminectomy was performed at either the cervical, thoracic, or lumbosacral levels so that the spinal cord and spinal roots would be exposed for transection. In these experiments the animal was placed on its side to permit access to both the spinal cord and abdominal cavity.

The isolated nerves were mounted on bipolar silver electrodes for stimulation and recording. Stimulation was produced by rectanglular pulses of 0·05–0·5 msec duration at varying frequencies and intensities. The recorded action potentials were displayed on an oscilloscope and photographed on 35-mm film or averaged with a PDP-8E digital computer, the output of which was then plotted on a Cal Comp plotter. The magnitude of an averaged evoked potential was expressed as its amplitude in microvolts (μV) or as its area in μV sec determined by a computer programme.

In addition to the stimulus-evoked action potentials, asynchronous efferent firing was recorded monophasically from multifibre preparations at an amplifier band width of 0·3–10,000 Hz. The asynchronous firing was displayed on an oscilloscope and photographed on 35-mm film. A quantitative estimate of the firing rate was obtained with a differential amplitude discriminater-ratemeter. The frequency of neuronal firing was displayed on a rectilinear paper recorder.

In some experiments the relationship between efferent firing in l.c.n. or renal nerves and the cardiac or respiratory cycles was examined by cross correlation analysis using a PDP-8E digital computer. Aortic pressure and spontaneous firing were averaged simultaneously for fifty to one-hundred cardiac cycles using the R wave of the e.c.g. to trigger the computer. The correlation between neural activity and respiration was determined in a similar manner using thoracic expansion (pneumograph) as a monitor of respiration. The computer averages of neural activity,

blood pressure, and respiration were plotted on a Cal Comp plotter. The patterns of neural activity were also studied using autocorrelation analysis.

Arterial pressure was monitored from either the carotid or femoral artery with a strain gauge pressure transducer. End-tidal CO_2 was measured with a Beckman Medical Gas Analyzer. In many experiments the animals were paralysed by the intravenous administration of pancuronium

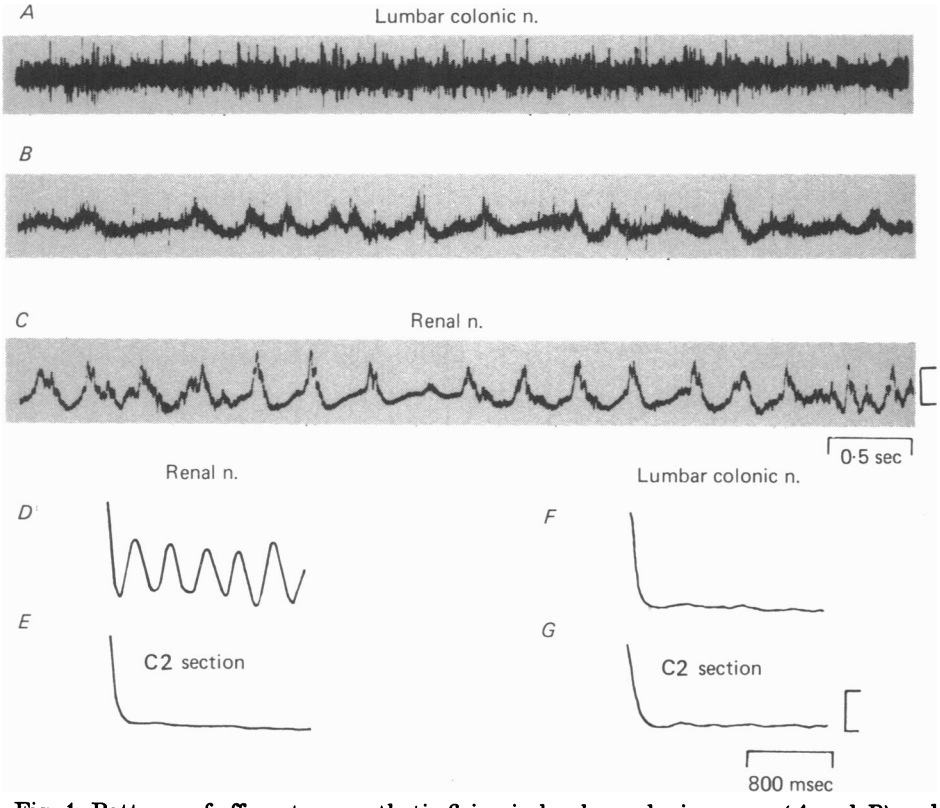

Fig. 1. Patterns of efferent sympathetic firing in lumbar colonic nerves (*A* and *B*) and renal nerves (*C*). Records *A* and *B* depict, respectively, tonic and irregular grouped discharge patterns in lumbar colonic nerves. Record *C* was obtained in the same experiment as *B* and depicts synchronous grouped discharges in a renal nerve. Horizontal calibration in *C* also refers to records *A* and *B*. Vertical calibration in *C* is equal to 75 μV, negativity upward and refers also to *A* and *B*. Records *D*, *E* and *F*, *G* depict, respectively, the autocorrelation functions of the neural discharge in renal and lumbar colonic nerves before (*D* and *F*) and after (*E* and *G*) transection of the spinal cord at the second cervical level. Horizontal calibration and vertical calibration (100 μV) in *G* refers also to records *D*–*F*.

bromide (0·15 mg/kg, I.V.) and artifically expired. In these animals end-tidal CO_2 was maintained between 3·5 and 4 % by regulating the rate and depth of ventilation. Experience with unparalysed preparations indicated that the dose of chloralose administered was sufficient to produce surgical anaesthesia for the duration of the experiments. In addition, during the experiments depth of anaesthesia was often checked by discontinuing the administration of pancuronium and allowing the animal to recover from paralysis.

Colonic motility was measured with water filled ballons which were attached to flexible polyethylene tubing. Pressures were recorded simultaneously from two regions of the colon (i.e. proximal and distal colon) or from the rectum and one region of the colon. Colonic balloons were 2·5 cm in length (uninflated) whereas the rectal balloon was smaller (1·5 cm in length, uninflated). In most experiments the balloons were tied to a metal rod which was inserted into the

anal canal. The rod was fixed to a frame supporting the animal so that the ballon did not move. The animals body temperature was maintained 36–38° with a heating pad.

The following drugs were used: atropine sulphate, hexamethonium bromide, nonadrenaline bitartrate, phenylephine hydrochloride, tetraethylammonium bromide and 2-diethoxyphosphenylthioethyldimethylamine acid oxalate (217A0).

RESULTS

Efferent discharge in lumbar colonic nerves

Patterns of firing. The lumbar colonic nerves (l.c.n.) subserve various functions including intestinal inhibition, vasomotor control and regulation of sphincter tone (Hulten, 1969; Garrett, Howard & Jones, 1974; Pahlin & Kewenter, 1976; Gillespie &

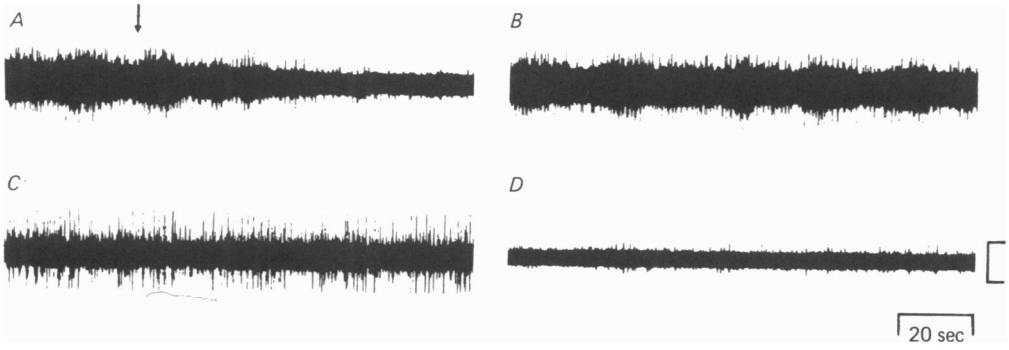

Fig. 2. Spontaneous efferent discharge in lumbar colonic nerves. Record *A* represents the discharge before and after (at the arrow) the intravenous injection of tetraethylammonium (TEA, 200 μg/kg, I.V.), a ganglionic blocking agent. Record *B* represents the response 25 min after the administration of TEA. Records *C* & *D* depict the discharge in another experiment, before (*C*) and after (*D*) transection of the preganglionic fibres to the inferior mesenteric ganglia. Horizontal calibration in *D* refers also to records *A*–*C*. Vertical calibration in *D* is equal to 75 μV, negativity upward and refers also to records *A*–*C*.

Khoyi, 1977). It was not unexpected, therefore, that multifibre recordings from l.c.n. might yield different patterns of activity. In cats anaesthetized with chloralose, pentobarbitone or urethane grouped discharges (Fig. 1*B*) were the most common type of activity although in very thin l.c.n. fibres a tonic asynchronous discharge could be recorded, presumably from a very small number of axons (Fig. 1*A*). In most experiments (fifty-three of sixty-three) the grouped dischages occurred at irregular intervals (Fig. 1*B*). Less frequently (ten of sixty-three experiments) rhythmic firing was correlated with either the respiratory or cardiac cycles or with Mayer waves (Fig. 3*J*, *K*, *M*, *N*) (Preiss & Polosa, 1974).

The irregular pattern of l.c.n. firing was also confirmed by autocorrelation analysis. In eleven of sixteen experiments the autocorrelation function of l.c.n. activity did not reveal a periodic component (Fig. 1*F*, *G*). In the remaining experiments a 2–3 Hz periodicity was observed. A similar periodicity was observed more consistently (nine of eleven experiments) (Fig. 1*C*) in recordings and autocorrelograms (Fig. 1*D*) obtained from the renal nerve, a nerve which contains primarily sympathetic vasoconstrictor efferents. The 2–3 periodicity recorded on both nerves was linked

with the cardiac cycle (*vide infra*). A 10 Hz periodicity which has been observed on other sympathetic nerves (Cohen & Gootman, 1970; McCall & Gebber, 1975) was never evident in autocorrelograms of l.c.n. activity.

Origin of firing. Firing in the l.c.n. was blocked by the administration of ganglionic blocking agents (Fig. 2*A*) (hexamethonium, 0·05–0·1 mg, I.A., 0·1–0·2 mg/kg, I.V.;

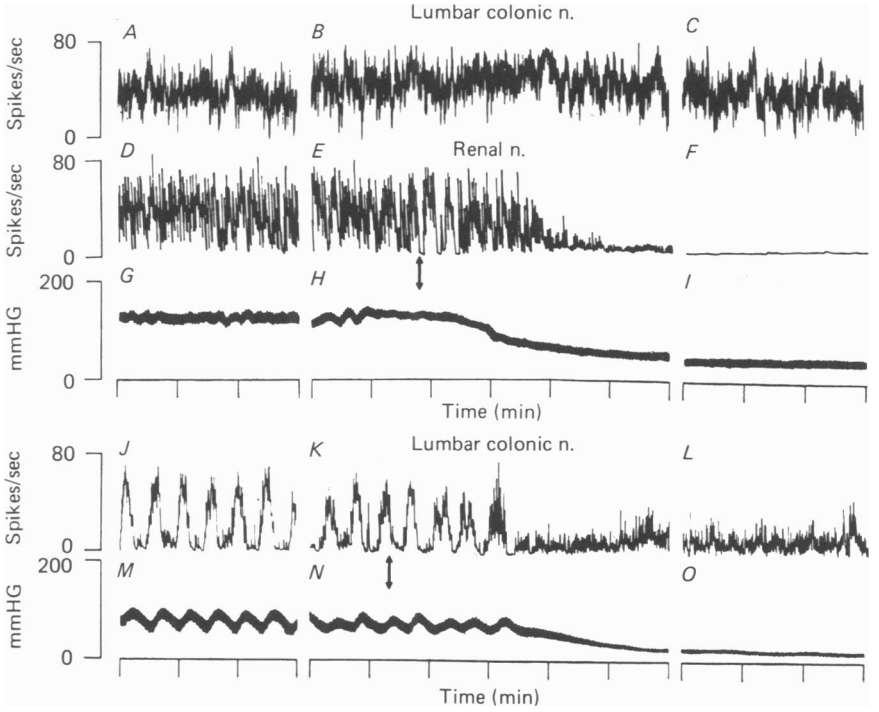

Fig. 3. *A–I*, simultaneous recordings of efferent firing in lumbar colonic (*A–C*) and renal nerves (*D–F*) and arterial B.P. (*G–I*). Records *A*, *D* and *G* depict the control responses while records *B*, *E* and *H* depict the responses before and after the intraspinal injection of procaine (0·3 ml. 1 % solution) into the cervical spinal cord (C2). The arrow indicates the injection of procaine. Records *C*, *F* and *I* depict the responses 3 min after transection of the spinal cord. Horizontal calibration is equal to 1 min per division. Vertical calibrations are equal to B.P. expressed in mmHg and the neural discharge expressed in spikes per second. *J–O*, simultaneous recordings of efferent firing in lumbar colonic nerve (*J–L*) and arterial pressure (*M–O*) in another experiment. Records *J* and *M* represent the control responses while records *K* and *N* depict the responses before and after the injection (indicated by arrows) of procaine into the cervical spinal cord (C2). Records *L* and *O* depict the responses 5 min after transection of the spinal cord. Vertical calibrations are equal to the neural discharge expressed in spikes per second and the systemic arterial pressure expressed in mmHg. Horizontal calibration is equal to 1 min per division.

tetraethylammonium, 0·1–0·2 mg, I.A.) and was markedly reduced by transection of the inferior splanchnic nerves (Fig. 2*D*). These data indicate the firing occurred in post-ganglionic axons and originated central to the inferior mesenteric ganglia. The origin of this firing was examined further by noting changes in activity following: (1) transection of the spinal cord at various levels, (2) transection of the lumbar dorsal

and ventral roots, (3) transection of the peripheral innervation to the colon, (4) destruction of the thoracic or lumbar segments of the spinal cord.

Rhythmic firing in the l.c.n. associated with Mayer waves and firing in the renal nerve (eight experiments) were abolished by transection of the cervical spinal cord (Figs. 1*E*, 3*E*, *F*, *K*, *L*). On the other hand, in the majority of experiments (sixteen of twenty) non-rhythmic grouped discharges and tonic firing on l.c.n. were not altered

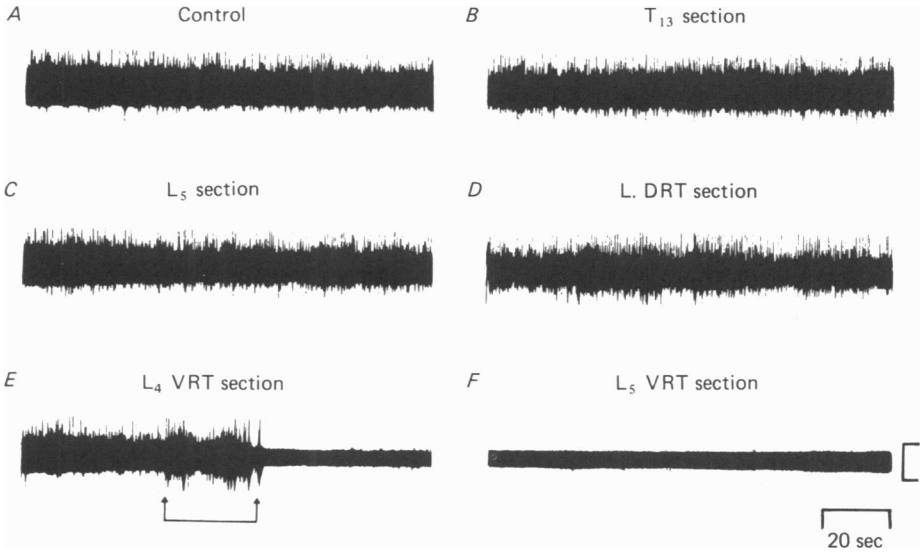

Fig. 4. Spontaneous discharge recorded in lumbar colonic post-ganglionic fibres. Record *A* represents the control response while records *B* and *C* depict the discharge after transection of the spinal cord in the lower thoracic (T13) and lower lumber levels (L5), respectively. *D*, spontaneous discharge in an isolated segment of the lumbar cord after bilateral transection of the lumbar dorsal roots (L1–L5). *E*, the discharge after bilateral transection of the lumbar ventral roots (L1–L3) and the depression of firing accompanying bilateral transection of the L4 ventral roots. *F*, depicts the spontaneous discharge after bilateral transection of the L5 ventral root. Horizontal calibration in *F* refers also to records *A*–*E*. Vertical calibration in *F* is equal to 50 μV, negativity upward.

by cervical cord transection (Fig. 3*B*, *C*). In four experiments, the firing was depressed 40–70% but in three of these it recovered to control levels within 15–30 min after transection.

L.c.n. firing also was not altered by spinal cord transection at T10–T13 in five of seven preparations (three cervical spinalized preparations, four intact spinal cord). In two experiments, however, in which the cervical cord had already been transected, section of the lower thoracic cord at the T13 level did reduce the tonic discharge by 20–50%. In all of these preparations, the upper thoracic cord was then destroyed by passing a flexible metal rod within the vertical canal from T13 to T1. This procedure also did not depress the discharge.

The contribution of sacral afferent fibre input to the tonic sympathetic discharge was also determined in six spinal cats. Bilateral transection of the sacral dorsal and ventral roots or section of the lumbar cord at the L5 level (Fig. 4*C*) did not reduce the level of the l.c.n. activity.

L.c.n. activity, however, was dependent upon preganglionic outflow from the lumbar segments of the spinal cord. This was demonstrated in four experiments where the upper lumbar segments were first isolated by transecting the cord at the L5 and T13 levels, and the thoracic cord was destroyed. These procedures did not depress the sympathetic firing. The lumbar dorsal roots from the L1 to L4 segment were then sectioned bilaterally without altering the spontaneous discharge (Fig. 4*D*). However, the injection of procaine into the cord at the L3–L4 level or sectioning the lumbar ventral roots bilaterally (four experiments) markedly depressed the discharge (Fig. 4*F*). These experiments indicate that the discharge on l.c.n. was spinal in origin and not dependent on afferent fibre input entering the cord via the dorsal roots. However, it should be noted that in the cat there is considerable evidence that the lumbar ventral roots contain afferent as well as efferent fibres (Coggeshall, Coulter & Willis, 1974). It was not possible to assess the contribution of ventral root afferent fibres to efferent firing in these preparations since sectioning the lumbar ventral roots would have abolished the preganglionic efferent outflow as well as afferent input to the cord. However, a major role of colonic afferent fibres in the generation of the firing was excluded by experiments in which peripheral nerves were sectioned. Section of the hypogastric nerves bilaterally or section of the remaining l.c.n. did not depress the l.c.n. firing in animals where the lumbar cord had been isolated previously by section at T13 and L5. In addition, similar l.c.n. activity was recorded in animals where the large and small intestine had been removed.

It is noteworthy, that after destruction of the thoracic and lumbar segments of the cord or section of the preganglionic fibres to the inferior mesenteric ganglia, a low level asynchronous l.c.n. discharge was present (Fig. 2*D*). The discharge represented in part activity in post-ganglionic axons since it was depressed by the administration of ganglionic blocking agents (tetraethylammonium, 0·1–1 mg/kg, I.V.). In four of five experiments the discharge was unaffected by transection of the hypogastric nerves or the remaining l.c.n., but in one experiment, transection of the remaining l.c.n. reduced the discharge by 40%.

Origin of l.c.n.-inhibitory input to the colon

To study the origin of l.c.n.-inhibitory input to the colon, a series of ablation experiments similar to those described in the previous section were conducted to record the changes in colonic motility following acute spinal transection, destruction of the lumbar cord or transection of the l.c.n. The data are summarized in Table 1.

The first set of experiments examined a possible supraspinal contribution to the inhibitory pathway by determining the effect of spinal transection and the effects l.c.n. transection in intact and acute spinal preparations. The animals were anaesthetized with chloralose. Most of the preparations had the abdomen open to allow simultaneous recording of neural activity, but similar results were obtained with the abdomen closed.

In ten of fourteen experiments the injection of procaine into the spinal cord at the C2 (seven experiments) or the T1 level (three experiments) followed by cord transection did not alter colonic activity (Fig. 5*A*). In four experiments the injection of procaine at C2 produced a transient increase (0·5–2 min) in base line colonic pressure. Subsequent transection of the cord did not produce a further enhancement. These

responses were observed in two experiments where the pelvic nerves were sectioned bilaterally to block the parasympathetic excitatory outflow to the colon and in two experiments where the latter nerves were intact.

TABLE 1. Changes in colonic motility following destruction of central and peripheral neural pathways

	Colonic motility increased*	Colonic motility unchanged*
Spinal transection at C2 or T10	4	10
Ablation of L1–L5 spinal segments†	6	2
Transection of l.c.n.		
Intact spinal cord	9	0
Acute spinal	4	0
After ablation of T1–L5 spinal segments	6	2

* Number of experiments.

† L1–L5 segments isolated by transections at T13 and L6 before ablation.

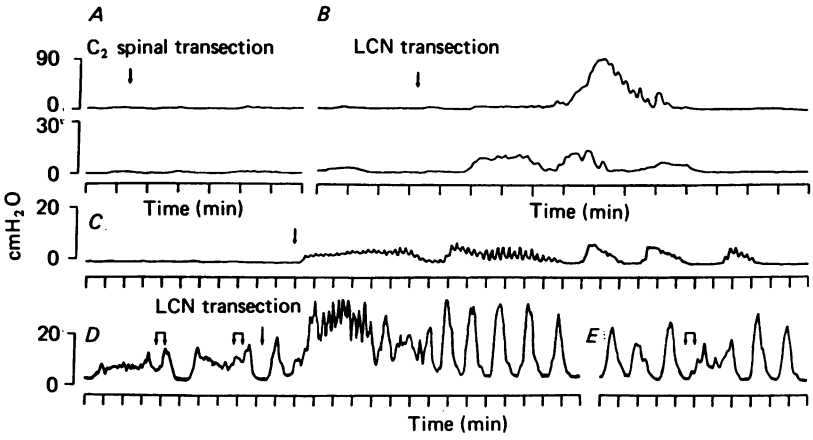

Fig. 5. Effects of local anaesthetic block and transection of the spinal cord and transection of the lumbar colonic nerves on the spontaneous activity of the colon and rectum. *A*, spontaneous contractions in the mid colon (upper trace) and rectum (lower trace). The arrow indicates the injection of procaine (0·3 ml. 1 % solution) into the cervical spinal cord (C2). *B*, activity of the mid colon and rectum in the same experiment 20 min after transection of the cervical spinal cord (C2). At the arrow the l.c.n. were sectioned. *C*, spontaneous activity of the distal colon in another experiment after transection of the cervical spinal cord (C2). The arrow indicates the injection of procaine (0·3 ml. 1 % solution) into the lumbar spinal cord (L2–L4). *D* and *E*, spontaneous activity of the proximal colon in another experiment 40 min after destruction of the lumbar and thoracic spinal cord. *D* and *E*, spontaneous colonic activity before and 20 min after transection of the lumbar colonic nerves. Double arrows in *D* and *E* indicate neurally evoked (electrical stimulation of the S2 VRT) contractions of the colon before and after transection of the lumbar colonic nerves. Vertical calibrations are the colonic and rectal pressures expressed in cm H_2O. Horizontal calibrations in *A*–*E* are equal to 1 min per division.

The effect of l.c.n.-transection on colonic motility was tested in nine animals with an intact neuraxis and in four animals after the spinal cord had been transected at C2. In all experiments, transection of the l.c.n. enhanced the resting tone (base line pressure) for periods ranging from 4 to 21 min (mean 12·2 min) and increased the

spontaneous activity (Fig. 5*B*). During the initial rise in colonic pressure the entire colon contracted and the recording balloons, if not fixed in place, were moved in the aboral direction and expelled through the anus. Slow rhythmic pressure waves, which in many experiments were not detectable before l.c.n. transection, were very prominent after transection (Fig. 5*E*).

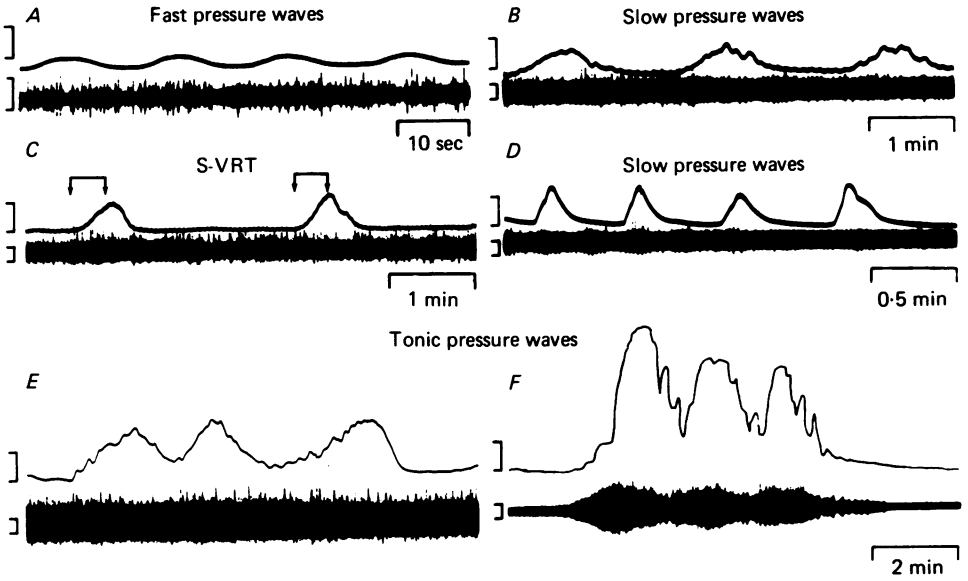

Fig. 6. Relationship between firing recorded in lumbar colonic nerves and spontaneous and stimulus evoked colonic contractions. The upper records in *A–E* represent the intraluminal pressures in five experiments recorded in the proximal (*A* and *D*) and distal colon (*B*, *C*, *E*) while the lower traces represent the neural discharge recorded in lumbar colonic nerves (l.c.n.). The records show the lack of correlation between the firing and: (*A*) fast pressure waves, (*B*, *D*) slow pressure waves, (*C*) pressure waves elicited by electrical stimulation of the S2 ventral root at 10 V, 10 c/s (0.05 msec duration), (*E*) a tonic pressure wave. *F*, the correlation between a tonic pressure wave and the neural discharge in sacral parasympathetic postganglionic fibres in another experiment. Upper vertical calibrations in records *A–F* are equal to 10, 25, 30, 50, 60, and 30 cm H_2O respectively. Lower vertical calibrations in records A–F are equal to 40, 60, 70, 50, 40, and 60 μV, respectively. Horizontal calibrations in *F* refers also to record *E*.

A second series of experiments examined the alterations in spontaneous colonic activity following destruction of L1–L5 spinal segments, and subsequent transection of the l.c.n. These experiments were performed in spinal cats (C2) or where the upper lumbar segments had been isolated by sections at T13 and L5. In six of eight experiments, the injection of procaine into the isolated segment of lumbar cord (L1–L5) followed by removal of the isolated cord enhanced base line intracolonic pressure and unmasked or enhanced slow rhythmic pressure waves in the mid-distal colon (Fig. 5*C*). Subsequent transection of the l.c.n. in these animals increased base line tone for periods of 5–60 min (six of eight experiments) (Fig. 5*D*) and increased the amplitude of slow rhythmic pressure waves by 20–50%. These data indicate that the isolated lumbar spinal cord as well as peripheral ganglia (Kuntz & Saccomanno, 1944; Szurszewski & Weems, 1976) can generate a tonic inhibitory input to the colon.

Reflex control of the efferent activity in l.c.n.

Relationship between intestinal motility and spontaneous l.c.n. firing. In twenty-five experiments efferent firing in l.c.n. and intraluminal pressure in the colon and rectum were recorded simultaneously. L.c.n. firing was not correlated with spontaneously occurring rhythmic (i.e. fast and slow) pressure waves (de Groat & Krier, 1978) (Fig. 6*A*, *B*, *D*), or with colonic contractions evoked by electrical stimulation of the sacral parasympathetic outflow to the colon (Fig. 6*C*). L.c.n. firing also did not change during the occurrence of non-rhythmic (tonic) pressure waves (Fig. 6*E*) which were

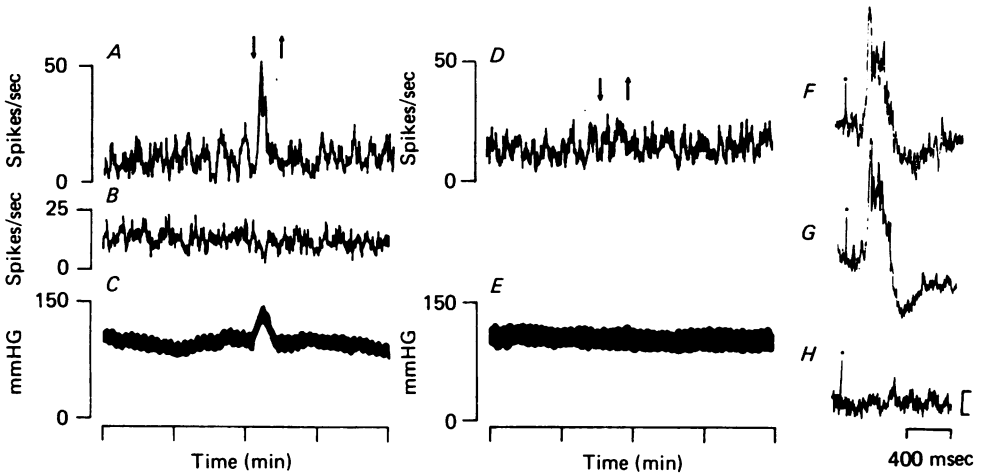

Fig. 7. Effects of colonic distention on efferent firing recorded in lumbar colonic (*A* and *D*) and renal nerves (*B*) and arterial blood pressure (*C* and *E*). Records *A*–*C* depict the responses during the addition and removal of 8 ml. fluid (indicated by arrows) to the proximal colon recording balloon. *D* and *E* depict the responses in the same experiment during distention of the mid colon with the same volume (indicated by arrows). Vertical calibrations are equal to the neural discharge in spikes per second and B.P. in mmHg. *F*, synchronous reflex discharges recorded in lumbar colonic post-ganglionic axons in response to stimulation of afferent fibres in mesenteric branches of the splanchnic nerves. *G*, the synchronous discharge 5 min after transection of the thoracic (T13) and lumbar cord (L5). *H*, depression of the response after bilateral transection of the lumbar dorsal roots (L1–L4). Vertical calibration in *G* is equal to 40 μV, negativity upward.

associated with a large increase in firing in sacral parasympathetic fibres (de Groat & Krier, 1978) (Fig. 6*F*). L.c.n. activity was not altered by atropine in doses (5–20 μg, I.A.) that depressed colonic motility (two experiments) (de Groat & Krier, 1978).

Effects of intestinal distention on the spontaneous l.c.n. firing. Distention of the rectum or colon (proximal, mid. or distal) by addition of 1 or 2 ml. of fluid to the recording balloons did not elicit a detectable change in l.c.n. activity, although this amount of distention was sufficient to reflexly activate the sacral parasympathetic pathway to the colon (de Groat & Krier, 1978). However, rapid distention of the proximal colon, caecum or small intestine with 6–10 ml. fluid or stretching or pinching these structures with forceps evoked a transient increase in efferent firing in the l.c.n. but not in the renal nerves (Fig. 7*A*). Similar stimuli to the rectum or mid-distal colon did not elicit a response (Fig. 7*D*). Relatively large intracolonic pressures were

necessary to evoke l.c.n. firing. The application of 10–40 cm H_2O constant pressure to balloons in the proximal colon did not evoke a detectable response, whereas 45–80 cm H_2O pressure produced graded increases in firing (two experiments). The firing did not adapt when the pressure was held constant for periods of 2–3 min but rapidly

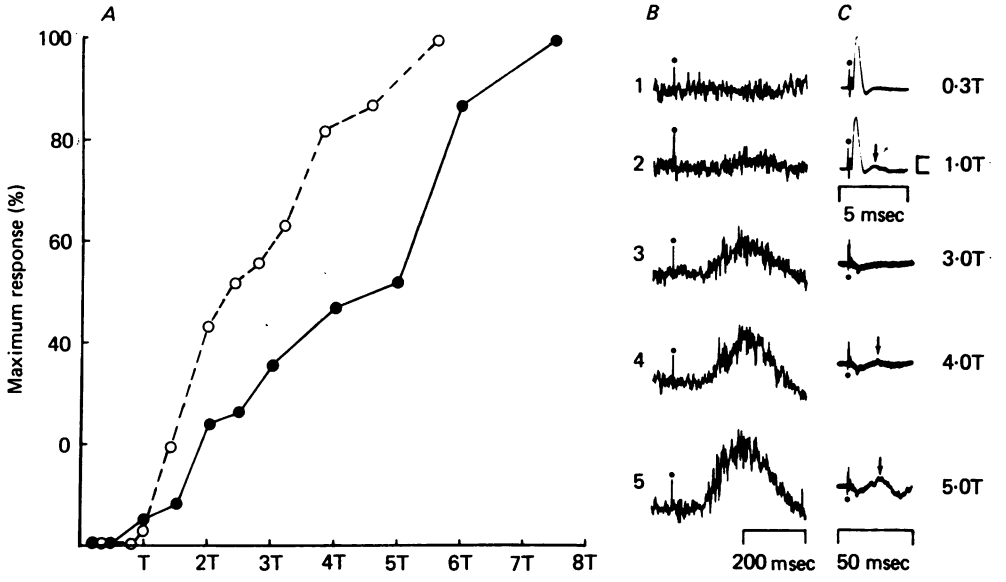

Fig. 8. *A*, plot of the relationship between the intensity of stimulation of afferent fibres in the lumbar colonic nerve (○—○) and in mesenteric branches of the splanchnic nerves (●—●) and the post-ganglionic discharges in lumbar colonic nerves. Ordinate: area of the post-ganglionic discharges expressed as a percentage of the maximum response. Abscissa: intensity of stimulation expressed as multiples of the threshold for evoking a reflex discharge. Simultaneous recordings of the afferent volley in mesenteric nerves (record *C*) and the reflex sympathetic discharge in lumbar colonic nerves (record *B*) evoked by stimulation of afferent fibres in mesenteric branches of the splanchnic nerves. The numbers to the right of record *C* indicate the intensities of mesenteric nerve stimulation expressed as multiple of the threshold for evoking a reflex discharge. Records *B* and *C* were obtained in the same experiment as record *A*. Records *C* and *B* depict, respectively, a short latency afferent volley (Aβ) in mesenteric nerves which occurred below the threshold for evoking a reflex discharge in lumbar colonic nerves. *C*–2, longer latency afferent volley (Aδ) in mesenteric nerves (indicated by the arrow) at the threshold (*B*–2) for evoking a reflex discharge. Records *C*–4, *C*–5 depict long latency C fibre volley in mesenteric nerves (indicated by arrows) at stimulus intensities four and five times the threshcld for evoking the sympathetic reflex. Calculated conduction velocities of the Aβ, Aδ, and C fibre afferent volleys were 72, 12 and 0·9 m/sec, respectively. Horizontal calibration in *B*–5 is equal to 200 msec and refers also to records *B*–1 and *B*–4. Horizontal calibration in *C*–2 refers also to record *C*–1. Horizontal calibration in *C*–5 refers also to records *C*–3 and *C*–4. Vertical calibation in *C*–2 is equal to 75 and 40 μV, negativity upward and refers respectively to all records in *B* and *C*.

returned to control levels following termination of the pressure stimulus. Distention or stretch-evoked increases in l.c.n. activity were accompanied by increases in blood pressure (Fig. 7*C*) but not by detectable changes in colonic motility as might be expected if the firing were occurring in a colonic inhibitory pathway. The reflexes

were observed in acute spinal animals and in animals with an intact spinal cord. They were abolished after the injection of procaine into the lumbar cord or after transection of the inferior splanchnic nerves, but were unaffected by transection of the remainder of the l.c.n.

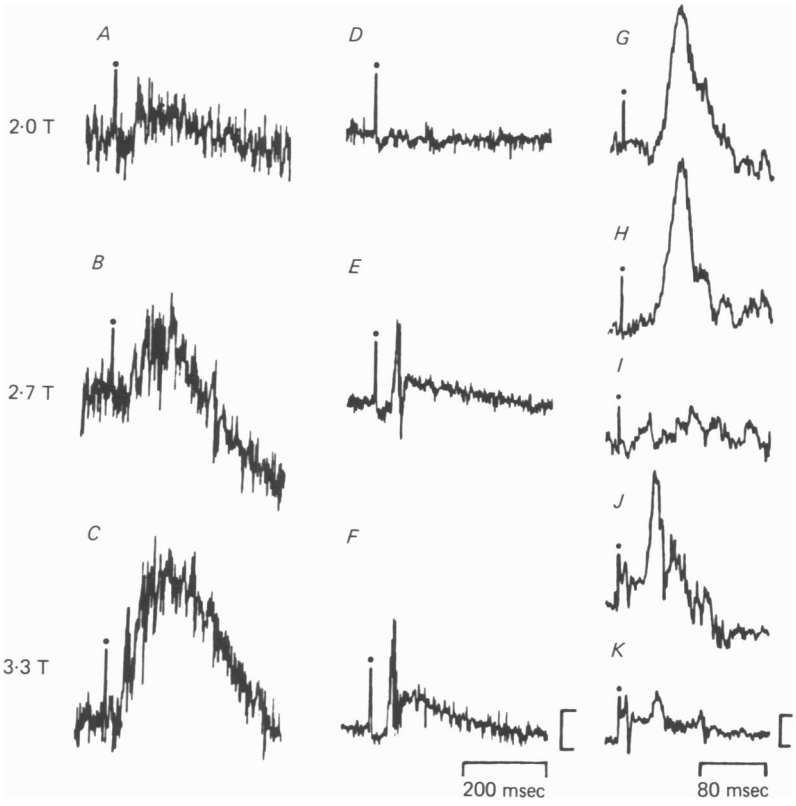

Fig. 9. Reflex discharges recorded in lumbar colonic post-ganglionic fibres in response to stimulation of afferent fibres in lumbar colonic nerves. Numbers to the left of records *A–C* refer also to records *D–F* and indicate the intensities of afferent stimulation expressed as multiples of the threshold for evoking a reflex discharge. *D–F*, reflex discharges in the same experiment after transection of the inferior splanchnic nerves. Records *G–K* represent the reflex discharges recorded in another experiment. *G*, the control response to electrical stimulation of lumbar colonic afferent fibres (10 V). *H*, discharge after transection of the lower thoracic (T13) and lower lumbar (K5) spinal cord. *I* and *J*, responses after bilateral transection of the lumbar dorsal roots (L1–L4) at intensities of 10 and 30 V, respectively. *K*, discharge elicited by 30 V stimulation after intravenous administration of tetraethylammonium (250 μg/kg, I.V.), a ganglionic blocking agent. Horizontal calibration in *K* refers also to records *G–J*. Horizontal calibration in *F* refers also to records *A–E*. Vertical calibration in *F* is equal to 50 μV, negativity upward and refers also to records *A–E*. Vertical calibration in *K* is equal to 40 μV, negativity upward and also refers to records *G–J*. All records are the computer averages of ten individual responses.

Effects of electrical stimulation of visceral afferents on l.c.n. firing. Electrical stimulation of afferent fibres in the l.c.n. evoked synchronous reflex responses in l.c.n. post-ganglionic fibres at latencies of 40–75 msec (mean 60 msec, eight experiments, Fig. 9*A*, *C*). The threshold stimulus necessary to produce a detectable response ranged

between 1 and 4·5 V (mean 2·4 V). Small reflex discharges were also recorded on the hypogastric and renal nerves at latencies ranging from 25 to 30 msec and from 55 to 65 msec, respectively.

The conduction velocities of the afferent fibres evoking l.c.n.-reflexes was determined in three experiments. The most rapidly conducting axons (Aβ, 50–70 m/sec); in the l.c.n. were maximally activated at stimuli (0·1–0·9 V) below the threshold stimulus necessary to produce a reflex response. Axonal volleys with conduction velocities of 8–12 m/sec (Aδ fibres) were detected at the threshold stimulus for evoking a reflex and C fibre volleys was elicited when the reflex response was 50–60 % of the maximum (i.e. at stimulus intensities three to five times the afferent threshold for the Aδ fibres) (Fig. 8*A*). The l.c.n. reflexes were depressed by the intra-arterial administration of hexamethonium (0·05–0·5 mg) but were unaffected by transection of the spinal cord at T10–T12 (seven experiments), L1 (two experiments), or L5 (three experiments). The reflexes were markedly reduced (80–90 %) by sectioning the lumbar dorsal roots (L1–L4, two experiments), or by removal of the lumbar spinal cord (four experiments) (Fig. 9*I*). However, in four of six experiments where the inferior splanchnic nerves were transected or the lumbar cord or roots were ablated, short latency discharges occurred in the l.c.n. in response to electrical stimulation of the same branch or other branches of the l.c.n. (Fig. 9*D*, *E*, *F*, *J*). The discharges were composed of synaptic and non-synaptic components and occurred only at high intensities of stimulation that activated C fibres (7–40 V). In two experiments the intravenous administration of hexamethonium depressed the discharges indicating that the responses represented activity in post-ganglionic axons (Fig. 9*K*). In one other experiment the responses were resistant to the I.V. administration of hexamethonium, indicating that they were non-synaptic occurring either in afferents or preganglionic fibres.

Electrical stimulation of afferents in mesenteric branches of the splanchnic nerves also evoked reflexes in l.c.n. (twelve experiments) at latencies ranging from 70 to 150 msec (mean 95 msec). Reflex discharges were first detected at stimulus intensities which activated Aδ fibres (conduction velocities ranging from 12 to 33 m/sec) and increased in magnitude as stimuli were raised above the intensity sufficient to activate C fibres (3·5–4·5 $\times T$ for the l.c.n. reflexes) (Fig. 8). Afferents with conduction velocities of 50–70 m/sec (Aβ) did not appear to contribute to the reflexes. The reflexes were depressed by the intravenous administration of hexamethonium indicating that they represented activity in post-ganglionic axons. The mesenteric-l.c.n. reflexes were organized in the lumbar cord since the discharges were not altered by transection of the cord between T10–L1 (six experiments), or at L5 (six experiments). The reflexes were totally abolished, however, by either sectioning the lumbar dorsal roots (L1–L4), inferior splanchnic nerves, or by injecting procaine into the lumbar cord at the L3 level (four experiments) (Fig. 7*H*). Activation of mesenteric Aδ and C fibres also elicited discharges in renal (Fedina, Katunski, Kharjutin & Mitsanyi, 1966) and hypogastric nerves as well as the lumbar sympathetic chain (L5) (three experiments), at latencies of 117–121, 75–85 and 117–140 msec, respectively.

Relationship between the cardiac-respiratory cycles and l.c.n. and renal nerve acitivity. All experiments were performed on chloralose anaesthetized cats with an intact spinal cord. Gross inspection of renal nerve activity as well as cross-correlation analysis revealed that the efferent firing on this nerve was synchronized with the

cardiac cycle (eight of ten experiments, Fig. 10*C*). Peak firing was noted during early systole. A similar correlation for l.c.n. activity was detected in the computer averaged records in five of fifteen experiments, but was not obvious in the gross neurograms. As illustrated in Fig. 10*A*, in most preparations cross-correlation analysis of the irregular grouped discharges in l.c.n. exhibited no cardiac synchronization.

In normally respiring animals activity in renal nerves was not modulated by the respiratory cycle. However, when the animals were paralysed and artifically respired,

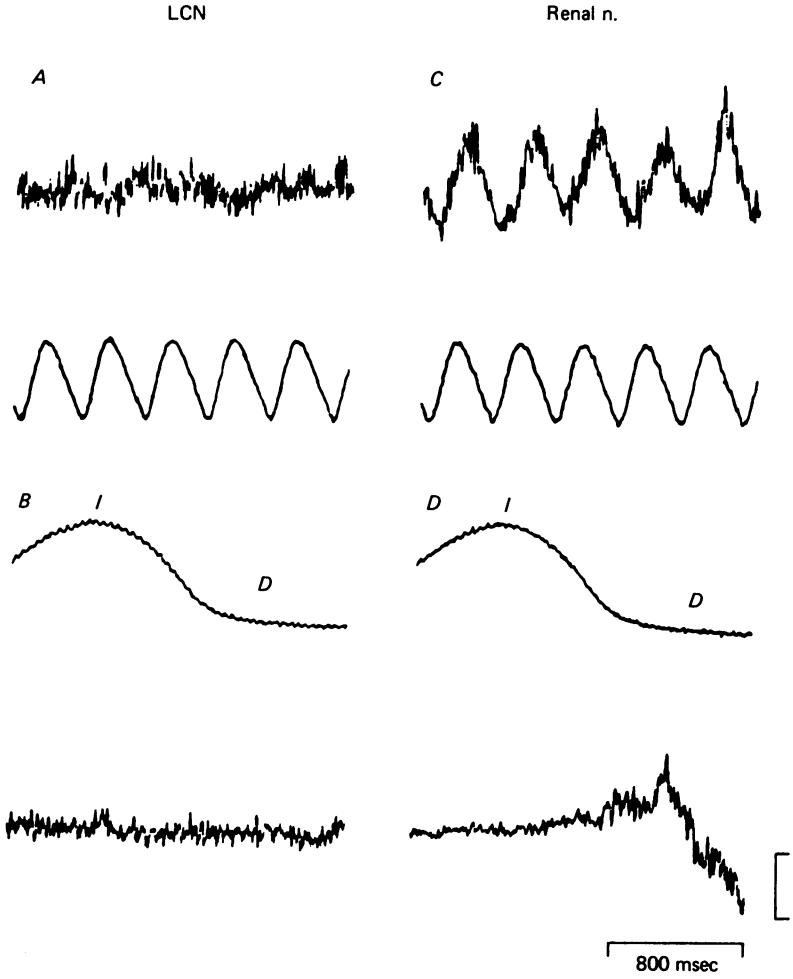

Fig. 10. Relationships between efferent firing in the l.c.n. and renal nerves and the cardiac or respiratory cycle. The upper traces in records *A* and *C* depict the computer average of the sympathetic discharge in l.c.n. and renal nerves, respectively, while the lower traces represent the computer average of arterial B.P. Records *B* and *D* depict the relationship between the respiratory cycle (upper traces) and neural discharge (lower traces) in l.c.n. and renal nerves. Data was obtained in an artifically respired, paralysed preparation. *D* and *I* indicate deflation and inflation, respectively. Records *A–D* were obtained from the same animal. Horizontal calibration in *D* refers also to records *A–C*. Vertical calibration in record *D* is equal to 80 μV, negativity upward and refers also to the upper traces of records *A–C*. Each record represents the computer average of forty sweeps.

spontaneous firing in renal nerves increased during deflation (expiration) and decreased during inflation (inspiration) (Fig. 10) (five of seven experiments). A similar pattern of activity was noted in l.c.n. in only three of ten experiments.

Baroreceptor and chemoreceptor modulation of l.c.n. and renal nerve activity. In nine cats (three urethane anaesthetized and six chloralose anaesthetized) the discharge in l.c.n. and renal nerves was monitored during activation of baroreceptor afferent fibres. In nine experiments electrical stimulation of the aortic depressor nerve at intensities and frequencies that produced a fall in blood pressure (1–3 V, 10–100 c/s) virtually

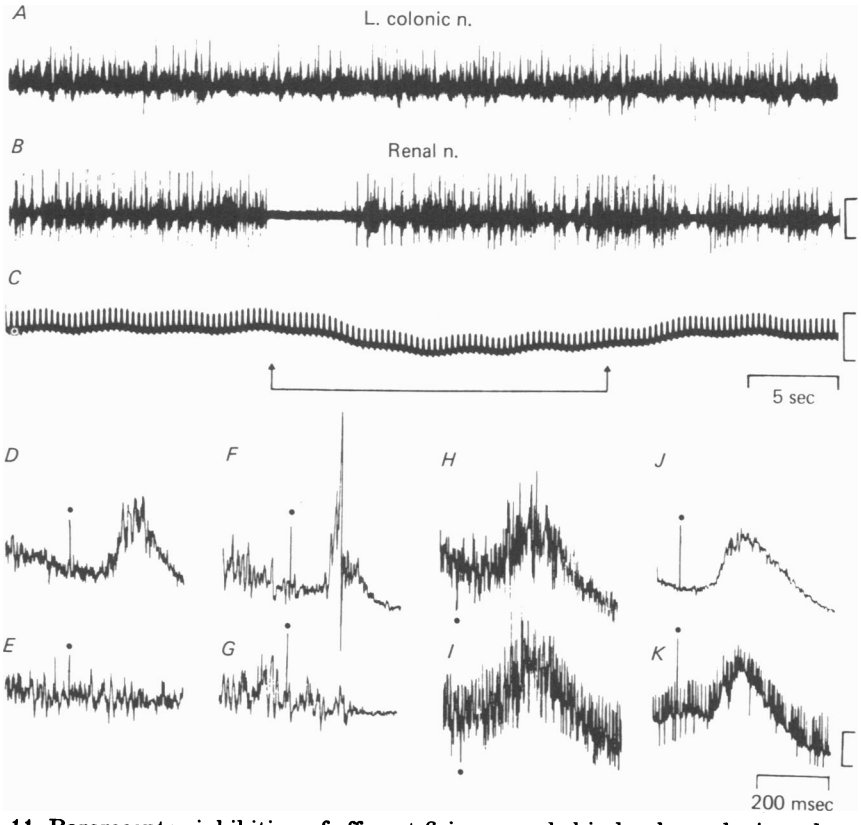

Fig. 11. Baroreceptor inhibition of efferent firing recorded in lumbar colonic and renal nerves. Spontaneous discharge recorded in lumbar colonic (*A*) and renal nerves (*B*) and the arterial blood pressure (*C*) during electrical stimulation of the aortic depressor nerves (1 V, 70 c/s, 0·05 msec duration) (indicated by arrows). *D–G*, records obtained in another experiment showing reflex responses in lumbar colonic (*D* and *E*) and renal nerves (*F* and *G*) evoked by electrical stimulation of the carotid sinus nerve (10 V, 0·5 c/s, 0·05 msec duration). *E* and *G*, depression of the reflexes during electrical stimulation of the aortic depressor nerves (2 V, 100 c/s, 0·05 msec duration). *H–K*, records of reflex discharges evoked in lumbar colonic post-ganglionic axons by electrical stimulation (10 V, 0·5 c/s, 0·05 msec duration) of afferent fibres in lumbar colonic nerves (*H* and *I*) and in mesenteric branches of the splanchnic nerves (*J*, *K*). *I* and *K* depict the discharges during electrical stimulation of the aortic depressor nerves (1 V, 100 c/s, 0·05 msec duration). Horizontal calibration in *K* is equal to 200 msec and refers also to record *D–J*. Horizontal calibration in record *C* is equal to 5 sec and refers also to records *A* and *B*. Vertical calibration in *K* is equal to 75 μV, negativity upward and refers also to records *D–J*. Vertical calibration in *B* is equal to 100 μV, negativity upward and refers also to record *A*. Vertical calibration in record *C* is equal to 150 mmHg.

abolished the renal nerve discharge (Fig. 11*B*) but had no effect (five experiments, Fig. 11*A*) or only slightly depressed the sympathetic discharge in l.c.n. (four experiments). Stimulation of the aortic depressor nerve did not depress the reflexes in l.c.n. evoked by stimulation of l.c.n. or mesenteric afferent fibres (*vida supra*) (three experiments) (Fig. 11*I*, *K*). The effects of electrical stimulation of the carotid sinus nerves was also tested on l.c.n. (nine experiments) and renal nerve activity (two experiments). Repetitive stimulation of the carotid sinus nerve at intensities that produced a fall in blood pressure (6–10 V, 20–50 c/s, 0·05 msec duration) depressed renal nerve activity but did not depress the l.c.n. discharge. Activation of baroreceptor afferent fibres by administration of noradrenaline (1–10 μg/kg, I.V., five experiments) depressed the spontaneous discharge in l.c.n.

Vasomotor function of a population of l.c.n. efferent fibres was also suggested by their reflex response to stimulation of chemoreceptor afferents. Electrical stimulation of carotid sinus nerve afferent fibres (de Groat & Lalley, 1974) at intensities (1-3 V, 0·05 msec duration) (ten experiments) that elicited an increase in blood pressure evoked reflex firing in l.c.n. and renal nerve at latencies ranging from 100 to 135 msec. These reflexes were depressed by electrical stimulation of baroreceptor afferent fibres in the aortic depressor nerves (three experiments) (Fig. 11*D*, *G*).

DISCUSSION

Sympathetic post-ganglionic fibres in the l.c.n. exhibited tonic activity which was generated primarily in the central nervous system. In multiunit recordings this activity usually had the appearance of irregular grouped discharges which were not correlated with spontaneous or stimulus evoked colonic contractions or with the cardiac or respiratory cycles.

Post-ganglionic pathways in the l.c.n. probably subserve two major functions: vasomotor control and intestinal inhibition (Langley & Anderson, 1895; Hulten, 1969; Hulten *et al.* 1977). Vasomotor function was suggested by various observations in the present experiments. L.c.n. activity was depressed by electrical stimulation of baroreceptor afferent fibres in the aortic depressor nerve or by the intravenous administration of pressor agents. Furthermore electrical stimulation of chemoreceptor afferent fibres in the carotid sinus nerve evoked reflex responses in the l.c.n. that were in turn blocked by baroreceptor activation. It is noteworthy however, that baroreceptor inhibition of l.c.n. spontaneous activity was observed in only one half of the experiments and was smaller in magnitude than baroreceptor inhibition of renal nerve activity, which is assumed to be predominately vasomotor in function. In addition l.c.n. firing was unaffected by stimulation of baroreceptor afferent fibres in the carotid sinus nerve. Thus, sympathetic vasoconstrictor outflow represents a significant but varying proportion of the l.c.n. activity recorded in the present experiments. It is distinguished from the vasoconstrictor outflow to the kidney by its absence of cardiac periodicity, its differential sensitivity to sinus and aortic baroreceptors and its apparent spinal origin in contrast to the supraspinal origin of renal nerve activity.

Since transection of the l.c.n. enhanced colonic motility a considerable proportion of the spontaneous discharge in the l.c.n. must also represent firing in inhibitory

pathways. This inhibitory outflow originated at two sites: (1) the lumbar spinal cord and (2) prevertebral sympathetic ganglia. A spinal locus was established by monitoring colonic and l.c.n. activity before and after destruction of the lumbar outflow. Ablation of the lumbar cord or transection of the lumbar ventral roots in cats with an intact neuraxis enhanced spontaneous colonic motility often unmasking slow or fast rhythmic pressure waves (Fig. 5) and markedly diminished l.c.n. firing. Supraspinal input was not essential for the generation of the lumbar inhibitory outflow since transection or local anaesthetic block of the upper cervical or lower thoracic cord did not consistently alter colonic motility or l.c.n. firing, whereas in acute spinal animals destruction of the lumbar cord enhanced colonic activity. Similar findings have also been reported in decerebrate unanaesthetized cats (Garry, 1933). Supraspinal mechanisms are also not required for the thoracic sympathetic inhibitory outflow to the small intestine (Johnansson, Jonsson & Ljung, 1968).

Dorsal root afferent input to the lumbosacral spinal cord was also not essential for the maintenance of l.c.n. activity. The activity remained after isolation of the upper lumbar segments by transection of the cord at T13 and L5 and after bilateral transection of the dorsal roots in the isolated lumbar segments. Thus, there are several possible mechanisms for the central generation of l.c.n. activity: (1) the preganglionic neurones in the lumbar cord are spontaneously active, (2) preganglionic neurones are synaptically driven by interneurones which are spontaneously active, or (3) the spontaneous activity is reflexly mediated by afferent fibres in the lumbar ventral roots.

Intrinsic rhythmic activity has been observed in other regions of the mammalian central nervous system. For example, it has been proposed that the periodic discharge of medullary respiratory neurones could be due to their inherent properties (Salmoiraghi & Baumgarten, 1961; Wyman, 1977). Similarly, circuits in medullary cardiovascular centres are believed to be rhythmically active (Gebber, Taylor & McCall, 1975). In addition, spontaneously active preganglionic neurones have also been identified in a decentralized, deafferented segments of the thoracic spinal cord (Polosa, 1968; Mannard & Polosa, 1973).

The alternative explanation for the present findings is that the spontaneous discharge was generated reflexly by activity in afferent fibres in the lumbar ventral roots. There have been numerous reports of non-myelinated and myelinated afferent fibres in lumbar as well as sacral ventral roots (Duncan, 1932; Coggeshall, Coulter & Willis, 1973, 1974; Clifton, Coggeshall, Vance & Willis, 1976) and in certain roots they represent a considerable portion of the fibre population. Mikeladze (1965) reported that the afferent fibres which enter the spinal cord through the lumbar ventral roots terminate primarily in the lateral horns. It was not determined whether these afferent fibres have their peripheral receptive fields in the colon. However, many of the afferent fibres which enter the sacral ventral roots have their receptive fields in the distal colon and rectum (Clifton *et al.* 1976). Thus, it seems reasonable to assume that similar inputs would exist at the lumbar level. Nevertheless, it is clear that colonic afferent pathways are not essential since transecting various peripheral nerves to the colon (lumbar colonic nerves, hypogastric nerves) did not block the l.c.n. firing.

Although not dependent upon dorsal root afferent pathways spontaneous firing in l.c.n. could be modulated by activation of visceral afferent fibres. Electrical stimu-

lation of Aδ and C fibre afferents in the l.c.n. and in the mesenteric branches of the splanchnic nerves as well as distension of the small intestine or proximal colon elicited reflexes in l.c.n. These reflexes were organized in the lumbar cord and were abolished by transection of the lumbar dorsal roots. Similar reflexes have been recorded in lumbar white rami in response to stimulation of Aδ and C fibre axons in splanchnic and lumbar segmental nerves (Beacham & Perl, 1964; Franz, Evans & Perl 1966). Various evidence indicates that these reflexes occur in both vasomotor and inhibitory pathways. For example, activation of Aδ fibres in lumbar segmental nerves elicited a reduction in femoral blood flow and an increase in arterial pressure (Fernandez de Molina & Perl, 1965). Furthermore, distention of the small intestine or electrical stimulation of high threshold (C) fibres in mesenteric nerves elicited a rise in arterial pressure and inhibition of the small and large intestine (Dowman & McSweeney, 1946; Johansson & Langston, 1964; Fedina, Katunski, Khayutin & Mitsani, 1966; Hulten, 1969; Gardett & Gonella, 1974). Gardette and Gonella (1974) proposed that the l.c.n. constitute one part of the efferent pathway mediating the intestino-colonic inhibitory reflexes since transection of the lumbar cord at or below the L1 level diminished the responses.

A role for peripheral ganglionic reflexes in the initiation of an inhibitory input to the colon is suggested by the finding that transection of the l.c.n. enhanced colonic motility in animals where the thoracic and lumbar segments of the spinal cord were destroyed. The presence of an inhibitory input to the colon in the absence of central connexions is consistent with the observations of Szurszewski and co-workers (Crowcroft, Holman & Szurszewski, 1971; Szurszewski & Weems, 1976; Weems & Szurszewski, 1977; Kruelin & Szurszewski, 1977), who demonstrated that neurones in prevertebral sympathetic ganglia (i.e. inferior mesenteric ganglia (i.m.g.) and coeliac ganglia) receive excitatory synaptic inputs from intestinal mechanoreceptors as well as from preganglionic neurones in the spinal cord.

In the guinea-pig i.m.g.-colon preparation, *in vitro*, sectioning the l.c.n. did not alter colonic motility, indicating that peripheral reflex mechanisms in this preparation are too weak to generate a significant inhibition of the colon (Weems & Szurszewski, 1977). Thus it was proposed that the inhibitory outflow from the i.m.g. of the guinea-pig is dependent upon the integration central and peripheral inputs. On the other hand, the present results in the cat indicate that peripheral mechanisms are capable of maintaining an inhibitory outflow from the i.m.g. to the colon. This may reflect differences between species or the presence in the *in situ* preparation of additional afferent input to the i.m.g. via its connexions with other prevertebral gangla (coeliac and superior mesenteric) (Kruelin & Szurszewski, 1977).

The dependence of the sympathetic inhibitory outflow to the colon on peripheral ganglionic reflexes and on local circuits within the spinal cord contrasts with the mechanisms involved in the regulation of sympathetic inhibitory outflow to the other major excretory organ, the urinary bladder. Activity in sympathetic inhibitory pathways to the bladder is initiated primarily by a spinal reflex with an afferent limb in the pelvic nerve entering the sacral cord and an efferent limb in the hypogastric nerve. Distension of the bladder or electrical stimulation of bladder afferent fibres (Aγδ) elicits reflex firing in vesical sympathetic post-ganglionic fibres resulting in depression of transmission in vesical ganglia and inhibition of detrusor smooth muscle (de Groat

& Lalley, 1972; de Groat & Theobald, 1976). The vesico-sympathetic reflex represents a negative feed-back mechanism which facilitatss vesical accommodation and urinary continence (Edvardsen, 1968; de Groat, 1975). This pathway is in turn inhibited by supraspinal mechanisms during micturition thereby promoting the complete emptying of the bladder (de Groat & Lalley, 1972). In contrast the central sympathetic outflow to the colon is not modulated during defecation and seems to be controlled by a more primitive system which is independent of supraspinal mechanisms and spinal afferent input. It is possible, however, that the sympathetic pathways to the colon are regulated by mechanisms within the myenteric plexus.

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