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A STUDY OF PERIPHERAL INPUT TO AND ITS CONTROL BY POST-GANGLIONIC NEURONES OF THE INFERIOR MESENTERIC GANGLION

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SUMMARY

1. Intracellular recordings were made, *in vitro*, from neurones of guinea-pig inferior mesenteric ganglia (IMG) attached, via the lumbar colonic nerves, to segments of distal colon.

2. 'Spontaneous' synaptic input from colonic afferent fibres was observed in 79% of the neurones tested. In any given preparation, the level and pattern of this synaptic input to different neurones varied considerably.

3. Superfusion of colonic segments with drugs (papaverine, isoprenaline, and adenosine triphosphate) which reduce colonic motility decreased colonic afferent input to IMG neurones.

4. Superfusion of colonic segments with acetylcholine or stimulation of pelvic nerves, both of which increase colonic motility, increased colonic afferent input to IMG neurones.

5. Superfusion of colonic segments with either atropine or tubocurarine reduced the level of 'spontaneous', colonic afferent input. However, distension of these relaxed segments increased the colonic afferent input.

6. Repetitive stimulation of preganglionic inputs to the IMG inhibited afferent input from drug relaxed segments of colon that were moderately distended by the injection of air into the lumen. Superfusion of the colon with phentolamine blocked this inhibition.

7. The results of this study suggest that IMG neurones receive afferent input from mechanoreceptors located in the distal colon and that the mechanosensitivity of this afferent pathway is in part controlled by efferent noradrenergic neurones of the IMG. The IMG–colon neural circuitry can therefore be considered to form a feed-back control system which participates in the regulation of colonic motility.

INTRODUCTION

It was previously shown that neurones of the inferior mesenteric ganglion of the guinea-pig receive 'spontaneous' excitatory synaptic input from afferent fibres leaving the distal colon and that efferent output from the inferior mesenteric ganglion depressed the level of this input (Crowcroft, Holman & Szurszewski, 1971). It was suggested that these afferent fibres provide the ganglion with direct sensory information regarding some parameter of the distal colon. The nature of this sensory input was not identified and the mechanism of noradrenergic inhibition of this input was not established.

The purpose of this paper is to present evidence supporting the hypothesis that neurones in the inferior mesenteric ganglion receive input from colonic sensory fibres whose electrical activity results from activation of unidentified mechanoreceptors located in the distal colon. We did not attempt to determine if the receptor end-organ was part of the colonic sensory neurone. The data also indicate that the mechanosensitivity of this afferent pathway (i.e. the relationship of colonic afferent discharge to colonic tension) is in part controlled by efferent noradrenergic neurones of the inferior mesenteric ganglion.

Parts of this study have been communicated (Weems & Szurszewski, 1974*a*, *b*).

METHODS

Young male guinea-pigs (200–350 g) were stunned and bled. The method described by Crowcroft *et al.* (1971) was used to remove preparations consisting of the inferior mesenteric ganglion (IMG), connected inferior splanchnic, intermesenteric, hypogastric and colonic nerve trunks and an attached segment, 6–8 cm in length, of distal colon. The nerve connecting the IMG with the superior mesenteric ganglion has been referred to by various names. By calling the nerve intermesenteric, we have conformed to the nomenclature used by Kuntz (1940) and Skok (1973). Crowcroft *et al.* (1971) referred to the same nerve as the ascending mesenteric nerve. To obtain preparations with pelvic nerves which innervated the segment of distal colon, this method was combined with the procedure described by Gillespie (1962).

Six guinea-pigs received intraperitoneal injections of reserpine (5 mg kg^{-1} day^{-1}) for 4 days to deplete the stores of transmitter in noradrenergic terminals.

Preparations were placed in an organ bath consisting of two compartments separated by a 1 mm thick wall made of Sylgard (Dow Corning). The IMG and associated nerve trunks were pinned down in one compartment and the colonic segment in the other. Pelvic nerves, when present, were pinned down in the compartment containing the colon. The mesocolon, containing the inferior mesenteric artery, vein and colonic nerves, was draped over the centre wall and covered by moistened strips of tissue paper to prevent dehydration. Both compartments were perfused separately with modified Krebs solution containing (mM): Na^+, 137·4; K^+, 5·9; Ca^{2+}, 2·5; Mg^{2+}, 1·2; Cl^-, 134; HCO^-_3, 15·5; $H_2PO^-_4$, 1·2; glucose, 11·5; equilibrated with 97 % O_2 + 3 % CO_2 and warmed to 35–37° C.

Within 5 min after placing preparations in the organ bath, peristaltic contractions emptied the colonic lumen of faecal pellets. This extrusion of faecal pellets was prevented in four preparations by placing a ligature on the distal end of the segment.

Methods used to stimulate nerve trunks and record intracellularly have been described (Crowcroft & Szurszewski, 1971). Since the voltage used for nerve stimulation depended on the size of the nerve trunk and on the amount of adherent connective tissue, the values of the stimulus strength used in each experiment will not be indicated. In all experiments that involved electrical stimulation of nerves associated with the IMG, a stimulus voltage was used which was slightly greater than the one which produced a maximal synaptic depolarization.

The following drugs were used: acetylcholine chloride (Sigma Chemical Co.), adenosine-5-triphosphate disodium salt (ATP) (Sigma Chemical Co.), atropine sulphate (Sigma Chemical Co.), carbamylcholine chloride (carbachol) (Sigma Chemical Co.), L-isoprenaline hydrochloride (Sigma Chemical Co.), papaverine (Sigma Chemical Co.), phentolamine mesylate (CIBA Pharmaceutical Co.), reserpine (Serpasil, a pure crystalline alkaloid of rauwolfia root, CIBA Pharmaceutical Co.), tetrodotoxin (Sigma) and tubocurarine chloride (Eli Lilly and Co.). Since papaverine was available to us as the base, 10 mg of it was dissolved in 10 ml. glass-distilled water to which was added 60 μl. 2 N-HCl. Drugs were introduced into either compartment by switching the perfusion system from normal Krebs solution to one containing the desired drug(s) at the desired concentration(s). Drug concentrations are expressed as molar concentrations of the salt.

To distend the colon, the proximal end was tied off and a fine polyethylene tube, which led to a syringe, was tied into the distal end. The segment was distended by injection of small quantities of air (0·5–4 ml.) into the lumen. Air distension was used because it could be quickly injected and rapidly removed.

RESULTS

General observations

Intracellular recordings were made from 334 ganglion cells impaled in sixty-two experiments. Resting potentials ranged from -35 to -75 mV with a mean value of $-51{\cdot}6$ mV $\pm$ 0·53 (S.E. of mean). In any single preparation, the majority of cells showed 'spontaneous' synaptic activity which consisted of excitatory post-synaptic potentials (e.p.s.p.s) which sometimes gave rise to action potentials. Distension of the colon by air injection into the lumen increased the level of 'spontaneous' activity. Superfusion of only the colon with tetrodotoxin (3×10^{-6} M) reversibly abolished this activity but had no effect on the e.p.s.p.s produced by electrical stimulation of nerve trunks pinned down in the compartment containing the ganglion. All these observations confirm the findings of Crowcroft *et al.* (1971) that e.p.s.p.s and spikes in the IMG are caused by synaptic input from neural fibres leaving the colon.

The patterns of electrical activity and configuration of the action potentials were also similar to those described by Crowcroft *et al.* (1971). The level and pattern of synaptic input, however, varied considerably among cells in any given preparation indicating that not all neurones

received identical patterns of colonic input (Fig. 1). Input patterns to individual neurones were never observed to change spontaneously. Variation in input was not related to the location of neurones along the horizontal plane of the ganglion.

Of 334 ganglion cells tested, seventy had no 'spontaneous' synaptic input and air distension of the colon did not induce synaptic input. However, excitatory synaptic potentials and action potentials were observed following electrical stimulation of the intermesenteric nerve. Although a systematic study of their preganglionic innervation was not conducted, hypogastric and/or inferior splanchnic nerve stimulation often

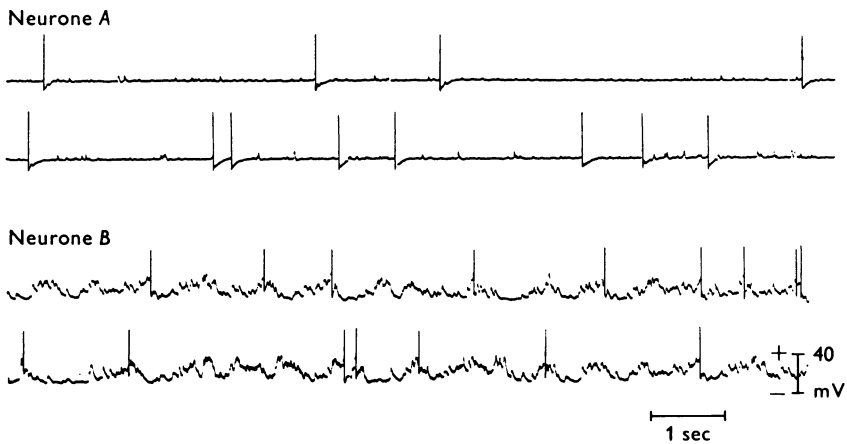

Fig. 1. Intracellular recordings of electrical activity obtained from two IMG neurones located in the same IMG–colon preparation. The electrical activity of neurone *A* was characterized by e.p.s.p.s that occurred mainly as single events whereas the activity of neurone *B* was characterized by clusters of compound e.p.s.p.s. These two patterns are representative of the ends of continuum of inputs from several cells in a single preparation. No alteration in the pattern of input to an individual neurone occurred spontaneously. Synaptic input was abolished when the ganglion was superfused with tubocurarine ($1{\cdot}4 \times 10^{-5}$ M). In this and subsequent Figures, time and voltage calibrations apply to all traces. Action potentials have been retouched to darken trace.

produced e.p.s.p.s in these quiescent cells. Action potentials could also be produced in these cells by intracellular current injection. In a few instances, antidromic invasion was observed following stimulation of the hypogastric nerve.

To determine whether the level of synaptic input to the inferior mesenteric ganglion reflects the mechanical state of the colon we studied the effect of smooth muscle relaxants and stimulants.

Effect of smooth muscle relaxants

Papaverine. Superfusion of faecal-free colonic segments with Krebs solution containing papaverine (10^{-6} M), virtually abolished 'spontaneous' synaptic input to neurones in the IMG. The pattern of synaptic input in normal Krebs solution is shown in Fig. 2*A* and the effect of papaverine in Fig. 2*B*. Distension of the colon during superfusion with papaverine produced synaptic input to the IMG indicating that the inhibitory effect of papaverine was not due to inhibition of the afferent neural pathways leaving the colonic segment (Fig. 2*C*). The inhibitory effect of papaverine was reversible (Fig. 2*D*).

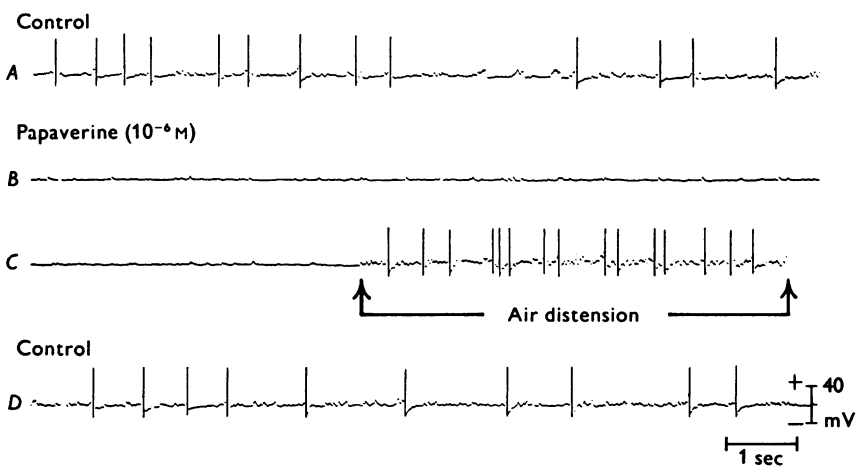

Fig. 2. Effect of superfusing the colon with papaverine (*B*, *C*) on colonic input to an IMG neurone. Panel *A*, control. Panel *B*, 5 min after adding papaverine. Panel *C* continuous with *B*. Panel *D*, 5 min after washout of papaverine. In *C*, first arrow indicates onset and second offset of air distension.

When segments of colon containing faecal pellets were treated with papaverine, there was no reduction in synaptic input. This ineffectiveness of papaverine to reduce 'spontaneous' synaptic input under these conditions resulted from maintained distension due to the presence of faecal pellets in the lumen.

Superfusion of only the IMG with papaverine had no effect on either 'spontaneous' or electrically evoked e.p.s.p.s indicating that papaverine did not interfere with cholinergic transmission.

Isoprenaline. There is evidence which suggests that α-adrenoceptors are located primarily on enteric cholinergic neurones whereas β-adrenoceptors are located primarily on smooth muscle cells (Paton & Vizi, 1969).

β-adrenoceptor stimulation would therefore be expected to relax smooth muscle without interfering with synaptic transmission in the enteric plexus. Thus, the effects of isoprenaline were studied in five preparations. Superfusion of colonic segments with isoprenaline (2×10^{-5} M) reversibly reduced 'spontaneous' synaptic input to the IMG (Fig. 3*B*). Distension of these segments produced increases in synaptic input that were equal to or greater than control levels (Fig. 3*B*).

Superfusion of only the IMG with isoprenaline had no effect on either 'spontaneous' or electrically evoked synaptic activity.

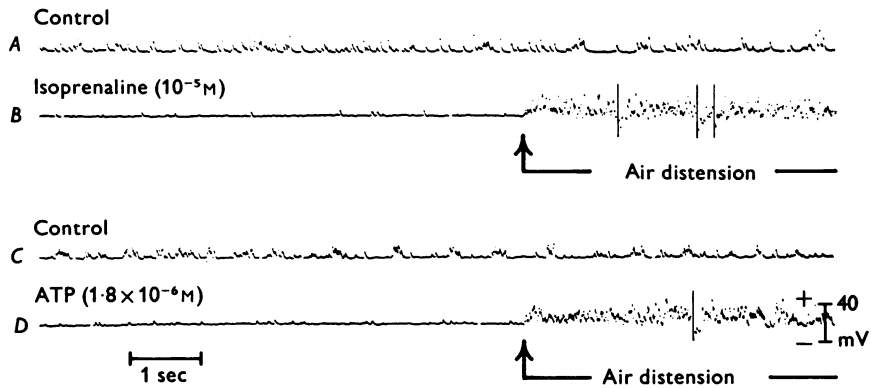

Fig. 3. Effect of superfusing the colon with the smooth muscle relaxants isoprenaline (*B*) and ATP (*D*) on colonic input to IMG neurones. In *A* and *C*, colon in normal Krebs solution. In *B* and *D*, recordings taken 5 min after adding isoprenaline and ATP, respectively. Recordings in panel *A* and *B* taken from same neurone. Recordings in panel *C* and *D* taken from a second neurone in same preparation. For details see text.

Adenosine triphosphate (*ATP*). ATP is known to relax smooth muscle of the guinea-pig colon (Furness, 1970*b*). Based on chemical analysis and pharmacological studies, it has been proposed as the transmitter released from the non-adrenergic, non-cholinergic inhibitory fibres of the enteric nervous system (Axelsson & Holmberg, 1969; Burnstock, Campbell, Satchell & Smyth, 1970; Satchell & Burnstock, 1971; Su, Bevan & Burnstock, 1971; Burnstock, 1972). We found that superfusion of the colon with ATP ($1{\cdot}8 \times 10^{-6}$ M) had an effect similar to that produced by papaverine and isoproterenol (Fig. 3*D*). 'Spontaneous' synaptic input was nearly abolished (reversibly) and distension of the colon during exposure to ATP increased the level of synaptic input.

Superfusion of only the IMG with ATP produced no alterations in spontaneous or evoked synaptic activity.

Atropine. The above data suggest that 'spontaneous' synaptic input to neurones in the IMG is a function of mechanoreceptor activity in the

colon. In the isolated intestine of the guinea-pig, the myenteric plexus tonically releases acetylcholine (Paton & Zar, 1968). Furness (1970*b*) has shown that spontaneous mechanical activity of the isolated guinea-pig colon is in part due to a neurogenic component which is sensitive to tetrodotoxin and hyoscine. To determine if the 'spontaneous' synaptic input to the IMG is due in part to mechanoreceptor monitoring of neurogenically induced contractions, the colon was superfused with atropine (7×10^{-6} M). Within 5 min after the start of atropine superfusion, the level of 'spontaneous' synaptic activity was reduced (Fig. 4*B*). Distension of the colon during exposure to atropine always increased the level of synaptic activity (Fig. 4*C*).

Superfusion of the IMG with atropine had no effect on synaptic activity.

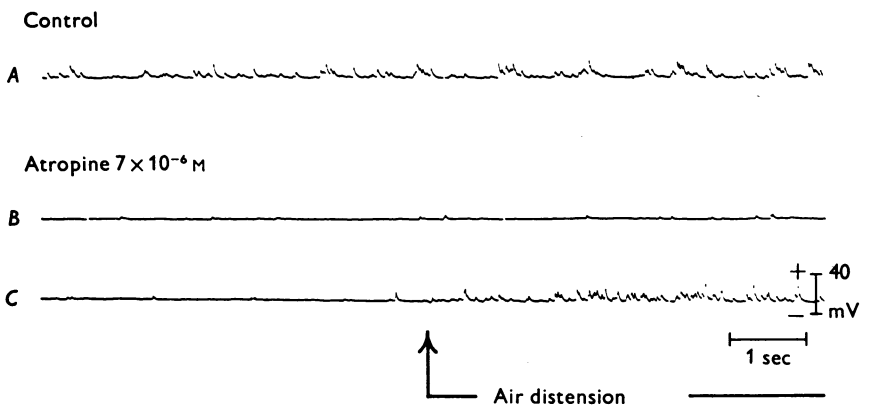

Fig. 4. Effect of superfusing the colon with atropine (*B*, *C*) on colonic input to an IMG neurone. Panel *C* continuous with *B*. Recordings from same neurone. *A*, normal Krebs solution; *B*, 5 min after adding atropine. For details see text.

Effect of smooth muscle stimulants and pelvic nerve stimulation

Acetylcholine and carbachol. Synaptic input to the IMG was increased during superfusion of colonic segments with either acetylcholine or carbachol. The effect of acetylcholine is shown in Fig. 5. In this cell, the level of synaptic input in normal Krebs solution was low (Fig. 5*A*). Addition of acetylcholine (10^{-6} M) increased synaptic input (Fig. 5*B*). This increased level of activity could have resulted from activation of muscarinic receptors located on smooth muscle or of nicotinic synapses located in the afferent pathway between the colon and the IMG or on plexus neurones which produce an excitatory drive on the colon. Superfusion, however, of colonic segments with atropine (7×10^{-6} M) prevented the response to both

acetylcholine and carbachol suggesting that the increase in motility was due to activation of muscarinic receptors.

Pelvic nerve stimulation. Stimulation of pelvic nerves, *in vitro*, attached to segments of distal colon results in colonic contraction (Furness, 1970*a*). To determine if the increase in colonic motility during pelvic nerve stimulation increases synaptic input to the IMG, preparations were tested in which the pelvic innervation to the colon remained intact. In three of

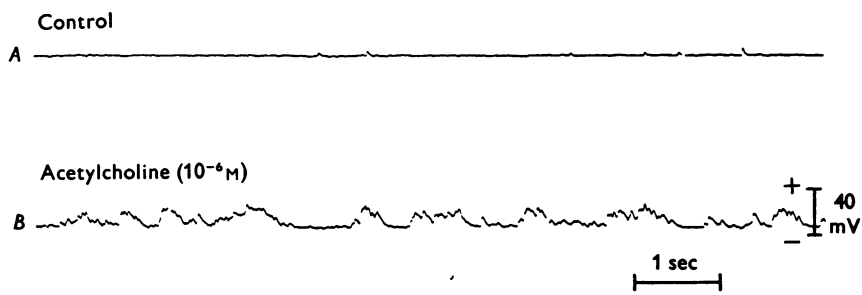

Fig. 5. Effect of superfusing the colon with acetylcholine (*B*) on colonic input to an IMG neurone. Recordings from same neurone. *A*, normal Krebs solution; *B*, 5 min after adding acetylcholine. For details see text.

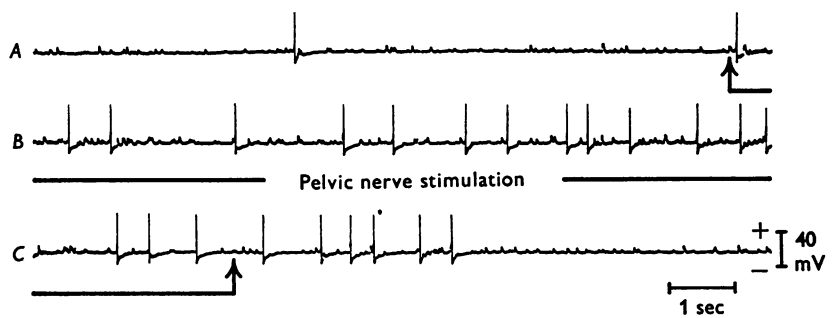

Fig. 6. Effect of pelvic nerve stimulation (3 Hz) on colonic input to an IMG neurone. Continuous record.

six preparations, stimulation of the pelvic nerves at frequencies as low as 3 Hz resulted in increased levels of synaptic input (Fig. 6). This effect remained after cutting the hypogastric nerves indicating that the increase in synaptic input was not from neural pathways (Crowcroft & Szurszewski, 1971) known to connect some pelvic nerves with neurones in the IMG.

Modulation of 'spontaneous' synaptic input

Repetitive stimulation (10 Hz, 4 sec) of either the hypogastric, inferior splanchnic or intermesenteric nerves transiently inhibited synaptic input

from the colon. By convention, most if not all the ganglion cells of the prevertebral ganglia are considered to be noradrenergic. Crowcroft *et al.* (1971) demonstrated that repetitive stimulation of neurones in the IMG transiently abolished synaptic input to the ganglion. If excitation of these neurones releases noradrenaline from their terminals in the wall of the colon, then the inhibition should be absent in animals in whom the stores of neurotransmitters are depleted. In reserpine treated animals, repetitive stimulation of any of the nerve trunks attached to the IMG failed to inhibit synaptic input from the colon. Furthermore, in these reserpine treated animals the level and pattern of synaptic input were not much different when compared to input found in normal animals. These findings support the conclusion that inhibition of synaptic input to the IMG results from the release of noradrenaline from the axon terminals of these neurones.

Crowcroft *et al.* (cf. Fig. 16, 1970) suggested that this inhibition of afferent input was mediated through α-adrenoceptors located on cholinergic motor neurones or on cholinergic neurones which are driving them. We found, however, that nerve stimulation during maintained distension of the colon transiently inhibited the afferent input. Since maintained distension should prevent the colon from returning to the control level of tension, except possibly by noradrenergic relaxation of the musculature, it was postulated that the transient inhibition of afferent input during distension could have resulted from a decrease in the mechanosensitivity of the afferent pathway. To test this hypothesis, the colon was relaxed with papaverine, atropine and isoprenaline to insure that repetitive stimulation of noradrenergic fibres did not produce further relaxation. Papaverine was used to relax myogenic tone, atropine to block neurogenic tone and isoprenaline to ensure further relaxation by β-adrenoceptor stimulation. An example of such an experiment is shown in Fig. 7. The level of synaptic activity before distension was low. When the colon was distended with 1 ml of air (Fig. 7*A*), there was an increase in afferent synaptic input. Repetitive stimulation of the intermesenteric nerve (10 Hz, 4 sec) during the distension transiently reduced the afferent input. When the lumen was distended with 2 and 3 ml. air (Fig. 7*B*, *C*), the level of synaptic input increased but the degree of transient inhibition of afferent synaptic input was less (Fig. 7*B*, *C*).

This modulation of mechanosensitivity by noradrenergic efferent fibres was mediated by α-adrenoceptors. Synaptic input in normal Krebs solution is shown in Fig. 8*A* and the effect of repetitive stimulation of the intermesenteric nerve in Fig. 8*B*. The effect of phentolamine ($3{\cdot}5 \times 10^{-6}$ M) is shown in Fig. 8*C* and *D*. In this and all other preparations tested, phentolamine increased the level of synaptic input and blocked the inhibitory effect of repetitive nerve stimulation.

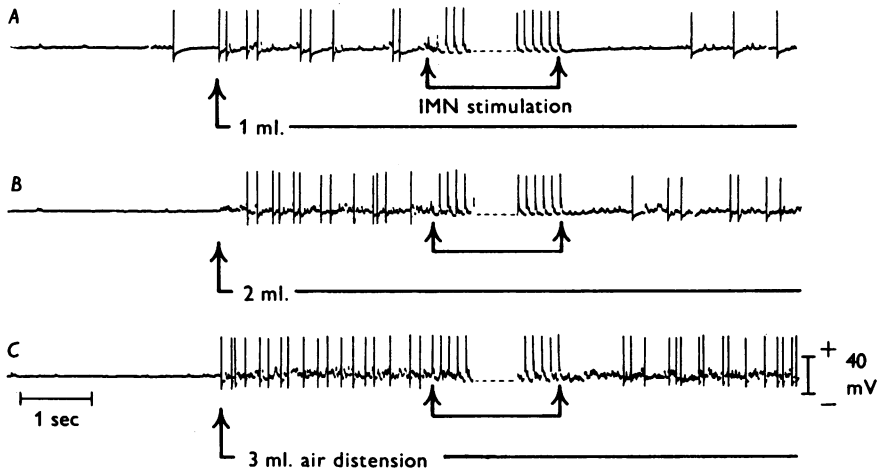

Fig. 7. Effect of increasing levels of distension on transient inhibition of colonic input to an IMG neurone following repetitive stimulation of the intermesentric nerve (IMN). Papaverine (10^{-6} M), atropine (7×10^{-6} M) and isoprenaline (10^{-5} M) present in colon bath throughout experiment. In panels *A*, *B* and *C*, record interrupted at interrupted line. In each instance, duration and frequency of nerve stimulation, 4 sec and 10 Hz, respectively. Recordings taken from same neurone. For details see text.

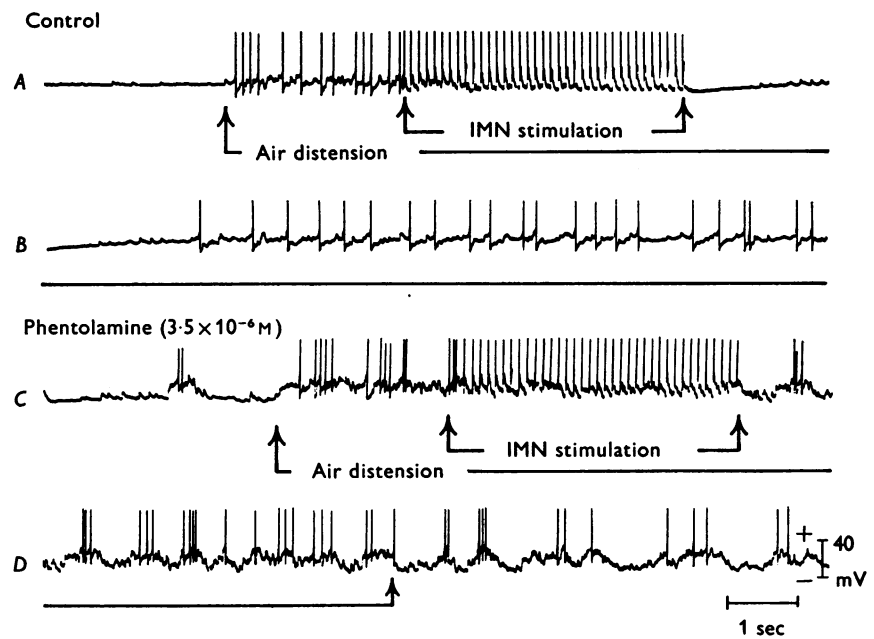

Fig. 8. Effect of superfusing the colon with phentolamine (*C*, *D*) on the transient inhibition of colonic input following inferior mesenteric nerve (IMN) stimulation (4 sec, 10 Hz) in an air distended (1 ml.) colonic segment. Panel *B* continuous with *A* and panel *D* continuous with *C*. Records taken from same neurone. *A* and *B* normal Krebs solution; *C*, 10 min after adding phentolamine. Note increase in 'spontaneous' synaptic input during superfusion with phentolamine.

The data presented above do not indicate if mechanoreceptors project directly to neurones in the IMG or if there are one or more neurones interposed between the mechanoreceptor and the ganglion. To determine if the afferent pathway in the colon is interrupted by nicotinic synapses, tubocurarine was added to the colon side of the bath. In concentrations ranging from $1{\cdot}4 \times 10^{-7}$ to $1{\cdot}4 \times 10^{-4}$ M, tubocurarine reduced the level of spontaneous synaptic input. This inhibitory effect on spontaneous input is shown in Fig. 9*B*. However, when the colon was distended by 1 ml. air, synaptic input was restored (Fig. 9*C*). Increased spontaneous input following distension may have been due either to incomplete relaxation

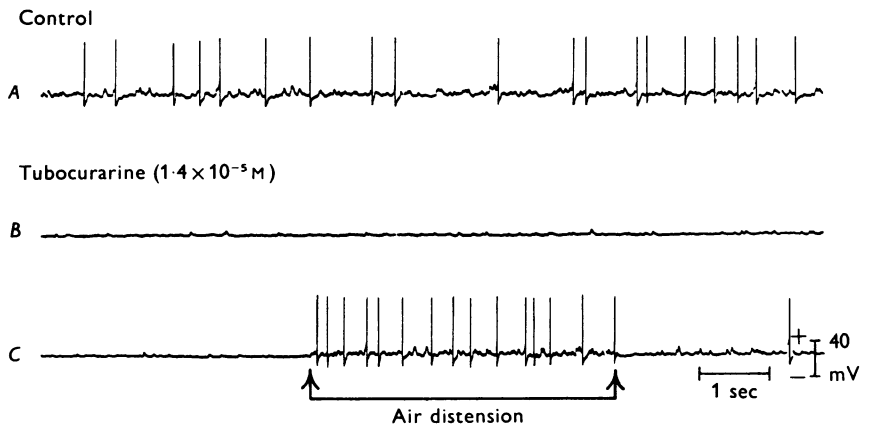

Fig. 9. Effect of superfusing the colon with tubocurarine on the colonic input to an IMG neurone. *A*, normal Krebs solution; *B*, 5 min after adding tubocurarine. Panel *C* continuous with *B*. Records from same neurone. For details see text.

following distension or to incomplete removal of the stimulus. These data suggest that there are no nicotinic synapses located in the afferent pathway. The reduction in 'spontaneous' synaptic input may be due to blockage of transmission between higher order neurones and cholinergic motor neurones.

DISCUSSION

The main findings of this study are: (1) mechanoreceptors in the distal colon transmit to neurones in the IMG information regarding the mechanical state of the colon and (2) the mechanosensitivity of this afferent pathway can be modulated by noradrenergic neurones originating in the IMG. The IMG therefore has the capability of modifying the level of mechanoreceptor input it receives from the distal colon and of integrating this input with input from the C.N.S.

Superfusion of the colon with drugs (papaverine, isoprenaline and ATP) which reduce colonic motility decreased 'spontaneous' synaptic input to neurones in the IMG while procedures known to increase colonic motility (superfusion with acetylcholine or pelvic nerve stimulation) increased this input. These data indicate that the 'spontaneous' synaptic input to the IMG results from mechanoreceptor activity in the distal colon. During pharmacological procedures which reduce colonic motility, mechanical stress (distension) applied to the colon always reactivated synaptic input to the IMG. This indicates that these drugs did not affect the neuronal elements of the afferent pathway and further supports the hypothesis that synaptic input from colonic afferents reflects the activity of mechanoreceptors. It is reasonable to predict, however, that not all mechanoreceptors will be freed from mechanical stress when the colon is relaxed because factors such as bends in the segment, residual tone, and possible low levels of motility could continue to deform some mechanoreceptors and produce low level synaptic input to IMG neurones. This predicted input was observed from most preparations during drug relaxation of colonic smooth muscle.

The observation that the level of afferent discharge from colonic afferent fibres is directly related to the contractile activity of colonic muscle suggests that a fraction of these mechanoreceptors is located in series with smooth muscle cells. Mechanoreceptors with an in-series arrangement (tension receptors) have been demonstrated to exist in the gastrointestinal system (Iggo, 1955; Leek, 1969) and to respond to smooth muscle stimulation, inhibition, and distension (Leek, 1972) in a manner similar to the responses observed in this study. The presence of tension receptors does not preclude the possibility that a fraction of the colonic afferent discharge induced by air distension could have resulted from the activation of mechanoreceptors located in parallel with colonic smooth muscle (volume receptors). The results of this study would be compatible with the hypothesis that the IMG receives information from both tension and volume receptors. The techniques employed in this study, however, did not permit us to detect the presence of volume receptors because the output of single mechanoreceptors could not be monitored during isotonic contractions of the colon.

The reduction in synaptic input during colonic superfusion with tubocurarine is consistent with the suggestion by Crowcroft *et al.* (1971) that some afferent pathways projecting to the IMG are interrupted in the colon by cholinergic synapses. Hirst & McKirdy (1974) have demonstrated that some enteric neurones in the guinea-pig small intestine receive mechanoreceptor synaptic input, and that some of these synapses are cholinergic. However, the induction of synaptic input to IMG neurones by

distension during superfusion of the colon with tubocurarine seems to indicate that most colonic afferent pathways are not interrupted by cholinergic synapses. Two alternative explanations, however, must be considered: (*a*) the pathways carrying on-going synaptic activity are synaptically interrupted and that colonic distension activates other pathways which are not synaptically interrupted, and/or (*b*) the blocking effect of tubocurarine at nicotinic synapses in the afferent pathway is easily overcome by distension induced input to the mechanoreceptors. Initially, it may appear that the observed reduction in 'spontaneous' input during superfusion of the colon with tubocurarine restricts consideration to the alternative explanations, but it is possible that the reduced input resulted from lowered activity of cholinergic motor neurones and not from blockage of synapses located in the afferent pathway. Since superfusion of the colon with atropine significantly reduced synaptic input, a sizable fraction of the 'spontaneous' input to neurones in the IMG resulted from colonic motility induced by the activity of enteric cholinergic motor neurones. Thus, any reduction in their activity would reduce the level of synaptic input to the IMG. Since no evidence has been found to suggest that these motor neurones are intrinsically active, (Yokayama, 1966; Wood, 1970, 1973, 1975; Wood & Mayer, 1973; Nishi & North, 1973*a*; Ohkawa & Prosser, 1972; Hirst, Holman & Spence, 1974; Hirst & McKirdy, 1974), the possibility exists that they are driven by other cholinergic neurones. In this case, tubocurarine would reduce the excitatory input to these motor neurones which in turn would lead to a reduction in input similar to that observed. Therefore, the question as to whether mechanoreceptors project directly to the IMG or on enteric neurones which synapse with neurones in the IMG still remains to be elucidated.

Considerable evidence supports the hypothesis that colonic motility of the guinea-pig is under inhibitory control of noradrenergic neurones in the IMG. Furness (1970*a*) demonstrated that axon terminals of these neurones are associated with ganglion cells in the myenteric plexus of the guinea-pig colon and with smooth muscle cells of the circular muscle layer. Electrical stimulation of these neurones results in inhibition of colonic motility (Gillespie, 1962; Furness, 1969, 1970*b*). This inhibitory response appears to be mediated by two mechanisms: a direct inhibitory action of noradrenaline on colonic smooth muscle, which is blocked by propranolol (Furness, 1970*b*) and a direct inhibitory action of noradrenaline on cholinergic neurones located in the enteric nervous system (Beani, Bianchi & Crema, 1969; Paton & Vizi, 1969), which is blocked by phentolamine. Since noradrenergic neurones in the IMG inhibit colonic motility and since decreased motility results in a reduction in 'spontaneous' synaptic input

to the IMG, then repetitive stimulation of neurones in the IMG might be expected to produce the observed decrease in synaptic input by activating both of these inhibitory mechanisms. However, neither of these mechanisms would produce the transient inhibition of synaptic input that resulted from noradrenergic nerve stimulation during maintained distension. It is conceivable that mechanoreceptors might be geometrically arranged so that receptor tension could be reduced by relaxation of muscle contractile elements even though intestinal volume remained relatively constant. This possibility can be rejected because repetitive stimulation also transiently inhibited synaptic input produced by distension of drug relaxed colons. The degree of inhibition was indirectly related to the level of applied stress. Therefore, it is concluded that noradrenergic neurones of the IMG not only control colonic motility but also modulate the mechanosensitivity of the colonic–IMG afferent pathway. Thus, for a level of constant tension, the afferent neural activity would be expected to decrease as efferent activity increases. This modulation is mediated by α-adrenoceptors because superfusion of the colon with phentolamine abolished the effect of repetitive stimulation on both 'spontaneous' and distension induced synaptic input. The precise location of these receptors, which is probably on mechanoreceptors or synapses in the afferent pathway, remains to be determined.

This finding of a neural pathway modulated by noradrenergic neurones is not peculiar to this system (cf. Chernetski, 1964). The mechanosensitivity of pacinian corpuscles in cat mesentery and mesocolon is modulated by sympathetic post-ganglionic fibres which stimulate pacinian β-adrenoceptors (Loewenstein & Altamirano-Orrego, 1956; Schiff, 1974). Stimulation of sympathetic nerves inhibits ganglionic transmission in cat stomach and small intestine (Kewenter, 1965; Jansson & Martinson, 1966) and in the guinea-pig inhibits acetylcholine output in response to pelvic nerve stimulation (Beani *et al.* 1969). Nishi & North (1973*b*) also found that noradrenaline inhibits the release of acetylcholine at some synapses located in the myenteric plexus of the guinea-pig, and anatomical evidence indicates that neurones of the chick ciliary ganglion are adrenergically innervated (Cantino & Mugnaini, 1974). It therefore appears that noradrenergic modulation of neural pathways may occur as a modulating or gating mechanism in various neuronal circuits.

In summary, mechanoreceptors in the distal colon transmit information regarding the mechanical state of the colon to noradrenergic neurones in the IMG. These noradrenergic neurones synaptically receive and integrate this colonic input with synaptic input from splanchnic, hypogastric and intermesenteric nerves (Crowcroft & Szurszewski, 1971). The output of the noradrenergic neurones, which results from integration of multiple

synaptic inputs, is transmitted to the colon where it (1) decreases activity of cholinergic motor neurones, (2) inhibits the myogenic component of smooth muscle contraction, and (3) modulates the mechanosensitivity of the afferent pathway. It is not known whether the output of each noradrenergic neurone mediates all three of these control functions or whether each function is independently controlled by separate populations of neurones within the IMG.

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