Studies *in vivo* of the ileocaeco-colic sphincter in the cat and dog

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EDITORIAL SYNOPSIS A study of the response of the ileocaeco-colic sphincter² of the cat and dog to sympathomimetic and parasympathomimetic drugs and to stimulation of the autonomic nerves is reported. The response to drugs *in vivo* is identical with that previously noted *in vitro*, namely, contraction of the sphincter by adrenaline, noradrenaline, and acetylcholine, and relaxation by isoprenaline. Stimulation of the sympathetic nerves consistently resulted in contraction of the sphincter, but stimulation of the parasympathetic nerves (vagus) sometimes resulted in contraction and at other times relaxation of the sphincter. In view of the presence of β receptors in the sphincter, which, when stimulated cause relaxation of the muscle, it is suggested that the vagus contains adrenergic nerves which supply these receptors.

The text-book description of the ileocaeco-colic sphincter is probably based largely on the work of Hinrichsen and Ivy (1931) in the dog. These workers recorded the sphincteric tone in anaesthetized dogs with a 2 cm. balloon lodged in the terminal ileum and showed that stimulation of the sympathetic nerves and systemic administration of sympathomimetic drugs consistently resulted in sphincteric contraction. Administration of a parasympathomimetic drug (pilocarpine) also caused contraction, but stimulation of the vagus nerve gave variable results. Balloon studies have also been carried out in human patients with caecostomies. White, Rainey, Monaghan, and Harris (1934) and Buirge (1944) found that adrenaline consistently relaxed the sphincter. In contrast, Liotta *et al.* (1957), using varying doses of adrenaline, noted both an increase of sphincteric tone in some experiments and a decrease in others. In a previous study (Gazet and Jarrett, 1964), using isolated circular muscle from the terminal ileum, it was found that adrenaline, noradrenaline, and acetylcholine consistently produced a contraction in muscle from man, monkey, dog, and cat. Isoprenaline, however, consistently relaxed the 'sphincter' muscle. Further, the antagonist drug phentolamine, which blocks α receptors, reversed the stimulation of the sphincter by adrena-

line and noradrenaline, relaxation of the sphincter occurring instead. The significance of these β receptors in the sphincter was not apparent. Therefore, a study of the response of the sphincter to drugs and to nervous stimulation was performed in two experimental animals, the cat and dog, *in vivo*.

MATERIALS AND METHODS

Cats and dogs of either sex were used. They were anaesthetized either by the intravenous injection of thiopentone (40 mg./kg. body weight) or intraperitoneal pentobarbitone (26 mg./kg.). A cuffed endotracheal tube was inserted into the trachea of the dogs. In cats, a tracheotomy was performed. The blood pressure was recorded directly via a polythene cannula in the right femoral artery connected to a mercury U-tube manometer. A second polythene cannula was introduced into the left femoral artery so that its open end lay over the origin of the superior mesenteric artery. This served to introduce drugs as directly as possible to the ileocaeco-colic area. The vagi were isolated in the neck. The sympathetic (splanchnic) nerves were isolated, towards the end of each experiment, in the chest via a seventh rib thoracotomy, alternate animals having the left or right side of the chest opened.

At a distance of 10 cm. from the ileo-caecal junction a polythene tube of 5 cm. bore was inserted and so arranged that its open end abutted against the sphincter. It was then sutured in position, proximally.

The proximal ileum was then ligated to prevent back flow of fluid. A caecostomy was performed and a large polythene tube inserted and sutured in position. This served as a sump drain to prevent over distension of the

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²In this study the term ileocaeco-colic sphincter is preferred to the more usual ileo-colic sphincter due to the various morphological differences between species.

FIG. 1. A diagrammatic drawing of the animal preparation, and, below, of the apparatus. Saline flows at a constant pressure into the terminal ileum. Pressure changes in the ileum are transmitted to the manometer and recorded on the smoked drum. Blood pressure changes are recorded simultaneously.

caecum. The bowel was then returned to the abdomen and the wound loosely closed. The position of the intra-ileal tube was checked periodically throughout the experiment. Normal saline or Tyrode solution was then run into the ileum through the tube at a constant rate of 30 drops a minute. In the absence of the sphincteric opening, this gave an increase in pressure of approximately 1 cm. water every 500 seconds. A side arm connected to a water float manometer recorded changes in pressure on a smoked drum. A conventional time marker recorded five-second intervals. The vagi and splanchnic nerves were stimulated with platinum electrodes placed across the end of the cut nerves. The stimulator provided simple rectangular voltage pulses of variable duration (0.01-300 msec.) and intensity (0-200 volts). Stimulation was

usually maintained for 30 seconds with 1, 5, or 50 pulses per second of 0.3 milliseconds in duration at 40 volts.

Figure 1 shows the animal preparation and the apparatus.

RESULTS

DRUGS Figure 2 shows the effects of the intra-arterial injection of from 25 to 50 μ g. of adrenaline, noradrenaline, isoprenaline, and acetylcholine upon the sphincter and upon the blood pressure. The effects *in vivo* of the drugs upon the sphincter correlated exactly with the results *in vitro*, namely, stimulation by adrenaline, noradrenaline, and acetylcholine, and relaxation by isoprenaline. The apparently brisker response to acetylcholine may have been due to the associated contraction of the more proximal ileum. The ileum proximal to the sphincter

FIG. 2. The effect of intra-arterial injection of (1) 25 μ g. adrenaline, (2) 25 μ g. noradrenaline, (3) 50 μ g. isoprenaline, and (4) 25 μ g. acetylcholine in the dog.

is, of course, relaxed by both adrenaline and noradrenaline. The effects of the drugs were consistent in 10 animals of each species (Table I). There was no correlation between the response of the sphincter to the drugs and their effects on the blood pressure.

SYMPATHETIC NERVE STIMULATION Figure 3 shows the response to stimulation of the distal end of the

TABLE I

RESPONSE OF THE ILEOCAECO-COLIC SPHINCTER OF THE CAT AND DOG TO INTRA-ARTERIAL INJECTION OF DRUGS

	Cat			Dog		
	Contraction	Relaxation	No Response	Contraction	Relaxation	No Response
Acetylcholine	10	0	0	4	0	0
Adrenaline	12	0	1	9	0	0
Noradrenaline	7	1	1	12	0	0
Isoprenaline	0	11	1	0	6	0

cut splanchnic nerves. No difference was observed between the response to stimulation of the right or left nerve. In both cases there was a contraction of the sphincter associated with a rise of blood pressure. The magnitude of the effects was directly proportional to the frequency of the stimulating current. It seemed possible that the response of the sphincter might have been secondary to release of catecholamines from the adrenal medulla. The ileo-caecal and right colic arteries were therefore dissected out and the mesentery widely divided. Stimulation of the vessels, and the sympathetic nerves running with them, caused a similar contraction of the sphincter without a concomitant rise in blood pressure

(Fig. 4). Relaxation of the sphincter was never observed following stimulation of the splanchnic nerves or the ileo-caecal or ileo-colic arteries.

VAGAL STIMULATION The response to distal vagal stimulation varied both between animals and in the same animal at different times. Figure 5 indicates some of the variation observed. At 50 cycles/second, there is sphincteric contraction in both dog and cat. At 5 cycles/second, the cat shows relaxation of the sphincter and the dog contraction. At 1 cycle/second, the cat again shows a relaxation and the dog no response. The fall in blood pressure with vagal stimulation was consistent and related to the fre-

FIG. 3. 50

5

1

FIG. 4. 50

5

1

FIG. 3. The effects of stimulation of the distal right (cut) splanchnic nerve in the cat at 50, 5, and 1 cycles per second, for 30 to 60 seconds.

FIG. 4. The effects of stimulation of the distal (cut) ileocaecal artery of the cat at 50, 5, and 1 cycles per second, for 30 to 60 seconds.

TABLE II
RESPONSE OF THE ILEOCAECO-COLIC SPHINCTER OF THE CAT AND DOG TO STIMULATION OF THE DISTAL END OF THE CUT VAGUS NERVE

Pulses per Second									
50			5			1			
Contraction	Relaxation	No Response	Contraction	Relaxation	No Response	Contraction	Relaxation	No Response	
Stimulation left or right vagus (contralateral nerve intact)									
Cat	17	0	0	5	1	3	0	1	4
Dog	6	3	0	6	1	1	1	1	2
Stimulation left or right vagus (contralateral nerve cut)									
Cat	10	2	1	2	2	5	0	2	7
Dog	8	4	1	7	2	4	0	0	5
Totals	41	9	2	20	6	13	1	4	18

FIG. 5. The effects of stimulation of the distal right vagus nerve of the cat at 50, 5, and 1 cycles per second for 30 seconds.

quency of the stimulating current. The variation in response is seen in Table II. Cutting the contralateral vagus had no significant effect upon the results. Stimulation of the proximal end of the cut vagus with the contralateral nerve intact resulted in contraction or relaxation of the sphincter with approximately equal frequency.

DISCUSSION

In a previous communication (Gazet and Jarrett, 1964) it was demonstrated that the terminal 1.5 cm. in the cat, and 1.5-2.5 cm. in the dog, of the ileal circular muscle responded to sympathomimetic drugs in a manner different from that of both the proximal ileum and the caecum and colon. Both adrenaline and noradrenaline contracted this small segment of muscle and isoprenaline relaxed it. This

pharmacologically distinct region corresponds with the anatomical sphincter demonstrable in giant sections of the region (Gazet, 1965). The present studies *in vivo* confirm the distinctive response to the sympathomimetic drugs obtained *in vitro*. The ileocaeco-colic sphincter thus resembles the cardiac sphincter in its response to sympathomimetic drugs (Clark and Vane, 1961; Trounce, 1961). However, the response to acetylcholine differs in these two sphincter. Both *in vivo* and *in vitro* the ileocaeco-colic sphincter of the cat is contracted by acetylcholine (Clark and Vane, 1961), but *in vitro*, in human specimens it is contracted (Trounce, 1961). Relaxation of the cardiac sphincter in response to acetylcholine would be compatible with the effects of direct stimulation of the vagus nerve (Clark and Vane, 1961). However, in the present experiments, direct stimulation of the vagus had mixed effects upon the ileocaeco-colic sphincter even at high frequencies of stimulation. Hinrichsen and Ivy (1931), in their original experiments in the dog, also noted variable responses to vagal stimulation. It may be, therefore, that the vagus carries both excitatory and inhibitory fibres to the ileocaeco-colic sphincter. Paton and Vane (1956) suggested that both adrenergic and cholinergic nerves occurred in the vagus. However, as both noradrenaline and acetylcholine, the accepted autonomic neurotransmitters, contract the sphincter, this does not at first appear to be the likely mechanism. In this context, however, it is interesting to speculate on the function of those β receptors in the sphincter which respond to isoprenaline. Trounce (1961), using transverse muscle strips from the human cardiac sphincter, reported that electrical stimulation of the intrinsic nerves or application of nicotine caused a relaxation of the muscle, an effect which was not blocked by atropine. Relaxation could also be induced by isoprenaline or by noradrenaline/adrenaline after pre-treatment with phentolamine. Trounce suggested that there were two types of adrenergic receptor, both functional. He did not elaborate upon this theory, but it is not inconceivable that an anatomical

separation of adrenergic nerve supply to the two types of receptor exists. Such an arrangement could account for the response of the ileocaeco-colic sphincter. Thus stimulation of sympathetic nerves or cholinergic fibres in the vagus would result in contraction, while stimulation of adrenergic fibres running in the vagus would bring about relaxation.

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