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SENSITIVITY OF THE SMALL INTESTINE

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In the earliest days of experimental physiology it was shown that the properties of the deep and surface sensory fields were different. William Harvey in 1668 noted that touching the human heart caused no sensation. von Haller (1755) demonstrated that many viscera could be severely injured without evidence of pain, both in man and in other animals.

With regard to the sensitivity of the small intestine, modern work has led to contradictory concepts. Sherrington (1906), in his analysis of the sensory fields, recognized an intero-receptor area including the intestine. This definition was based on the demonstration that stimulation of the viscera produced reflex responses in animals. To Ross (1888), Mackenzie (1920) and Morley (1931) the hollow viscera could be the source of nerve impulses provoking pain sensation, although these authors differed in their views on the physiological basis of the pain. On the other hand, Lennander (1902) again affirmed the apparent insensitivity of the intestine to such trauma as cutting, crushing, burning and stretching. No sensation was provoked by these stimuli applied to intestine exposed at operation, using local anaesthesia. Lennander suggested that pain accompanying disease of a hollow viscus is due to irritation of parietal peritoneum and of the sensory endings of cerebrospinal nerves therein. This would imply that the intestine lacks the neural apparatus which subserves pain sensation. Hurst (1911) attempted to bridge the gap between these concepts by invoking tension as an adequate stimulus for pain endings, but Lewis (1942) pointed out that destructive treatment could scarcely fail to stimulate all nerves and nerve endings in the intestine. In the experiments of Lewis & Kellgren (1939) it was found that pinching the intestine caused no reflex movements of skeletal muscle in spinal cats, whereas pinching the pancreas did so. In both instances there was rise of arterial pressure. Lewis (1942) has suggested that the apparent sensitivity of the intestine to some forms of stimulation and not to others depends upon the spread of the stimulus to adjacent mesentery. This does raise the question whether the intestine is sensitive to the same sorts of stimuli which affect the adjacent mesentery. Meyer (1919) obtained results in lightly etherized cats which suggested that pain arose only from the mesentery and not from the intestine. The pain-provoking stimuli—spasm induced by barium chloride, and distension—caused no response of the animal if the mesentery was protected from stretching. Certainly, whatever may be discovered about intestinal sensitivity, the mesentery is highly sensitive.

In the following paper an account is given of an experimental attack upon the problem of intestinal sensitivity. The principle of the work has been to record reflex actions following intestinal stimulation, taking care that the stimulus was confined to the intestine and that the preparation was responsive to any afferent impulses set up.

METHODS

Certain reflex responses were used as tests for the production of afferent impulses by nerve endings in the intestine. These were (*a*) pupil dilation in chloralosed cats (McDowall, 1925; Bain, Irving & McSwiney, 1935); and (*b*) leg movements and rise of arterial pressure in decerebrated-chordotomized cats (Downman & McSwiney, 1946).

In the first group of animals, chloralose 60–80 mg./kg. body weight, was injected intravenously during preliminary ether anaesthesia. In the second group of animals, the spinal cord was divided between the eighth cervical and first thoracic spinal roots after removing the first thoracic lamina and immediately afterwards the brain above the superior colliculi was removed through a trephine hole in the cranium. Bleeding from the severed cerebral vessels was controlled by tying both common carotid arteries and by temporarily compressing the vertebral arteries. The animals were left for 3 hr. to excrete the ether. Leg movements were observed with the naked eye, and pupil dilatation was observed through a low-power microscope; change of arterial pressure was recorded from a cannula in one carotid artery. The intestine was exposed by an incision through the linea alba, or by an incision through the belly wall in the right flank running forward from the renal area parallel to the lowest ribs. The latter incision exposes duodenum, jejunum, pancreas, and upper part of the colon. When the intestine was drawn out through the incision it was kept warm and moist by applying pads soaked in warmed 0·9% sodium chloride solution, or by immersing the trunk of the animal in a deep bath of Locke's solution (formula in Bain, 1938) at 37–38° C.

RESULTS

Entry of nerve impulses into the spinal cord may be signalled by dilatation of the pupil, rise of arterial pressure and movements of the hind legs. In this work these reflex responses have been used as an index of the production of afferent impulses on stimulating the intestine or mesentery. It may be remarked, in parenthesis, that the absence of such responses does not necessarily signify that no nerve impulses were set up by the applied stimulus. As pointed out in a previous paper (Downman & McSwiney, 1946), the condition of the central nervous system determines whether or not viscero-motor reflexes are obtainable. Deterioration of the preparation is shown by a loss of reflex leg movements upon pinching the intestine, although this stimulus still elicits a rise of blood pressure, showing that afferent nerve fibres have been stimulated. During these experiments the impression was gained that the chloralosed cat might respond to weaker mechanical stimuli than did the acute spinal animal. Otherwise the results obtained in the two preparations were similar.

Stimulation of Small Intestine

Mechanical stimulation. Stimulating any region of the small intestine mechanically sets up afferent impulses in mesenteric nerves, these being signalled by reflex responses. The effective stimuli include compressing or cutting the intestine and also scratching or rubbing its surface with the pointed or blunt ends of a needle. Distension with a balloon is also effective.

The effectiveness of compression was shown in the following ways. The intestine could be pinched with the tips of blunt dissecting forceps or with Halsted's forceps, the tips of the blades being covered with thin rubber tubing to prevent the serrations on the blades breaking the surface. The pinches were effective if the blades of the forceps lay across the intestine or if the blades were directed lengthwise along the gut. Using a pair of Babcock's tissue forceps it was possible to pinch the whole thickness of the gut, over a length of 1 cm., at any site between the free edge of the intestine and the edge bearing the mesentery. It was found that pinches were equally effective when made at the free edge, or near the mesenteric attachment or at any intermediate place. No attempt was made to calibrate the strength of the pinches, but responses followed pinches which could be borne comfortably on the webs of the fingers and which produced no rupture of the serosa, subserosa or muscle. As described in a previous paper, evidence of deterioration of the decerebrated-spinal preparation was the need to pinch the gut more strongly to elicit reflex responses; chloralosed cats tended to show increasing threshold to distension and progressive widening of the pupil. Under these circumstances the threshold pinches had to be so strong that the muscle layers were felt to break beneath the blades of the forceps.

Cutting the intestine was an effective stimulus. This was shown by cutting with a razor-sharp blade along the 'watershed' line at the free edge of the intestine, making an incision which was generally 1–2 cm. long. Cutting lengthwise anywhere between the free and the mesenteric border was effective, but away from the watershed line larger blood vessels were divided and produced copious bleeding. Comparing the reactions of different animals it was noted that all those sensitive to cutting were sensitive to light pinches, but in others cutting was ineffective when light pinches were still effective. The cuts were effective when only the serous coat and the more superficial muscle fibres were severed.

Scratching the surface of the intestine with a needle point, or stroking it with the blunt head of a needle, elicited reflex responses. The pressure of the needle was sufficient to cause a slight depression of the serosa, and when using the point the serosa was torn, as shown by the subsequent line of punctate haemorrhages. When using the blunt head of the needle no macroscopic damage was caused, but it was noted that a single stroke of the needle was insufficient, five or more consecutive strokes being required. It must be emphasized that the two sorts of stimuli just described were effective in cats which seemed to be very sensitive to other stimuli, and were the first type to become inadequate as the preparation deteriorated.

Squeezing the intestine firmly between finger and thumb without tautening the mesentery elicited vigorous reflex response. Even when the condition of the animal was deteriorating, as shown by rising threshold to pinching, squeezing remained an effective stimulus. Indeed, when the animal did not respond to squeezing about an inch of the intestine firmly, it did not respond to any other stimulus applied to the intestine or adjacent mesentery.

Stimulation by heat. Heating the intestine, by applying a hot body to it, set up afferent impulses. This was shown most easily by very gently dabbing the intestine with pledgets of cotton-wool dipped in hot 0·9% sodium chloride solution. A better method was to touch the surface of the intestine with the bend of a thin silver tube, 2 mm. bore, bent sharply into a U-shape, and through which hot water was sucked as quickly as possible. Using the silver tube applicator it was found that all parts of the intestinal surface, between its free and mesenteric edges, was sensitive to heat. The lowest effective temperature was 46° C.

Cold did not produce afferent impulses. No reflex response followed even the application of ice directly to the intestine, or of the tip of a brass rod, 8 mm. diameter, cooled to $-15°$ C. in ice and salt, although the latter process produced a hard white plaque where the tissue froze.

Stimulation by chemicals. Solutions of potassium chloride 1·3%, sodium chloride 10% and hydrochloric acid 1 N. or 0·1 N. were all effective stimuli. The solutions were applied to the surface of the intestine in pledgets of cotton-wool soaked in the solution without allowing any to run on to and wet the mesentery.

Electrical stimulation. Induced currents from an induction coil were effective at a stimulus strength which produced strong contraction of the gut, and was too strong to be borne comfortably on the human tongue.

Stimulation of the mesentery

All the stimuli which have been described as adequate for the intestine elicited reflex actions when applied directly to the mesentery close to the intestine. In addition, rubbing the surface of the mesentery gently with a finger tip or a moist pledget of cotton-wool was also effective, these stimuli being ineffective when applied to the intestine itself.

Origin of the impulses

It has just been pointed out that stimuli which are effective when applied to the intestine are also effective when applied directly to the mesentery nearby. It may be, and indeed has been, postulated that all the reflexogenic impulses arise by indirect stimulation of the mesentery, the stimulus spreading in some way from the intestine. When, however, care was taken that such spread should be prevented, application of the stimuli to the intestine still elicited reflex responses. The conclusion is drawn that the intestine is itself the source of the impulses. The experimental evidence for this, with some consideration how the stimulus might have spread to the mesentery and how this was prevented, is given below.

Elimination of mechanical spread. The act of pinching, cutting or rubbing the surface of the intestine might affect the mesentery if movement of the gut caused the sensitive mesenteric surface to rub on any adjacent surface or if the

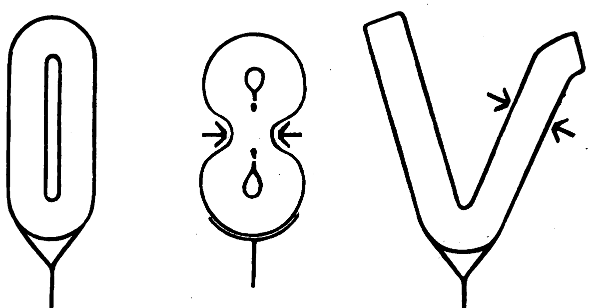

Fig. 1. The small intestine, *A*, when pinched from side to side may bulge and distort the mesenteric attachments, as in *B*. After laying open the intestine along the watershed line, *C*, the wall can be pinched without affecting the mesentery; reflex responses are still obtained. Diagrammatic cross-section.

mesentery was unintentionally tautened. These stimuli were still effective, however, if the intestine was firmly anchored between finger-and-thumb and the stimulus applied to the exposed outer edge of the intestine; or if the loop of the intestine was slung up from two cotton loops threaded through the intestine wall at places 2 in. apart, leaving the mesentery hanging free. Furthermore, with the mesentery and gut floating freely in the bath of Locke solution, pinches were effective before any local contractions of the intestine were seen and without visible movement of the mesentery. Conversely, moving the gut in the bath to produce considerable side-to-side displacement of the mesentery caused reflex response only when the mesentery was pulled taut.

It may be objected that pinching the intestine caused a slight bulging of the wall alongside the forceps blades. Such bulging might affect the mesentery by causing a separation of its intestinal attachments. If the gut was laid open by incising it along its free edge, one thickness of its wall could be pinched. This still produced reflex responses, but it is difficult to see how the mesenteric attachment could be affected (Fig. 1).

Distending the intestine may fail to be an adequate stimulus while other stimuli applied to the intestine are still effective. In some chloralosed cats it was noted that distending a loop of small intestine with a balloon to 100 mm. Hg pressure elicited no dilation of the pupil. Pinching the same piece of intestine with foreceps elicited pupil-dilation. It is difficult to see how the pinch could have affected the mesentery more than did the distension.

Elimination of spread of thermal stimulus. Applying the hot silver tube to the intestine along its free edge could conceivably raise the temperature of the mesentery by direct conduction of heat and by the return of heated blood along the intestinal veins. No attempt was made to counteract this, but it may be pointed out that when the hot tube was placed inside the intestine, temperatures much higher than those which stimulated the outer surface were now ineffective (see later).

Elimination of spread of chemical stimuli. Clearly any solution placed on the intestine may spread quickly by diffusion on to the mesentery. This was counteracted by covering both sides of the mesentery with vaseline which had been warmed until soft. The vaseline was also spread over the mesenteric edge of the intestine itself. When potassium chloride solution was placed on the bare intestine reflex action resulted, but placing the solution on the vaseline-coated mesentery was without result.

Stimulation of intestinal mucosa

Attempts were made to elicit the reflex responses described. It may be said at the outset that drastic stimuli applied to the mucosa were apparently ineffective. The stimuli included heat, cold, chemical substances including strong irritants, pinching and scraping.

Heat was applied by slipping the silver U-tube, 2 cm. long, into the lumen of the intestine, bringing the rubber tubes connected to it out through the small incision made in the intestinal wall. Heating the tube to 60° C. was ineffective; heating it to 80° C. did elicit reflexes but this temperature is so high that the outer layers of the intestine may have been heated.

Solutions were passed through 3 to 6 in. of the lumen of the small intestine by tying into the intestine two wide glass tubes inserted through short incisions in the wall. Perfusing 1·3% potassium chloride, 10% sodium chloride, 70% ethyl alcohol, 5% zinc sulphate, N. hydrochloric acid gave no results. Running in a 2% suspension of mustard in water, and leaving it in, was also ineffective although it caused the intestine to discharge much mucus from its lumen and the mucosa was reddened and haemorrhagic when examined subsequently. On the other hand, placing any of these on the external surface of the gut produced reflex responses.

The mucosa was scraped roughly with a knife edge, after laying the gut open along its free edge, without result. The mucosa was also pinched with forceps. This was done by laying open the intestine and then pulling up the mucosa from the underlying muscle, when it stripped away easily down to the line where large vessels run in through the muscle layers. Although pinching the mucosa gave negative results, pinching the muscle and serosa from which it had been stripped gave positive results (Fig. 2). It may also be noted that, when testing the sensitivity of the intestine to cutting, the reflexes were produced when the knife blade severed only serosa and the most superficial muscle fibres, leaving the mucosa untouched.

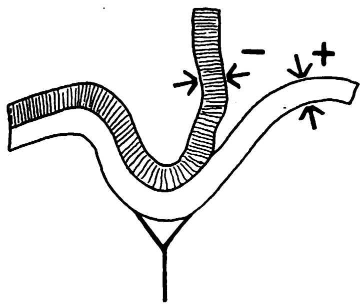

Fig. 2. Diagrammatic cross-section of small intestine, showing mucosa and muscle layers separated by splitting through the submucosa when the intestine had been cut open. Pinching the thickness of the mucosa produced no reflex response; pinching the muscle coats produced reflex responses.

DISCUSSION

These experimental results show that nerve impulses can be set up by applying a wide range of physical and chemical agents to the outer surface of the exposed intestine. The centripetal impulses are able reflexly to activate motoneurones, innervating skeletal and visceral muscle, in the spinal cord and the brain stem as high as the oculomotor nucleus. Further, in the acute spinal animal the occurrence of leg movements and blood pressure changes demonstrates that the centripetal impulses can activate spinal reflex arcs directly without the intervention of higher sensory centres. The role of such impulses in the normal animal is still unknown; indeed, the stimuli employed would not occur in a normal peritoneal cavity, and it is probable that the forms of stimuli used in these experiments are merely non-specific stimuli to nerve endings or nerve fibres. It is possible that these same nerve fibres may be activated in abnormal conditions of the intestine to produce the abdominal muscular rigidity associated with such abnormal conditions. Whether or not these fibres are pain fibres, that is, afferent fibres carrying impulses which ultimately affect high sensory levels to produce a conscious sensation of pain, is a question which awaits an answer.

In animal experiments one must beware of using reflex actions, not involving thalamus or cerebral cortex, to identify pain fibres.

The intestine itself reacts to the stimuli employed, at least when its outer surface is stimulated. Preventing the spread of the stimulating agent to the adjacent mesentery does not abolish the response of the intestine. It is to be concluded therefore that the affected nervous structures lie within the intestine. Broadly speaking the surface of the intestine and the mesentery are sensitive to the same qualities of stimulation, but the latter is also sensitive to the very mild stimulus of gentle rubbing. There is a great physiological difference, however, between the two sensory areas. As pointed out in this and in a previous paper, conduction through the reflex arcs associated with the intestine is lost before conduction through the arcs associated with the mesentery. This is seen experimentally in the loss of responses to intestine stimulation, with retention of those to mesentery stimulation. Sheehan (1932) has shown that the mesentery carries a fine meshwork of nerve fibres ending within the mesentery, and it is possible that these fibres are responsible for eliciting the reflexes from the mesentery when the condition of the animal is deteriorating. The ability of the afferent impulses to cause reflex actions may depend upon the number of nerve fibres involved, that is to say, upon the length of intestine affected. Thus a long scratch was an adequate stimulus whereas a prick of the serosa at one point was inadequate. Also, as the preparation became less sensitive to the stimuli, it was found that responses could be obtained only by stimulating larger areas of the intestine and the effectiveness of squeezing as a stimulus may depend upon the stimulation thereby of a large number of nerve fibres.

Meyer (1919) found that application of barium chloride or distension of the gut by a balloon caused no struggling of lightly etherized animals if care was taken to prevent the spasm or ballooning of the gut stretching the intestinal mesentery. The presence of struggling, when the mesentery was stretched, was interpreted as a reaction which would be accompanied by the sensation of pain in a conscious animal. Lewis & Kellgren (1939) also found that stimulating the intestine in spinal cats did not provoke reflex skeletal muscle movements whereas stimulating the pancreas, with the mesenteric covering, did so. All these authors concluded that there is missing from the intestine one set of nerve fibres—the pain-receiving system. It cannot be proved at the moment that this is not so, but it is very doubtful if one can use an objective reflex movement as a criterion that the same centripetal impulse could provoke a subjective sensation of pain if the pain-perceiving centres were intact and non-narcotized. Furthermore, the absence of responses on stimulating the intestine may represent no more than the deterioration of the reflex arcs associated with the intestine which is provoked by trauma to the intestine.

Confirmation that the intestine is provided with specific sensory fibres, including the small fibres associated with pain end-organs in other parts of the body, comes from electro-physiological investigation of intestinal sensitivity. Both Tower (1933) and Burns (1941) have recorded afferent impulses of low potential from frog gut during strong pressure or other injurious stimuli, and Tower has also recorded such impulses during stimulation of the gut mucosa. More recently Gernandt & Zotterman (1946) have shown that pinching or squeezing cats' intestine provoked slow small spike potentials in the mesenteric nerves, and touching the intestine at a few very localized points on its outer surface produced large rapid spike potentials. These authors, assessing the sensitivity of the intestine in terms of the pattern of nerve impulses, compared the intestine to skin lacking the fast conducting afferents which respond to vibration and light mechanical stimuli as well as to stronger pressure.

The reflexogenic impulses set up in our experiments came from the serosa and muscle layers. Applying destructive stimuli to the mucosa was ineffective, but stimulating the muscle-serosa layer after stripping off the mucosa was still effective. Since scratching was sometimes an adequate stimulus, it is suggested that at least some responsible nervous structure lies within the serosa or subserosa. Whether the impulses were set up by stimulating nerve endings, or whether they were set up by non-specific stimulation of nerve fibres, is an open question.

It should be pointed out that, after completion of this paper, one of the authors (C.B.B.D.) recorded a rise of blood pressure upon pinching the mucosa in chloralosed cats. The muscle coats were stripped back off the mucosa and submucosa without opening the lumen of the intestine. These positive responses re-open the question of mucosal sensibility but do not affect the authors' conclusions concerning the sensibility of the whole intestine or serosa-muscle layers.

SUMMARY

1. In cats, stimulating the exposed small intestine produced dilation of the pupil in chloralosed animals, and leg movements with rise of blood pressure in spinal-decerebrate animals.

2. Effective stimuli were pinching, squeezing, cutting, scratching with a needle point, rubbing with a needle head, heating above 46° C., and applying such solutions as 1·3% potassium chloride, 1 N. or 0·1 N. hydrochloric acid or 10% sodium chloride.

3. Ineffective stimuli were local cooling or freezing, and rubbing the surface gently with the finger tip.

4. These stimuli were effective when the possibility of their spreading on to the adjacent mesentery was prevented.

5. Attempts to elicit reflexes by application of heat or irritant chemicals to the mucosa were ineffective in this series of experiments.

6. It is concluded that the intestine has a sensory nerve supply which is anatomically and physiologically distinct from that of the adjacent mesentery.

7. No conclusion can be drawn as to the nature of the nervous structures stimulated. The relationship between the reflexogenic impulses and pain impulses is discussed.

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