THE INTESTINO-INTESTINAL INHIBITORY REFLEX: THRESHOLD VARIATIONS, SENSITIZATION AND SUMMATION

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The qualitative features of the reflex inhibition of the intestine which occurs in response to stimuli arising from alterations of pressure within it have been studied in several laboratories. This information has been summarized in a collective review (5). The present study is concerned with (i) the factors that cause variation in the effectiveness of a given distention, in eliciting reflex inhibition of intestinal motility, and (ii) the relation of length of intestine distended to the pressure that is required to initiate the reflex.

METHOD

Four dogs were prepared, each having one Thiry and one Thiry-Vella fistula which were made from adjacent segments of the upper jejunum. All extrinsic nervous pathways were left intact. Motility from an intestinal segment in the form of a Thiry fistula (indicator segment) was recorded by the balloon-mercury-manometer method (7) in unanesthetized, unmedicated animals. A measured volume of water was introduced into the balloon-mercury-manometer system by means of a side-arm, and this volume remained unchanged throughout the experiment. Motility in this segment served as an indicator for the effects of pressure changes produced by means of balloons in a Thiry-Vella fistula. Pressures in the two balloons used for distending portions of the Thiry-Vella Fistula were controlled by connecting a gravity pressure bottle with the balloon-mercury-manometer systems. In some studies, balloons of varying length were successively introduced, so as to include the same section of the

Thiry-Vella fistula. In other experiments, balloons were placed one within the proximal and the other within the distal end of the Thiry-Vella fistula, and a distending pressure was established alternately or simultaneously in the two balloons.

RESULTS

The observations described are based on 60 experiments in 4 dogs, involving more than 300 distentions.

I. Variations in effectiveness of a single distention. Previous studies of the reflex in unanesthetized animals have indicated that intensity, duration and rate of change of the stimulus are factors which alter the reflex response. The response to graded distentions of a segment of intestine is a graded reflex inhibition of the indicator segment. A single distention may be ineffective, subthreshold, threshold, submaximally effective or maximally effective. Further observations confirm the previous report (7) that the threshold for an effective distention is elevated when there is a slow rate of increase in the pressure; and that a sudden increase in pressure is more effective in producing inhibitory effects than a step-by-step increase to the same or even to a somewhat higher level. There is slow adaptation to a distending pressure, and sustained pressures result in prolonged inhibitory effects.

A distending pressure in one end of a Thiry-Vella loop, when just sufficient to inhibit the opposite end of the segment, may cause no inhibitory effects in the indicator segment which has no intrinsic

connections with the loop distended. This result is illustrated in Fig. 1. This is further evidence that the intrinsic mechanisms of the intestine contribute to the inhibitory influences of intestinal distention.

There is a variability in the minimal pressure that is required to elicit the reflex, in different animals and in the same animal under altered conditions. Youmans, Karstens and Aumann (6) observed that wide individual variations exist between animals. Pressures from 35 to 100 mm. of Hg. were required to elicit the reflex. In the present study, the pressure required to elicit comparable inhibitory effects in the same animal, on different days, has varied not more than 8 mm. of Hg. Theoretically, it might be expected that a distention in one part of the jejunum would have a different reflex effect than an identical distention in a more distal part. However, comparable submaximal inhibitory effects were obtained in the indicator segment from identical distending pressures in the same balloon, placed first in the distal then in the proximal end of the Thiry-Vella fistula. The fistulas were 30 cm. long. The possibility remains that a gradient effect might be demonstrated, by comparing reflex effects of distention of two intestinal segments that are more widely separated than those used in the present study.

II. Sensitization by a previous distention. Lalich, Herrin, and Meek (3) reported that the intestino-gastric inhibitory reflex is reinforced by subjecting a Thiry fistula to a continuous distending pressure for twenty-four hours before redistention. It has been shown that after a

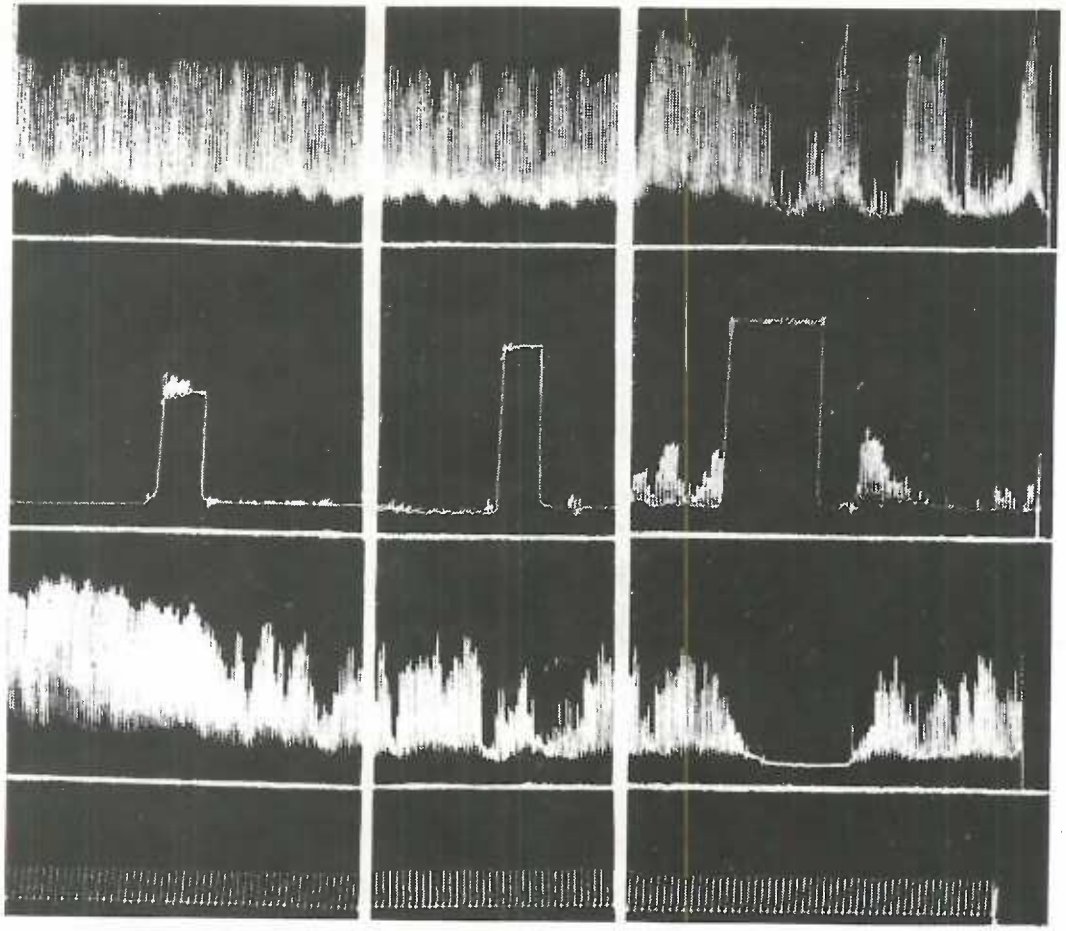

Fig. 1. Comparison of responses in the proximal end of a Thiry-Vella loop with response in a Thiry loop, produced by distention of the distal end of the Thiry-Vella loop. From above downward there is illustrated 1, motility of Thiry loop; 2, zero pressure level; 3,distal end of Thiry-Vella loop; 4, zero pressure line; 5, proximal end of Thiry-Vella loop; 6, zero pressure level; 7, time in 10 second intervals. Breaks in record, duration of 10 and 20 minutes respectively. Distending pressures, 45, 60 and 72 mm. Hg respectively. See text for further explanation.

previous distention of the jejunum, if the rate of change of the stimulus is not altered, a second distention of shorter duration will surpass the first in causing inhibitory effects in an indicator segment (7). No attempt was made to determine whether the reinforcement was on the basis of a central or a peripheral sensitization. In the present study, it was found that the threshold for the intestino-intestinal reflex could be reduced by as much as one-half, by a series of brief, effective distentions. The successive distention of the same section of a Thiry-Vella loop with subthreshold pressures will finally produce reflex inhibitory effects in the indicator segment. If a single subthreshold pressure is maintained for a prolonged period of time, it may so sensitize the reflex mechanism that redistention will result in inhibition of the indicator segment. This result is illustrated in Fig. 2.

Possible sites in the reflex arc at which sensitization might occur are at receptor end organs, at synapses or at the neuro-effector junction. The following results indicate that the sensitization is peripheral and at the site of distention. If the threshold effective pressure is determined for a section of the Thiry-Vella fistula, distention of a second section of the segment with a pressure which would ordinarily sensitize that area to redistention does not influence the threshold for the reflex in the first section. A sustained and prolonged subthreshold distention in one end of the Thiry-Vella fistula will sensitize locally, so that a subsequent distention of similar intensity at the same site will elicit the reflex. However, a subsequent identical distention of the opposite end of the segment is ineffective. This result is illustrated

in Fig. 2.

The exact nature of the peripheral sensitization has not been determined. The alteration in irritability of receptors is roughly proportional to the intensity and duration of the distending pressure. Sensitization to redistention occurred when a distending pressure of 26 mm. of Hg. was used. This is illustrated in Fig. 2. Thus sensitization occurs at pressures significantly lower than those required to block the local circulation (2) and well within the range of pressure created by intestinal contractions. This result introduces the possibility that the sensitization observed in these experiments may be a physiologic phenomenon.

III. Relation of length of intestine distended to pressure required to elicit the reflex. The minimal pressure which will elicit the intestino-intestinal inhibitory reflex is comparatively high, when a distending balloon 5 cm. in length is used. Pressures ranging from 35 to 100 mm. of Hg. are required (6). Such pressures far exceed intraenteric pressures recorded from clinical cases of intestinal obstruction (4), though they are approximated by the pressures developed in the closed-loops of experimentally obstructed animals (1). Previous studies do not indicate whether the intestino-intestinal reflex functions within physiologic limits, or if it can be elicited only by high, artificially-produced, distending pressures. It is on this basis that one might question the role of reflex inhibition of intestinal motility by intestinal distention as a contributing mechanism to the perpetuation of distention, in ileus and intestinal obstruction. However, the minimal

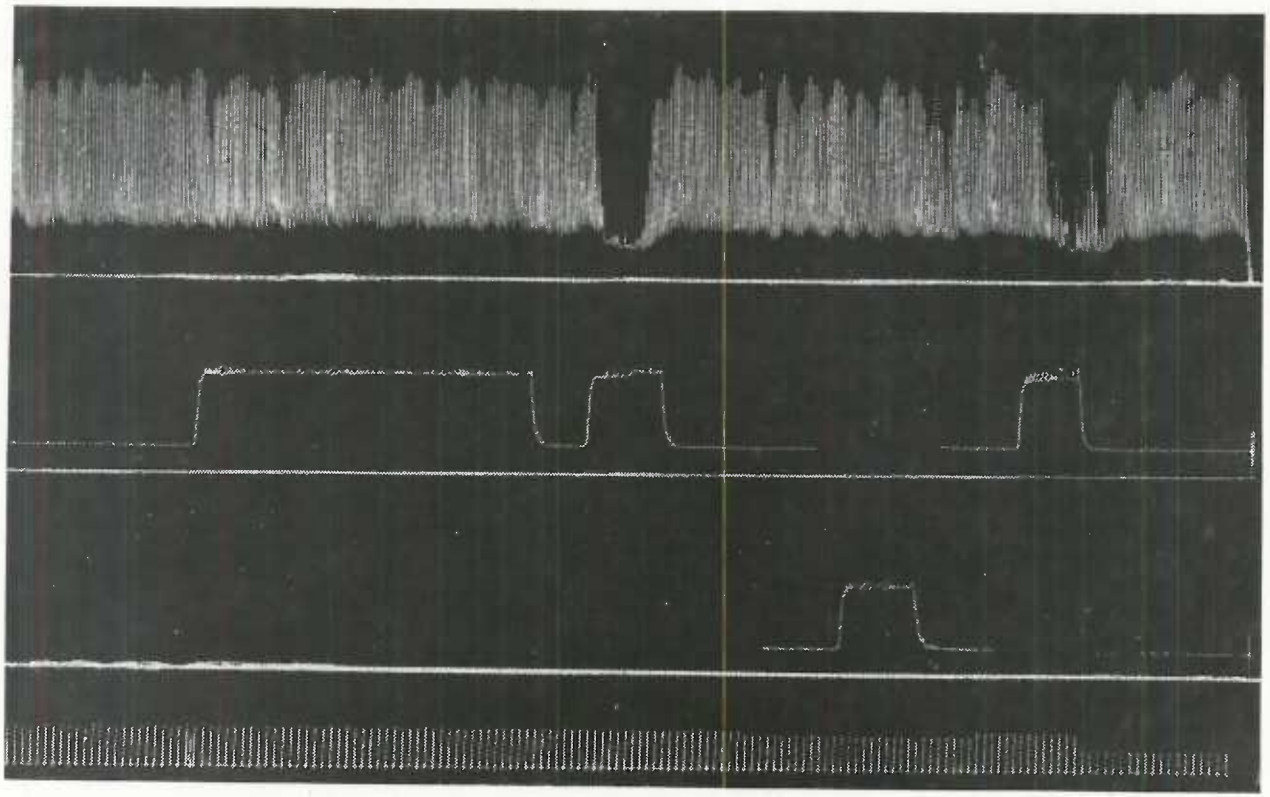

Fig. 2. Sensitization of the intestino-intestinal inhibitory reflex by a previous distention, and demonstration that sensitization is peripheral and at the site of distention. From above downward there is shown 1,. balloon-mercury-manometer record of jejunal Thiry loop (indicator segment) in an unmedicated, unanesthetized dog; 2, zero pressure level; 3, pressure record in proximal end of a Thiry-Vella loop, distending pressure of 26 mm. Hg in a 5 cm. balloon; 4, zero pressure level; 5, pressure record in distal end of the Thiry-Vella loop, distending pressure of 26 mm. Hg in a 5 cm. balloon; 6, zero pressure level; 7 time in 10 second intervals. See text for further explanation.

pressure that is required to elicit the reflex when a 5 cm section of bowel is distended provides no information concerning the fundamental problem of the minimal intraluminal pressure that will initiate impulses on the afferent side of the reflex arc.

The role of spatial summation in the production of a normal reflex discharge indicates that this phenomenon would be expected to occur, when the intestino-intestinal reflex is activated. It can be shown in several ways that summation does occur. The results of one type of experiment demonstrating summation are illustrated in Fig. 3. The simultaneous combination of subthreshold distentions in two distending balloons of equal length, placed in opposite ends of a Thiry-Vella fistula, is followed by inhibition of tonus and motility of the indicator segment. Control distentions, before and after simultaneous combination of the distending pressures, offer evidence that sensitization by previous distention of either segment is not responsible for the inhibition.

Another type of experiment demonstrating summation is illustrated in Fig. 4. The proximal end of a Thiry-Vella fistula was first distended by a pressure of sufficient magnitude to elicit severe inhibition when a 15 cm. segment of the Thiry-Vella loop was utilized. An identical distending pressure was less effective after the balloon had been changed, so as to involve only a 5 cm. segment. The possibility that the results of this experiment may be explained by sensitization, or by differences in the threshold on the basis of an intestinal gradient, is ruled out by the following facts. The distention of the shorter section is less effective following a previous distention in the longer section of the

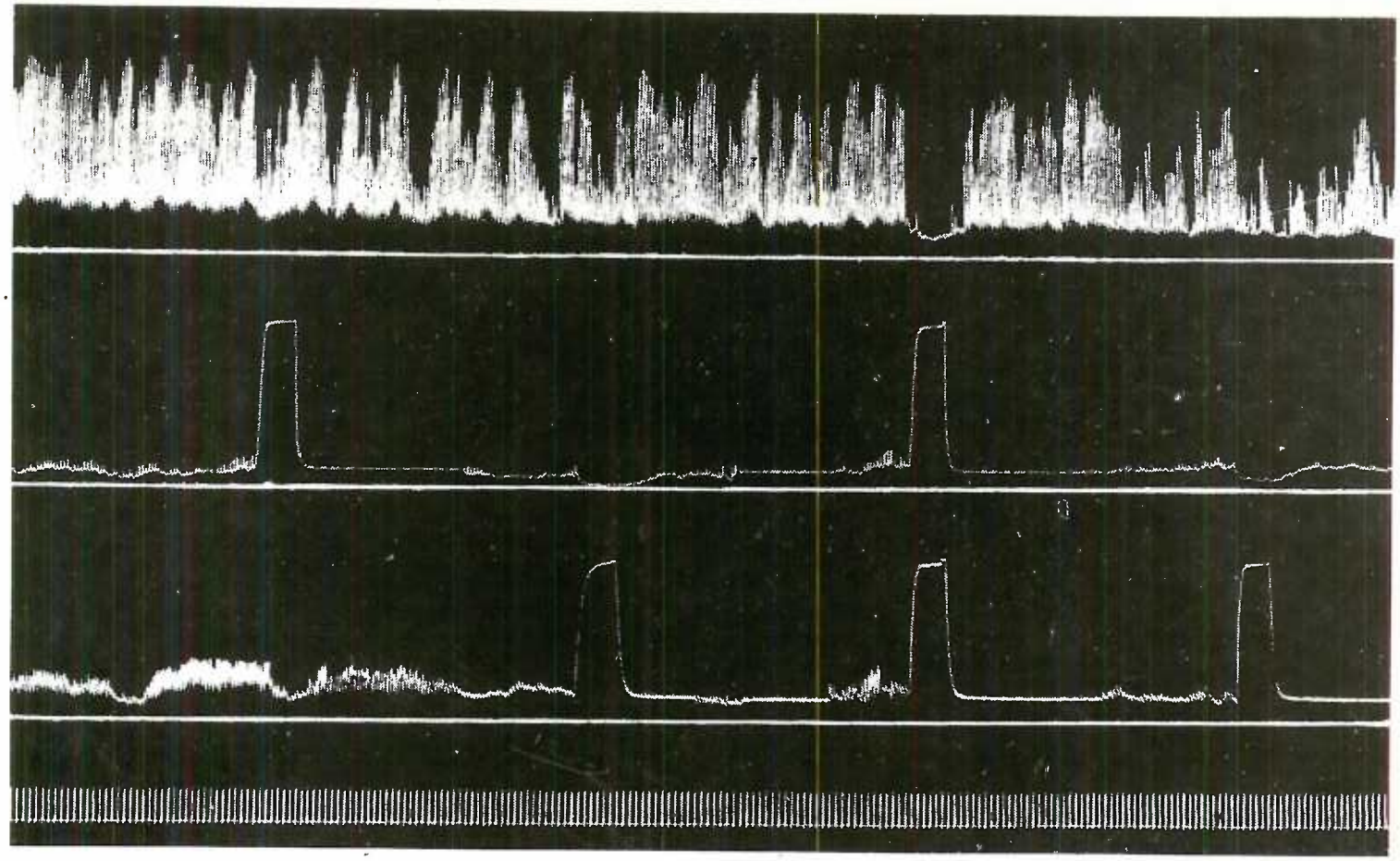

Fig. 3. Summation of the intestino-intestinal inhibitory reflex, shown by inhibitory effects on the indicator segment from the combination of separately subthreshold distentions of the proximal and distal ends of a Thiry-Vella loop. From above downward the writing points are arranged as in figure 2. See text for further explanation.

segment with an identical pressure, in spite of the fact that sensitization would tend to make the second distention more effective, if the balloon length were unchanged. The results presented in section I indicate that gradient effects do not require consideration in these experiments, where the balloons are not more than 20 cm. apart. Moreover, adjacent segments of intestine were distended in these experiments.

SUMMARY AND CONCLUSIONS

1. The factors that determine the minimal pressures required to elicit the intestino-intestinal inhibitory reflex have been studied in unanesthetized dogs, by recording the responses of one intestinal segment (Thiry fistula) during the distention of another segment (Thiry-Vella fistula) with balloons of various lengths and utilizing various pressures.

2. The minimal pressure required to elicit the reflex is lowered as the length of the jejunum distended is increased. The effectiveness of a given pressure in eliciting the reflex is greater as the length of the jejunum distended is increased. These results may be readily explained on the basis of spatial summation in the central nervous system, or in the autonomic ganglia involved.

3. An effective distention of any duration, or a prolonged subthreshold distention, will sensitize the intestinal segment to redistention. Evidence

is presented that this is a peripheral sensitisation occurring at the site of distention.

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