

THE EFFECT OF ADRENALINE AND NORADRENALINE ON THE ACTIVITY OF ISOLATED PREPARATIONS OF THE GUT FROM THE FOETAL GUINEA-PIG

BY

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A motor response to adrenaline which occurs in the terminal part of the guinea-pig ileum and is stronger in small than in large animals has previously been described (Munro, 1951a). In view of this apparent relation between the adrenaline response and the size of the animal, it was considered worth while making some observations on the response of the foetal gut to adrenaline. The first few observations suggested that the terminal part of the isolated foetal ileum was relaxed by adrenaline. Further work, however, showed that considerable differences in the nature and the degree of response to adrenaline occurred in different terminal segments. The response was often purely motor, as in the adult; but in those segments whose response was a relaxation continued washing, associated with a reduction of the prevailing tone, usually changed it to a contraction.

The present paper describes the distribution of the motor response to adrenaline in the foetal gut, and compares the characteristics of the intestinal response to adrenaline and noradrenaline. It has been shown by West and Shepherd (1951) that the foetal suprarenal glands contain a higher concentration of noradrenaline than of adrenaline. It was therefore of interest to determine the relative effects of these two substances on the foetal intestine.

METHODS

Mature guinea-pig foetuses were used whose weights varied from 50–70 g.; the appearance of the foetuses was very similar to that of the animal after birth. Ten pregnant animals each provided from two to four foetuses. Those which could not be used immediately were destroyed by cutting the carotid arteries and were placed in the refrigerator, to be used when convenient, which was always within four or five hours from death. Preparations made from foetuses which had been frozen for this length of time responded similarly to fresh preparations.

The foetal small intestine varied in length between 16 and 20 in. Segments about 2 in. in length were removed from the required levels of the intestine and suspended in a bath of capacity 100 ml. containing Krebs's physiological salt solution. Four segments taken from different levels of the same intestine were suspended in one bath at the same time, so that simultaneous records were obtained under identical conditions. Drugs were added to the bath in a concentration of $1:2 \times 10^4$ from a 2-ml. pipette. The concentration of *dl*-noradrenaline in the bath was twice that of *l*-adrenaline when responses to the two drugs were to be compared.

RESULTS

Fig. 1A shows the responses to adrenaline ($1:1 \times 10^6$) of segments taken from different levels of the foetal intestine. The terminal ileum contracted; immediately higher segments gave progressively smaller contractions, and at still higher levels the response changed to relaxation. In the region of the duodenum there was a biphasic response with initial relaxation followed by a gradual contraction above the original tonus level. However, some preparations from the foetal duodenum only contracted and others only relaxed. When relaxation occurred, it was usually found that a second dose of adrenaline added to the relaxed tissue cause a contraction. By comparison with the foetal duodenum, the adult duodenum was never found to show anything other than an inhibitory response to adrenaline. The caecum and the colon were invariably relaxed by adrenaline. The whole stomach, on the other hand, was contracted by a similar strength of adrenaline.

Atropine added by itself usually produced a reduction of tone, although this varied in degree between one preparation and another. The responses to adrenaline of intestinal segments after exposure to atropine are shown in Fig. 1B. The contractions of the terminal and immediately

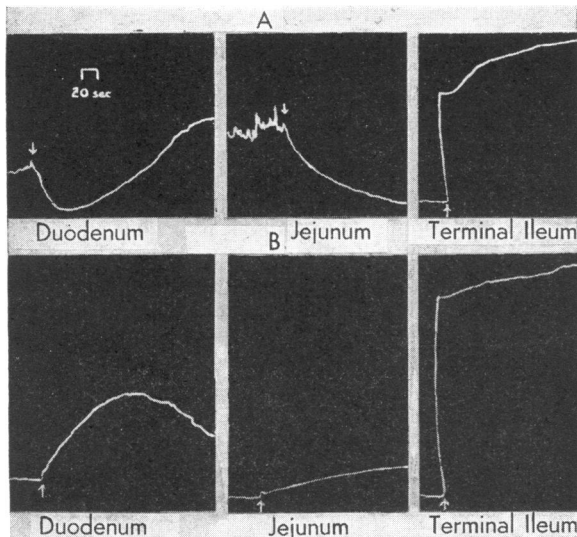


FIG. 1.—The response to adrenaline of isolated segments from different levels of the foetal intestine. (A) Adrenaline ($1:1 \times 10^6$) was added at the points indicated by the arrows. (B) The responses to adrenaline ($1:1 \times 10^6$) of the same segments after they had been washed and atropine ($1:7 \times 10^6$) added to the fresh fluid in the bath.

adjacent segments of the ileum were potentiated by atropine, the relaxation of the intermediate segments was changed to a contraction diminishing in strength with their distance from the ileo-caecal junction, and the biphasic response of the duodenum became purely motor. On the other hand, atropine did not reverse the inhibitory responses of the foetal large intestine or the adult duodenum to adrenaline.

These changes of response after exposure to atropine are to some extent related to changes in the state of tone. But this is not the whole explanation, as is evident from a consideration of the tracings shown in Fig. 2. Fig. 2A shows a biphasic response by a duodenal segment to adrenaline, but only a contraction when a second dose of adrenaline is added during the motor phase of the first response. In Fig. 2B a duodenal segment relaxed on addition of the first dose of adrenaline, but contracted after the second dose, which was added soon after the original state of tone had been restored by histamine.

Both motor and inhibitory responses were produced by noradrenaline. The response in any segment was similar to that produced by adrenaline, but usually slightly weaker. Adrenaline and noradrenaline each tended to abolish, or more usually reduce, the response to the other. That adrenaline is distinctly more effective in this respect is illustrated by the tracings shown in

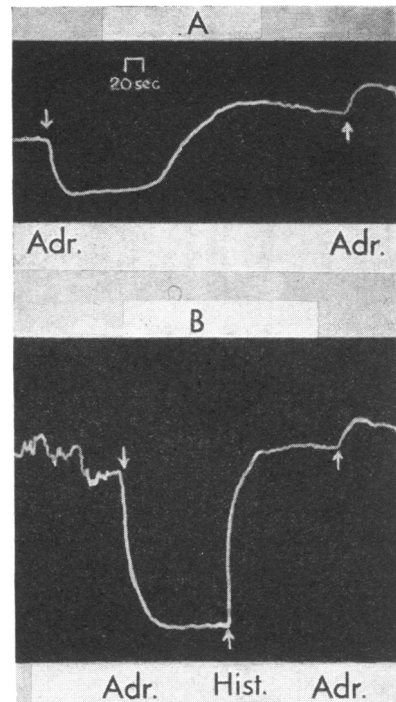


FIG. 2.—The state of contraction and the response of duodena preparations to adrenaline. (A) The first addition of adrenaline ($1:1 \times 10^6$) at Adr produced a biphasic response in this preparation; the second addition of adrenaline ($1:1 \times 10^6$) produced a contraction only. (B) In this preparation the first addition of adrenaline ($1:1 \times 10^6$) at Adr produced only relaxation. The initial level of tone was regained by the addition of histamine ($1:3 \times 10^8$) at Hist, and a second dose of adrenaline ($1:1 \times 10^6$) added at Adr caused only a contraction.

Fig. 3A and B. The relaxation of a duodenal segment by noradrenaline is cut short by adrenaline, while the relaxation of the same segment by adrenaline is only slightly affected by the equivalent dose of noradrenaline. The effects of adrenaline and noradrenaline on the same segment after it had been exposed to atropine are shown in Fig. 3C and D. Adrenaline is seen here to suppress the motor response to noradrenaline; but the motor response to adrenaline can still be produced in the presence of noradrenaline.

In earlier experiments (Munro, 1951b) employing isolated segments of the terminal ileum of adult guinea-pigs in which the prevailing tone was normally low, it was found that progressively smaller contractions were produced by diminishing the doses of adrenaline, and that a concentration in the region of $1:3 \times 10^7$ gave a threshold response. In the present experiments using segments of foetal ileum it was occasionally found that a contraction likewise was the only response to adrenaline in a concentration as low as

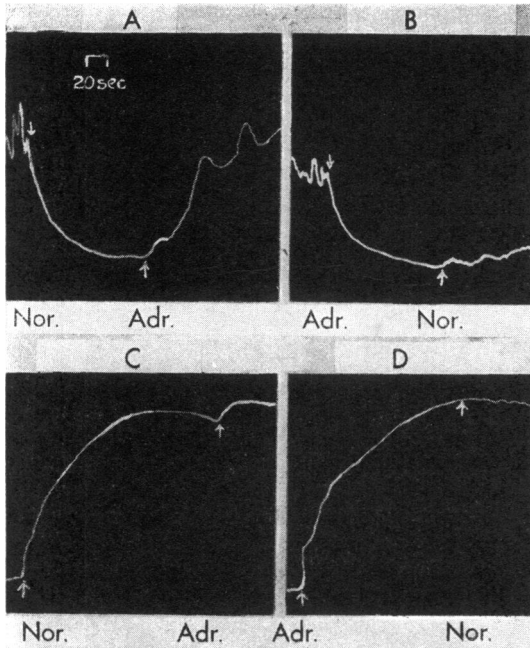


FIG. 3.—The effect of adrenaline on the responses of a duodenal segment to noradrenaline and vice versa. (A) *dl*-Noradrenaline (1.5×10^6) was added at Nor and adrenaline (1.1×10^6) at Adr. (B) The segment was washed and adrenaline (1.1×10^6) was added at Adr and *dl*-noradrenaline (1.5×10^6) at Nor. (C) The same segment was washed and atropine (1.7×10^6) was added 10 min. before the addition of *dl*-noradrenaline (1.5×10^6) at Nor; adrenaline (1.1×10^6) was then added at Adr. (D) The same segment again after washing and the addition of atropine (1.7×10^6). Adrenaline (1.1×10^6) at Adr and *dl*-noradrenaline (1.5×10^6) at Nor.

1.2×10^8 . However, it was often possible to show in segments of both foetal and adult terminal ileum, maintained in tone by histamine, that adrenaline in larger doses could produce contraction and in smaller doses relaxation of the same preparation. This is illustrated in a tracing from the isolated terminal ileum of an adult guinea-pig (Fig. 4). Tone was produced by exposure to histamine (1.3×10^8); the addition of adrenaline (1.7×10^7) then relaxed the preparation, but, when the initial tone was regained, the further addition of adrenaline to increase its concentration in the bath by 1.1×10^6 produced a strong contraction. Washing the preparation and adding adrenaline (1.1×10^6) again resulted in the segment contracting.

No part of the foetal intestine of the rabbit or the rat showed other than inhibitory responses to adrenaline either before or after exposure to atropine.

DISCUSSION

In most species adrenaline abolishes the tone and the rhythmicity of the longitudinal muscula-

ture of the small intestine. On the other hand, it contracts the sphincters, e.g., the ileo-caecal (Elliott, 1904). The fact that the duodenum and a variable length of the terminal part of the ileum are the parts of the small intestine which are contracted by adrenaline in the foetal guinea-pig rather suggests that in the foetus differentiation of function between sphincter and duodenal muscle (both of similar morphological origin) is as yet incomplete. But it is interesting that the motor component of the response to adrenaline should disappear from the duodenum during the further development of the animal, whilst it persists in the terminal part of the ileum. The motor response of the duodenum is at no stage so strong as that of the terminal ileum. A comparison of the contraction produced by adrenaline in foetal and adult segments shows that in the former it is usually more gradual in onset and more sustained. The foetal tracing is typically hump-backed with the initial rapid phase of the contraction relatively small in duodenal segments and large in segments from the terminal ileum.

The question arises whether these motor responses to adrenaline play any part in normal

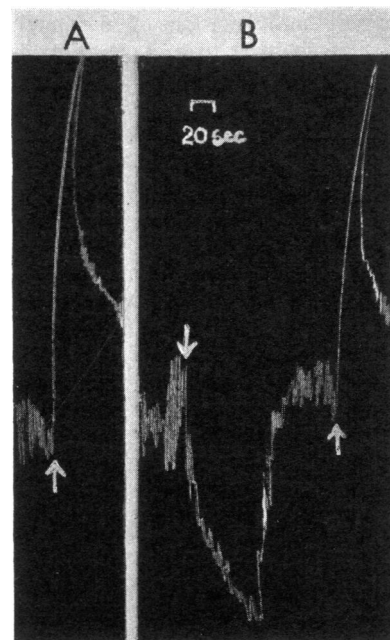


FIG. 4.—The relation between the dose of adrenaline and the type of the response. The preparation was taken from the terminal part of the ileum of an adult animal, and was maintained in moderate tone by the addition of histamine (1.3×10^8) to the bath fluid. (A) Adrenaline (1.1×10^6) was added at the point indicated by the arrow. (B) The same segment after washing and the addition of histamine as before. At the first arrow adrenaline (1.7×10^7) was added; at the second arrow adrenaline (1.1×10^6) was added.

function, either in the foetus or the adult. Since there is usually a reversal of the motor response in isolated preparations when the dose of adrenaline is sufficiently reduced, it appears likely that only relaxation would result from the concentration of adrenaline normally occurring in the circulating blood. Dale and Richards (1918) have described a similar type of reversal in the response of the blood vessels to adrenaline. A sufficiently great diminution in the dose of adrenaline may also change the response of the longitudinal muscle of the isolated rabbit ileum (Hoskins, 1912), but in this preparation it is the higher concentration of adrenaline which causes relaxation.

It would appear that the prevailing tone of the preparation has some effect in determining whether the response to adrenaline will be motor or inhibitory, but this is clearly not the only factor of importance. A single dose of adrenaline applied to a duodenal segment usually produces a biphasic response, but when successive doses of adrenaline are added to such a preparation without intervening washing, it is only the first dose which produces a response with the inhibitory component present. Adrenaline would thus appear to attach itself preferentially to the inhibitory receptors and to saturate them more readily than the motor receptors.

No great difference was observed in the strength of either the motor or the inhibitory responses of foetal intestinal preparations to equivalent concentrations of adrenaline and noradrenaline. Nevertheless, the observations showed that their action was not identical. Adrenaline was able to overcome the inhibitory response to noradrenaline, and, in those experiments in which the response to noradrenaline was motor, to produce

a superimposed contraction. Noradrenaline, on the other hand, was much less effective in modifying the responses, either motor or inhibitory, to adrenaline. If the difference were due to more rapid destruction of noradrenaline than of adrenaline it would be expected that the response of the preparation to noradrenaline would be less sustained than that to adrenaline. Since the responses were similar in this respect, some other explanation must be sought for the difference between the two drugs.

SUMMARY

1. Adrenaline and noradrenaline caused contraction of isolated segments taken from the two ends of the small intestine of the foetal guinea-pig. The intervening region was either relaxed or not affected. Atropine potentiated the adrenaline motor response and reversed the adrenaline inhibitory response.

2. A dual response to adrenaline has been demonstrated in segments from both foetal and adult terminal ileum. Larger doses cause contraction and smaller doses relaxation.

3. Adrenaline reduces or abolishes both the contraction and relaxation caused by noradrenaline in segments from the foetal ileum.

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