

THE ACTIONS OF PROSTAGLANDINS E_2 AND $F_{2\alpha}$ ON HUMAN FOETAL INTESTINE

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Human foetal small and large intestine responded to prostaglandins E_2 and $F_{2\alpha}$, the gestational age of the tissue being between 14 and 26 weeks. The predominant response to both prostaglandins was a contraction of each region of the intestine studied. The response to both prostaglandins was antagonized selectively by polyphlorethin phosphate.

Human foetal intestine contains muscarinic receptors (Boreus, 1967, 1968) and adrenoceptors (Hart & Mir, 1971a & b) at an early stage of gestation and in this work the response of the tissue to prostaglandins E_2 and $F_{2\alpha}$ is investigated.

Methods The whole of the gastro-intestinal tract was removed from the foetus after the legal termination of pregnancy. Termination was induced either with prostaglandin (Karim & Sharma, 1972) or with noradrenaline (J.J. Amy, personal communication). The tissue was stored in Krebs solution at 4°C. One to thirty hours after removal from the foetus, 2-3 cm of the intestine was suspended in a 10 ml bath containing Krebs solution bubbled with 5% CO_2 in O_2 at 37°C. Tone and movements of the longitudinal muscle were recorded with either an isometric transducer or a frontal writing lever under a tension of 1-2 grams. Tissue was taken from one of six regions of the intestine, namely, duodenum, ileum, distal ileum, ascending, transverse or descending colon, and was allowed to equilibrate for 2 h before the administration of drugs.

Each tissue was shown to be capable of responding to acetylcholine and to noradrenaline before the actions of the prostaglandins were studied. The action of noradrenaline was superimposed on an acetylcholine-induced contraction in those tissues with a low resting tone. In these circumstances, the prostaglandins were also administered during the acetylcholine-induced contraction.

Reproducible responses were obtained with a dose-cycle of 5 min and a contact period of 1-3 minutes. A contact time of 10 min was allowed for hyoscine and 1 min for polyphlorethin phosphate, before the administration of the agonist.

The drugs used were acetylcholine bromide, noradrenaline bitartrate, prostaglandin E_2 , the THAM salt of prostaglandin $F_{2\alpha}$, hyoscine hydrobromide and the sodium salt of polyphlorethin phosphate (PPP). The concentration of PPP refers to the salt and that of other drugs is the final bath concentration of the free base.

Results Twenty-five tissues from eight foetuses, of gestational age between 14 and 26 weeks, responded to acetylcholine (5-130 ng/ml) and noradrenaline (0.5-10 µg/ml). Two preparations of duodenum, ten of ileum and four of distal ileum were studied and, on eight of these, responses to noradrenaline were obtained only in the presence of acetylcholine. One preparation of ileum exhibited pendular movements.

An ileum preparation from an 18-week foetus, which relaxed in the presence of noradrenaline alone, gave a biphasic response, consisting of a small relaxation and a much larger contraction, to both prostaglandin E_2 and $F_{2\alpha}$. All other tissues from the small intestine contracted in the presence of prostaglandin E_2 and $F_{2\alpha}$. The threshold dose of prostaglandin E_2 was usually 0.1 µg/ml but one ileum preparation, from a 22-week foetus, responded to a concentration of 4 ng/ml. The small intestine usually responded to a concentration of prostaglandin $F_{2\alpha}$ of 0.4 µg/ml. The contractions to both prostaglandins were well maintained.

Nine tissues from the large intestine were studied, comprising six preparations of ascending colon, one of transverse colon and two from the descending colon. Only one preparation, of ascending colon, relaxed in the presence of noradrenaline alone. Each tissue contracted in the presence of prostaglandin E_2 but the large intestine was less sensitive than the small intestine and a concentration of 1 µg/ml was usually required. The large intestine was also less sensitive to acetylcholine. Prostaglandin $F_{2\alpha}$ was studied on four preparations and each contracted in the presence of the prostaglandin at a concentration of 7 µg/ml.

The sensitivity of the prostaglandin-induced contraction to hyoscine was investigated on four preparations of the small intestine and on one of ascending colon. In each case, the contraction due

to either prostaglandin E_2 or $F_{2\alpha}$ was unaltered in the presence of a concentration of hyoscine, 0.6 ng/ml, which produced more than 50% inhibition of the acetylcholine contraction.

The responses of the small and large intestine to both prostaglandin E_2 and $F_{2\alpha}$ were antagonized by PPP at a concentration of between 80-160 μ g/ml. A similar result was obtained on each of five tissues and, at this concentration of PPP, the response to acetylcholine was unaltered.

Discussion In previous studies of human foetal intestine, tissues were obtained after hysterectomy whereas, in the present study, terminations were induced with either prostaglandin or noradrenaline. This proved to be a disadvantage because the tissue from about half the foetuses examined was not viable. It is assumed that this was due to the long delay which sometimes occurred between the administration of the prostaglandin and the expulsion of the foetus.

The use of prostaglandin for the termination of pregnancy involves the intra-amniotic administration of the prostaglandin and it is possible that some prostaglandin reached the foetus. If this did occur, it is considered unlikely that it affected the response of the foetal intestine to the prostaglandins, because tissue from terminations induced with noradrenaline behaved in an identical manner to that from terminations induced with prostaglandins.

One advantage of foetal tissue over adult tissue is that it is possible to study several regions of the foetal intestine. No regional differences were observed in the responses of the foetal intestine to the prostaglandins and the responses were not dependent upon the gestational age of the tissue.

The response of foetal small intestine to prostaglandins was similar to that of adult ileum (Bennett, 1972). Adult descending colon contracts in the presence of prostaglandin E_2 whilst both contraction and relaxation have been observed with prostaglandin $F_{2\alpha}$. The foetal colon only contracted in the presence of the prostaglandins. The concentration of prostaglandin required to elicit a response on the foetal tissue (0.1 μ g/ml) was within the range used by Bennett & Posner (1971) on adult tissue (5.50×10^{-8} M). These authors reported that PPP, at a concentration of 600 μ g/ml, antagonized the prostaglandin response

on adult tissue, whilst on foetal tissue antagonism was obtained with a concentration between 80 and 160 μ g/ml.

Previous work has shown that intestinal tissue from an 11-week foetus is capable of responding to acetylcholine, amines and ganglion-stimulants (Hart & Mir, 1970). The youngest tissue in the present study was from a 14-week foetus and the response of this tissue to prostaglandins demonstrated that prostaglandin receptors, as well as muscarinic receptors and adrenoceptors, are present at an early stage of foetal development.

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