

Studies on the mode of action of cyclic 3'5'-AMP and prostaglandin E₂ on rat gastric acid secretion and mucosal blood flow

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Cyclic 3'5'-adenosine monophosphate (c-AMP) has been postulated to be the intracellular mediator of gastric acid secretion. Since prostaglandin E₁ (PGE₁) inhibits pentagastrin and histamine but not c-AMP induced secretion in the isolated bullfrog mucosa, it may act by preventing an increase in intracellular concentrations of c-AMP (Way & Durbin, 1969). Perfusion of c-AMP through the gastric lumen of the rat *in vivo* potentiates the secretory response to single injections of pentagastrin, although this effect is abolished by concomitant perfusion of PGE₁ (Shaw & Ramwell, 1968). In the dog, intravenous administration of c-AMP inhibits the secretory response to pentagastrin and histamine (Levine & Wilson, 1971). Since the effects of substances which act directly on the secretory process may be altered by their actions on gastric mucosal blood flow (MBF), the significance of these apparently conflicting results *in vivo* is difficult to assess.

In the present investigation, MBF was determined in the urethane anaesthetized rat by the ¹⁴C-aniline clearance technique (Main & Whittle, 1972). During the steady secretory response to submaximal doses of pentagastrin [0.2 (μg/kg)/min] and histamine [25 (μg/kg)/min], intravenous injection of c-AMP (4–20 mg/kg of the dibutyryl derivative) caused a dose dependent increase in acid output accompanied by a rise in MBF. During basal secretion, c-AMP in doses up to 40 mg/kg, caused comparatively small increases in acid output. However, these responses were potentiated by the simultaneous infusion of threshold doses of pentagastrin and histamine. These results indicate that the magnitude of the response to c-AMP depends on the level of secretion prior to administration, and emphasize that the results of experiments in which the effects of c-AMP in combination with another stimulant are inhibited by prostaglandins, must be interpreted with caution.

PGE₂ injected intravenously [2 (μg/kg)/min] or perfused through the gastric lumen [4 (μg/kg)/min] in doses sufficient to completely inhibit responses to pentagastrin and histamine, only partially reduced the response to c-AMP under basal conditions. This reduction is likely to be due to the lowered level of secretion observed during the period of PGE₂ infusion preceding c-AMP administration, rather than to a direct antagonism. Increases in MBF associated with secretory responses to c-AMP were greater during administration of PGE₂ by either route, suggesting a direct vasodilator effect on the mucosa.

The results show that in the rat, in contrast to the dog, intravenously injected c-AMP stimulates gastric acid secretion in a manner dependent not only on the dose but also on the initial level of secretion. The latter observation may account for the previously reported inhibition of oral c-AMP by PGE₁, which it has been shown cannot be attributed to a local effect on MBF. The inability of PGE₂ to inhibit markedly the response to c-AMP under basal conditions supports the hypothesis that prostaglandins inhibit other gastric secretagogues by preventing an increase in intracellular concentration of c-AMP.

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Inhibition of intestinal tone and prostaglandin synthesis by 5, 8, 11, 14 tetraynoic acid

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Using 5, 8, 11, 14, eicosatetraynoic acid (TYA), an acetylenic analogue of arachidonic acid which inhibits prostaglandin (PG) synthesis (Ahern & Downing, 1970) evidence was obtained that PGs may be involved in maintenance of the spontaneous tone of small intestine.

Isolated segments of guinea-pig ileum were suspended in aerated Tyrode's at 37° C for periods up to twenty min, during which a spontaneous increase in tone and motility occurred which was blocked by the addition of TYA (0.01-3.0 µg).

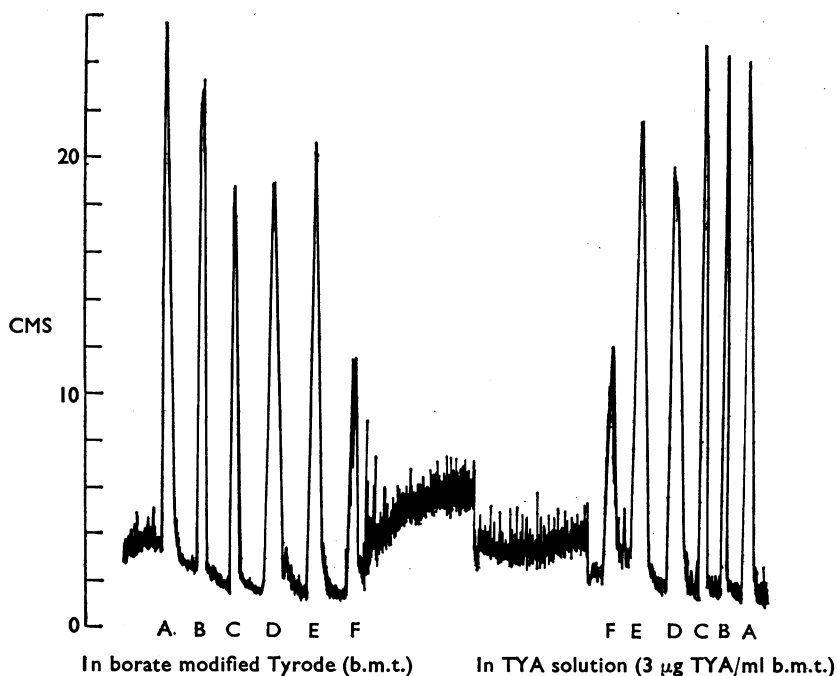


FIG. 1. Effect of 5, 8, 11, 14 eicosatetraynoic acid (TYA) (3 µg/ml) on submaximal contractions of isolated guinea-pig ileum to (A) 5-hydroxytryptamine (10 ng), (B) acetylcholine (56 ng), (C) histamine (40 ng), (D) bradykinin (50 ng), (E) nicotine (5 µg), and (F) PGE₂ (50 ng). The trace shows that the responses to these agents was not altered by the TYA. However, on allowing the tissue to rest for ten min the normal increase in tone was abolished by TYA (3 µg/ml).