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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  $\mu\text{g}$ ).

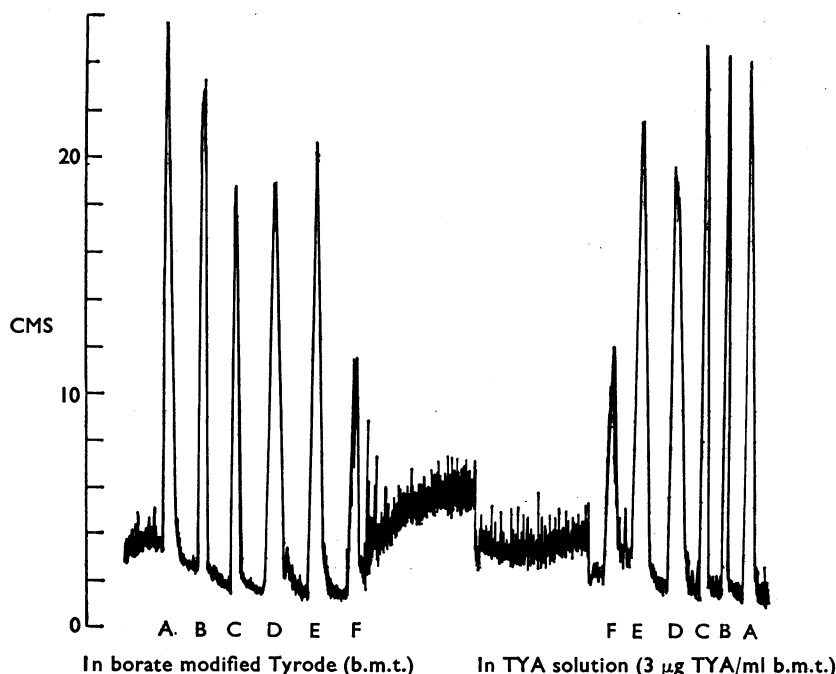


FIG. 1. Effect of 5, 8, 11, 14 eicosatetraynoic acid (TYA) (3  $\mu\text{g}/\text{ml}$ ) on submaximal contractions of isolated guinea-pig ileum to (A) 5-hydroxytryptamine (10 ng), (B) acetylcholine (56 ng), (C) histamine (40 ng), (D) bradykinin (50 ng), (E) nicotine (5  $\mu\text{g}$ ), and (F)  $\text{PGE}_2$  (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  $\mu\text{g}/\text{ml}$ ).

This effect could not be explained by a direct action at receptors in smooth muscle or by action at the nerves or ganglia, as contractions of guinea-pig ileum in response to acetylcholine, histamine, 5-hydroxytryptamine, PGE<sub>2</sub>, bradykinin or nicotine were unchanged (see Fig. 1). Inhibition of intestinal motility was also observed when the drug was administered intravenously or into the peritoneal cavity of guinea-pigs anaesthetized with nembutal (40 mg/kg, I.P.).

The effect of TYA on synthesis of prostaglandins in guinea-pig ileum was then examined using suspensions of guinea-pig ileum tissue powdered after rapid freezing in liquid nitrogen (Willis, Davison, Ramwell, Smith & Brocklehurst, 1972). PGE<sub>2</sub> and PGF<sub>2α</sub>, formed from arachidonic acid (Sigma) were isolated by selective solvent extraction (Shaw & Ramwell, 1969), and two stage thin layer chromatography in Green & Samuelsson's (1964) AI and AII solvent systems (Willis, 1970). TYA added five min prior to addition of arachidonic acid markedly inhibited PG synthesis in a graded dose-dependent fashion. The dose for 50% reduction being 1.5 µg/ml.

These results support and extend the findings of Bennett & Posner (1971) who used prostaglandin antagonists, and of Ferreira, Herman & Vane (1972) who used anti-inflammatory drugs.

This work was supported by NIH Grant NS-09585-02 and ONR Contract N-00014-67-0112-0055.

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#### The effect of caffeine on the antipyretic action of aspirin administered during endotoxin induced fever

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Since several 'over the counter' preparations contain mixtures of antipyretics and caffeine, it seemed important to assess the effect of caffeine on the antipyretic action of aspirin. Fever was produced by an i.v. injection of 0.05 µg 'Pyrogen E' into an ear vein, control animals received 0.9% sodium chloride solution. The fever was assessed by computing the area of the fever curve [°C × time (h)] during the