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Prostaglandins as regulators of bradykinin responses

A number of agents have been studied for their ability to induce the most important changes associated with inflammation—namely, increased permeability of small blood vessels and migration of leucocytes. For example, bradykinin produces the characteristic signs of inflammation in a variety of species and has been identified in inflammatory exudates including those from carrageenan oedema in the rat (as reviewed by Di Rosa & Willoughby, 1971). Both prostaglandin E_1 (PGE_1) and prostaglandin E_2 (PGE_2) are inducers of local vascular permeability in the rat (Crunkhorn & Willis, 1971; Freeman & West, 1972), and PGE_2 has also been detected in exudates from carrageenan oedema (Willis, 1969).

Ferreira, Moncada & Vane (1973) have recently reported that bradykinin reflexly increases the arterial blood pressure of dogs, proportional to the dose, when injected intra-arterially into the spleen, and that PGE_1 or PGE_2 potentiate these responses when injected together with the bradykinin despite the fact that the prostaglandins by themselves are vasodepressor. Furthermore, indomethacin (a non-steroidal anti-inflammatory drug which inhibits prostaglandin synthesis) reduced the pressor response to bradykinin which was then increased once more by PGE_1 or PGE_2. The authors suggested that the prostaglandins released within the spleen potentiated the nociceptive action of bradykinin.

We have now studied the effects of prostaglandins on the actions of bradykinin, histamine, 5-hydroxytryptamine (5-HT) and clinical dextran (molecular weight 110 000) on blood vessels in the skin of rats. Groups of at least 10 female Wistar rats of the ASH colony (150–210 g) had their backs shaved 24 h before being anaesthetized with pentobarbitone (40 mg kg^{-1}, i.p.). After the intravenous injection of azovan blue dye (20 mg kg^{-1}), intradermal injections of PGE_1 PGE_2 or $PGF_{2\alpha}$ alone, or with bradykinin, histamine, 5-HT or dextran, in dose volumes of 0·05 ml Tyrode solution, were made into the shaved areas. Forty-five min later, the rats were killed and the effects of the agents on vascular permeability were measured spectrophotometrically by estimating (in μg) the amount of dye in each weal, using the method of Harada Takeuchi & others (1971). To determine when potentiation or inhibition had occurred, the amounts of dye extracted from the skin after each agent separately were summated and subtracted from the amounts of dye extracted when two agents were given together and the differences were then expressed as percentages of the totals of the agents separately. In each rat, the amount of dye extracted from the skin after control Tyrode injections was subtracted from all other values before calculations

were made. In general, values of 40% or more above the summated responses showed significant potentiation ($P < 0.05$) and those of 40% or more below the summated responses indicated inhibition ($P < 0.05$).

Minimal effective intradermal doses were used in all experiments. These were of PGE_1 and PGE_2 25–100, of $PGF_{2\alpha}$ 500–1000, bradykinin 50–200, histamine 500, 5-HT 20–100 ng, and 25 μg of dextran. PGE_1 markedly and specifically potentiated the bradykinin responses (increases 60–130%) PGE_2 exerted no potentiation, but $PGF_{2\alpha}$ inhibited the responses (decreases always more than 40%). In other experiments doses as low as 5 ng PGE_1 also significantly potentiated the bradykinin responses. On the other hand, the histamine, 5-HT, and dextran responses were unaffected by all doses of PGE_1 and PGE_2 although $PGF_{2\alpha}$ inhibited these three responses (decreases always more than 60%).

Thus, threshold doses of PGE_1 selectively potentiated the effects of bradykinin on vascular permeability in the skin of rats whereas $PGF_{2\alpha}$ inhibited all the agents tested, including bradykinin. This latter effect occurred despite the fact that larger doses of $PGF_{2\alpha}$ by themselves (like those of PGE_1 and PGE_2) increased vascular permeability. As these effects have been obtained with near pathological levels of several putative mediators of inflammatory responses, it is possible that PGE_1 and $PGF_{2\alpha}$ act as modulators of the bradykinin response in inflammation in rats. The antagonistic actions of these two prostaglandins have been reported in other situations and in the present work $PGF_{2\alpha}$ antagonized the PGE_1 potentiation of the bradykinin action. It is not clear why PGE_2 failed to modify the bradykinin response, particularly as PGE_1 and PGE_2 are released together in many inflammatory states including inflamed skin of patients (Greaves, Sondergaard & McDonald-Gibson, 1971).

Although many non-steroidal anti-inflammatory drugs antagonize the bronchoconstrictor action of bradykinin in the guinea-pig, these compounds exert a less regular effect on some of the inflammatory reactions induced by bradykinin (Starr & West, 1967). In the present study, indomethacin (9 mg kg^{-1} orally) did not reduce either the potentiation of the bradykinin response by PGE_1 or the inhibition of the response by $PGF_{2\alpha}$. This dose of indomethacin, however, significantly blocks the carrageenan response in rat paws (Winter, Risley & Nuss, 1963) although it does not usually modify the individual responses to intradermal bradykinin and prostaglandins.

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