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ON THE ABILITY OF PROSTAGLANDIN E_1 AND ARACHIDONIC ACID TO MODULATE EXPERIMENTALLY INDUCED OEDEMA IN THE RAT PAW

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1 Prostaglandins E_1 and E_2 but not prostaglandin $F_{2\alpha}$, arachidonic acid or linolenic acid, produced slight oedema when injected into the rat hindpaw.

2 Prostaglandin E_1 potentiated hindpaw oedema produced by carrageenan, kaolin, bradykinin and trypsin but not that produced by 5-hydroxytryptamine (5-HT), histamine, dextran B or compound 48/80. Carrageenan- and bradykinin-induced paw oedemas were also potentiated by prostaglandin E_2. Arachidonic acid potentiated responses to carrageenan and kaolin but not responses to bradykinin, trypsin, 5-HT, histamine, dextran B or compound 48/80. Linolenic acid did not potentiate hindpaw oedema induced by carrageenan.

3 Potentiation of carrageenan-induced oedema by prostaglandin E_1 was not diminished by pretreatment with indomethacin, hydrocortisone or cyproheptadine. However, arachidonic acid potentiation of carrageenan oedema was reduced by pretreatment with non-steroidal anti-inflammatory drugs but not by anti-inflammatory steroids or by paracetamol.

4 The enhancement of the response to carrageenan and kaolin by prostaglandins E_1, E_2 and arachidonic acid is discussed in terms of kinin mediation.

Introduction

It has been proposed that prostaglandins are mediators of the inflammatory response (Vane, 1972). Indeed, the *in vivo* potency of non-steroidal anti-inflammatory drugs has been correlated with their ability to inhibit *in vitro* the synthesis of prostaglandins by enzyme preparations from several tissues including dog spleen (Flower, Gryglewski, Herbaczynska-Cedro & Vane, 1972) and sheep seminal vesicles (Ham, Cirillo, Zanetti, Shen & Kuehl, 1972). Non-steroidal anti-inflammatory drugs reduce prostaglandin E levels in carrageenan-induced inflammatory exudates (Willis, Davison, Ramwell, Brocklehurst & Smith, 1972). Furthermore, prostaglandins E_1 and E_2 increase vascular permeability when injected intradermally in rats (Arora, Lahiri & Sanyal, 1970; Kaley & Weiner, 1971) and produce a weal and flare reaction when injected intradermally in man (Crunkhorn & Willis, 1971).

The administration of nanogram quantities of prostaglandin E_1 into the rat hindpaw produces only slight oedema (Arora *et al.*, 1970). The response is not dose-related, for at higher concentrations (40-80 μg), prostaglandin E_1 does not cause inflammation (Glenn, Bowman & Rohloff, 1972). However, prostaglandins may play a modulatory role in inflammation. For example, Ferreira (1972) reported that prostaglandin E_1 potentiates the pain producing actions of intradermal injections of bradykinin and histamine in man. Furthermore, prostaglandins E_1 and E_2 potentiate carrageenan-induced paw oedema in the rat (Moncada, Ferreira & Vane, 1973; Ferreira, Moncada, Parsons & Vane, 1974). In order to determine whether prostaglandins modulate other oedemas, we have examined the effects of prostaglandins E_1, E_2 and $F_{2\alpha}$ and of a prostaglandin precursor, arachidonic acid, upon rat paw oedema induced by various phlogogenic agents. A preliminary report of part of this work has been published (Lewis, Nelson & Sugrue, 1974).

Methods

Male Wistar rats (CE/CFHB, Carworth Europe) weighing 80-100 g were used in groups of 7-10 animals in all experiments. Phlogogens, dissolved or suspended in 0.1 ml 0.9% w/v NaCl solution (saline), were injected into the subplantar region of the right hindpaw. The left hindpaw received an equal volume of saline. Phlogogens were injected

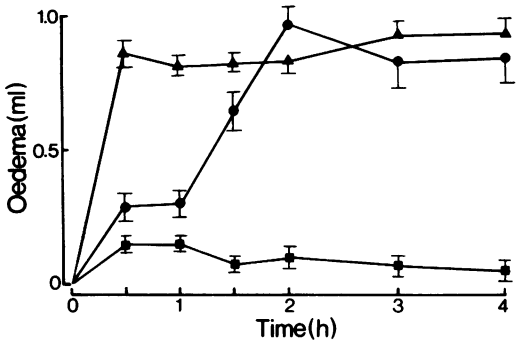

Figure 1. Increase in paw volume following subplantar injection of carrageenan (1 mg) (•), prostaglandin E_1 (0.1 μg) (■), or a combination of carrageenan (1 mg) and prostaglandin E_1 (0.1 μg) (▲). Each value is the mean ± s.e. mean of 7-10 observations. Potentiation of the carrageenan response by prostaglangin E_1 was significant ($P < 0.001$) at 0.5 h and 1.0 hour.

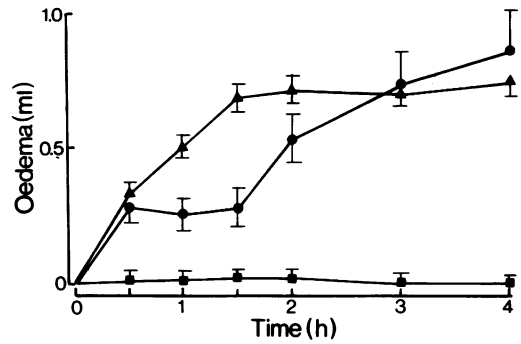

Figure 2. Increase in paw volume following subplantar injection of carrageenan (1 mg) (•), arachidonic acid (100 μg) (■) or a combination of carrageenan (1 mg) and arachidonic acid (100 μg) (▲). Each value is the mean ± s.e. mean of 7-10 observations. Potentiation of the response to carrageenan by arachidonic acid was significant at 1.0 h ($P < 0.01$) and 1.5 h ($P < 0.001$).

either alone or in combination with prostaglandins E_1, E_2, $F_{2\alpha}$, arachidonic acid or linolenic acid. Other groups of rats received either prostaglandin or fatty acid alone.

Anti-inflammatory agents were injected subcutaneously in propan-1, 2-diol (1.0 ml/kg) 1 h before induction of paw oedema. Preliminary experiments revealed that the subcutaneous injection of this volume of propan-1, 2-diol had no effect upon oedema induced in the rat paw by the phlogogens under study.

The volumes of both hindpaws of each rat were measured by mercury displacement plethysmometry at 0, 0.5, 1, 1.5, 2, 3 and 4 h after induction of paw oedema. Mean differences between right and left hindpaw volumes for each group were calculated for each time interval. The statistical significance of differences between treatments was determined by Student's *t* test (2-tailed).

Drugs

Arachidonic acid and linolenic acid (Grade 1, Sigma) were diluted with ethanol to give 40 mg/ml solutions. Aliquots (0.5 ml) were then sealed in glass vials under nitrogen and stored at −15°C until required. The ethanolic solutions were withdrawn from the vials and further dilutions made with saline immediately before use. Prostaglandins E_1, E_2 and $F_{2\alpha}$ were stored at −15°C as ethanolic solutions (10 mg/ml) in rubber capped bottles and aliquots withdrawn through a hypodermic needle and diluted with saline immediately before use.

Other drugs used in this study were: dextran B (150,000-200,000 mol. wt.), kaolin (light grade) and 4-acetamidophenol (paracetamol) (BDH), bradykinin BRS 690 (Sandoz), carrageenan (Viscarin, Marine Colloids), compound 48/80 (Wellcome), cyproheptadine hydrochloride and indomethacin (Merck, Sharp & Dohme), fluocinolone acetonide (ICI), histamine diphosphate, 5-hydroxytryptamine (serotonin) creatinine sulphate and trypsin (Koch-Light), hydrocortisone acetate (Organon), naproxen (Syntex) and phenylbutazone (Geigy). Where applicable doses refer to the appropriate salt.

Results

Interactions of prostaglandins or unsaturated fatty acids with carrageenan

Prostaglandin E_1 (0.1 μg) induced a mild paw swelling upon subplantar injection (Figure 1), maximum oedema (0.15-0.25 ml) being observed between 0.5 h and 1 hour. However, within 0.5 h of the administration of prostaglandin E_1 in combination with a submaximal dose of carrageenan (1 mg), a marked oedema had developed. The potentiation of carrageenan-induced oedema by prostaglandin E_1 (0.1 μg) was significant at 0.5 and 1 h ($P < 0.001$). Prostaglandin E_2 (0.1 μg) also caused mild oedema for up to 1 h after injection (0.13 ± 0.03 ml). Furthermore, oedema induced in the rat paw by carrageenan (1 mg; 0.33 ± 0.04 ml) was signifi-

cantly potentiated at 1 h ($P < 0.01$) by the concomitant administration of prostaglandin E_2 (0.1 μg; 0.64 ± 0.06 ml). In contrast to prostaglandins E_1 and E_2, $F_{2\alpha}$ (0.25 μg) did not elicit any oedema and did not enhance oedema induced by carrageenan (1 mg).

Subplantar injection of either arachidonic acid (100 μg) (Figure 2) or linolenic acid (100 μg) failed to elicit an inflammatory response. However, arachidonic acid (100 μg) potentiated the effect of carrageenan (1 mg), the oedema induced by administration of the combination being significantly greater than the additive effect at 1 h ($P < 0.01$) and 1.5 h ($P < 0.001$). In contrast, carrageenan-induced oedema was not altered by the concomitant administration of linolenic acid (100 μg).

The difference in the response to carrageenan (cf. Figures 1 and 2) is to be noted. It confirms reports that this response varies in different rats and on different days (Green, Green, Murray & Wilson, 1971; Crunkhorn & Meacock, 1972).

Table 1. Effect of drugs upon potentiation of carrageenan-induced paw oedema by arachidonic acid

	Dose (mg/kg)	*% reduction of carrageenan oedema*	*% reduction of potentiation*
Indomethacin	5	52.0 ± 8.2	52.2 ± 5.7
Naproxen	30	35.2 ± 11.9	47.6 ± 3.7
Phenylbutazone	75	30.7 ± 8.6	63.6 ± 3.1
Fluocinolone	1	40.8 ± 11.8	4.1 ± 4.0
Hydrocortisone	100	34.7 ± 9.1	3.7 ± 3.9
Paracetamol	200	61.9 ± 12.8	10.5 ± 5.9

Drugs were administered subcutaneously 0.5 h before, and paw volumes measured 1.5 h after subplantar injection of either carrageenan (1 mg) or carrageenan (1 mg) plus arachidonic acid (100 μg). Each result is the mean ± s.e. mean from 7-10 animals.

Effects of drugs upon prostaglandin E_1 and arachidonic acid-carrageenan interactions

Doses of drugs were chosen which inhibit by 30-60% the paw oedema developing 0.5-2 h after carrageenan administration. Indomethacin (5 mg/kg), hydrocortisone (100 mg/kg) or cyproheptadine (20 mg/kg) given subcutaneously 0.5 h before the combination of prostaglandin E_1 (0.1 μg) and carrageenan (1 mg), did not modify the resulting oedema at +0.5 hour. However, indomethacin (5 mg/kg), naproxen (30 mg/kg) and phenylbutazone (75 mg/kg) did reduce the archidonic acid (100 μg) potentiation of carrageenan-induced oedema at +1.5 h, whilst fluocinolone (1 mg/kg), hydrocortisone (100 mg/kg) and paracetamol (200 mg/kg) did not (Table 1).

Effects of prostaglandin E_1 and arachidonic acid upon rat paw oedema induced by various phlogogenic agents

Both prostaglandin E_1 (0.1 μg; Table 2) and arachidonic acid (100 μg; Table 3) potentiated oedema of the rat paw induced by submaximal doses of carageenan (1 mg) and kaolin (10 mg). Potentiation of both oedemas by prostaglandin E_1 and arachidonic acid was maximal at 0.5 and 1.5 h respectively. Prostaglandin E_1, but not arachidonic acid, potentiated oedema induced by bradykinin (4.5 μg) and trypsin (50 μg). Oedema induced by 5-HT (1 μg), histamine (10 μg), dextran B (6 μg) and compound 48/80 was not potentiated by either prostaglandin E_1 or arachidonic acid. At

Table 2. Effects of prostaglandin E_1 (PGE_1, 0.1 μg) upon paw oedema induced by various phlogogenic agents

Phlogogenic agent	*(a) Oedema induced by agent (ml)*	*(b) Oedema induced by PGE_1 (ml)*	*(c) Oedema induced by combination (ml)*	*Difference c − (a + b) (ml)*
Carrageenan (1 mg)	0.29 ± 0.05	0.15 ± 0.03	0.86 ± 0.05	0.42 ± 0.07**
Kaolin (10 mg)	0.09 ± 0.03	0.16 ± 0.03	0.45 ± 0.04	0.20 ± 0.06*
Bradykinin (4.5 μg)	0.13 ± 0.03	0.08 ± 0.01	0.42 ± 0.05	0.21 ± 0.06*
Trypsin (50 μg)	0.56 ± 0.07	0.17 ± 0.03	1.02 ± 0.06	0.29 ± 0.09*
5-HT (1 μg)	0.40 ± 0.04	0.10 ± 0.02	0.52 ± 0.03	0.02 ± 0.05
Histamine (10 μg)	0.02 ± 0.02	0.15 ± 0.02	0.20 ± 0.03	0.03 ± 0.04
Dextran B (6 μg)	0.17 ± 0.04	0.11 ± 0.03	0.30 ± 0.04	0.02 ± 0.06
Compound 48/80 (1 μg)	0.30 ± 0.02	0.19 ± 0.03	0.59 ± 0.05	0.10 ± 0.06

All measurements were made 0.5 h after induction of oedema. Each value is the mean ± s.e. mean for a group of 7-10 rats. Where potentiation occurs significance is indicated by ** ($P < 0.001$) or * ($P < 0.01$)

0.5 h the inflammatory response to bradykinin (4.5 μg; 0.11 ± 0.04 ml) was also potentiated ($P < 0.05$) by prostaglandin E_2 (0.1 μg; 0.31 ± 0.03 ml), the oedema induced by prostaglandin E_2 alone at this time being 0.05 ± 0.04 ml.

Discussion

Prostaglandins E_1 and E_2 injected into the rat hindpaw induced only a slight to moderate oedema of brief duration, confirming findings by Arora *et al.* (1970), Glenn *et al.* (1972), Moncada *et al.* (1973) and Thomas & West (1974). Prostaglandin $F_{2\alpha}$ (250 ng) did not induce paw oedema and although such an action has been reported by Thomas & West (1974), μg quantities were required.

When either prostaglandin E_1 or E_2 is administered in combination with carrageenan, a significant potentiation of carrageenan-induced oedema results 0.5-1 h later. Prostaglandin $F_{2\alpha}$ is without effect upon carrageenan-induced oedema. A similar potentiation of carrageenan-induced oedema by prostaglandins of the E series has recently been demonstrated in the rat (Moncada *et al.*, 1973). However, Glenn *et al.* (1972) failed to demonstrate potentiation of carrageenan oedema by prostaglandin E_1 in the same test system.

The two unsaturated fatty acids, arachidonic acid and linolenic acid, exhibit no phlogogenic activity. However, arachidonic acid potentiated the response to carrageenan, as recently reported by Smith, Ford-Hutchinson, Elliot & Bolam (1974). Since arachidonic acid is a substrate for prostaglandin synthetase (Bergstrom, Danielsson & Samuelsson, 1964), whilst linolenic acid is not, it is possible that the potentiation by exogenous arachidonic acid is due to its conversion to prostaglandins. The susceptibility of prostaglandin synthetase to drugs varies in different tissues. For example, paracetamol inhibits effectively prostaglandin synthetase from rat brain (Flower & Vane, 1972) and rat platelets (Vargaftig & Dao Hai, 1973) but only weakly that from dog spleen (Flower *et al.*, 1972). Furthermore, whereas non-steroidal anti-inflammatory drugs inhibit the enzyme(s) extracted from dog spleen and sheep seminal vesicles (Flower *et al.*, 1972; Ham *et al.*, 1972), steroidal anti-inflammatory drugs like hydrocortisone have been shown to inhibit prostaglandin synthetase from crude homogenates of human skin (Greaves & McDonald-Gibson, 1972) but not that obtained from a microsomal fraction of rat skin (Greaves, Kingston & Pretty, 1975). The observation that only drugs whose anti-inflammatory mechanism of action may be attributed to prostaglandin synthetase inhibition (Vane, 1972) reduce arachidonic acid potentiation of carrageenan-induced oedema, strongly argues that this potentiation is due to conversion of arachidonic acid to prostaglandins. The prostaglandin synthetase in the oedematous rat paw appears to resemble more closely, in its susceptibility to drugs, the enzyme(s) from dog spleen and sheep seminal vesicles than prostaglandin synthetase from rat brain or human skin.

Infiltrating white blood cells constitute a possible source of prostaglandin synthetase in the oedematous paw. The migration of polymorphonuclear leucocytes and monocytes into the inflamed site is a feature of both carrageenan-induced rat paw oedema (Di Rosa & Willoughby, 1971) and kaolin-induced pleurisy in the rat (Vinegar, Truax & Selph, 1972). Phagocytosing rabbit polymorphonuclear leucocytes produce considerable quantities of prostaglandins (Higgs & Youlten, 1972) and are

Table 3. Effects of arachidonic acid (AA, 100 μg) upon rat paw oedema induced by various phlogogenic agents

Phlogogenic agent	*(a) Oedema induced by agent (ml)*	*(b) Oedema induced by AA (ml)*	*(c) Oedema induced by combination (ml)*	*Difference c − (a + b) (ml)*
Carrageenan (1 mg)	0.29 ± 0.06	0.02 ± 0.02	0.69 ± 0.05	0.38 ± 0.08**
Kaolin (10 mg)	0.14 ± 0.03	0.22 ± 0.02	0.59 ± 0.04	0.23 ± 0.05**
Bradykinin (4.5 μg)	0.09 ± 0.03	0.08 ± 0.02	0.13 ± 0.03	−0.04 ± 0.05
Trypsin (50 μg)	0.26 ± 0.03	0.02 ± 0.02	0.28 ± 0.03	0.00 ± 0.05
5-HT (1 μg)	0.22 ± 0.04	0.12 ± 0.01	0.37 ± 0.03	0.04 ± 0.05
Histamine (10 μg)	0.10 ± 0.04	0.04 ± 0.03	0.15 ± 0.02	0.01 ± 0.05
Dextran B (6 μg)	0.15 ± 0.03	−0.01 ± 0.01	0.17 ± 0.03	0.03 ± 0.03
Compound 48/80 (1 μg)	0.17 ± 0.04	0.15 ± 0.03	0.32 ± 0.03	0.00 ± 0.06

Legend as for Table 2 except that all measurements were made 1.5 h after induction of paw oedema.

capable of converting exogenous arachidonic acid to prostaglandins *in vitro* (McCall & Youlten, 1973). It is of interest to note that at the time of maximum arachidonic acid potentiation of carrageenan-induced oedema, i.e. at 1.5 h, a significant increase in polymorphonuclear leucocytes has been observed in the carrageenan-induced oedemous rat paw (Di Rosa & Willoughby, 1971).

5-HT, histamine and kinins have been shown to be involved in the mediation of carrageenan-induced paw oedema (Crunkhorn & Meacock, 1971). In addition, kinins have also been implicated in kaolin-induced oedema (Bonta & De Vos, 1967; Di Rosa, 1972). Neither prostaglandin E_1 nor arachidonic acid potentiated the inflammatory response to histamine or 5-HT or to agents releasing them such as dextran B or compound 48/80 (Jori, Bentivoglio & Garattini, 1961). On the other hand, bradykinin-induced paw oedema was potentiated by both prostaglandin E_1 and E_2 but not by arachidonic acid. Since bradykinin is not chemotactic for leucocytes (Ward, 1971) the inability of arachidonic acid to potentiate the response to bradykinin possibly results from the lack of conversion of fatty acid to prostaglandins due to the absence of these cells. The potentiation by prostaglandin E_2 (0.1 μg) of the bradykinin response does not agree with the observations of Thomas & West (1974), who used only 0.025 μg prostaglandin E_2. These authors suggested that their conditions may not have been optimal for demonstrating synergism between prostaglandin E_2 and bradykinin.

Prostaglandins potentiate other responses to kinins. Increases in vascular permeability in guinea-pig skin induced by intradermal injection of bradykinin may be potentiated by the concomitant administration of prostaglandin E_1 and E_2 and to a lesser extent by $F_{2\alpha}$ (Williams & Morley, 1973). In the rat skin, the response to bradykinin is potentiated by prostaglandin E_1 but not by low doses of E_2 (Thomas & West, 1974) whilst $F_{2\alpha}$ inhibits the response. In humans, prostaglandin E_1 potentiates the pain producing effect of intradermal injections of bradykinin (Ferreira, 1972). Similarly the nociceptive activity of bradykinin in the dog knee joint (Ferreira, Moncada & Vane, 1974) is potentiated by infusion of prostaglandins E_1 and E_2 but not by $F_{2\alpha}$. The observations of this study that oedema of the rat paw induced by both carrageenan and kaolin is potentiated by prostaglandins of the E series and by arachidonic acid may constitute yet another example of prostaglandin potentiation of a kinin response.

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