Bioactivity in the perfusates, a large proportion of which is assumed to be slow-reacting substance in anaphylaxis (SRS-A) was modified minimally by TYA (<10%) but was considerably reduced by cromoglycate (>50%).

These results indicate that it is unlikely that SRS-A is formed from arachidonate, that SRS-A is not a prostaglandin of the $PG_2$ series and that it is probably not related to the $PG_1$ or $PG_3$ series. Cromoglycate reduced the release of SRS-A but did not modify PG release.

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## The concomitant release of bradykinin and prostaglandin in the inflammatory response to carrageenin

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Bradykinin (van Arman, Begany, Miller & Pless, 1965; Garcia Leme, Schapoval & Roche e Silva, 1967) and prostaglandins (Willis, 1969; Di Rosa, Papadimitriou & Willoughby, 1971) are both implicated in inflammation induced by carrageenin in the rat. Di Rosa *et al.* (1971) suggested that bradykinin was released transiently, after the initial release of histamine and that prostaglandins were responsible for the later phase of inflammation.

Prostaglandins sensitize pain receptors to mechanical or to chemical stimulation (Ferreira, 1972; Ferreira, Moncada & Vane, 1973). Inhibition of prostaglandin biosynthesis by aspirin-like drugs (Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971; Vane, 1971) abolishes this sensitization and thereby produces analgesia.

We and others have now shown that the oedema caused by bradykinin and various inflammatory stimuli is also potentiated by prostaglandins (Moncada, Ferreira & Vane, 1973; Thomas & West, 1973; Williams & Morley, 1973; Lewis, Nelson & Sugrue, 1974). Thus the anti-oedema properties of aspirin-like drugs, like the analgesia, can be explained by removal of the potentiation, through inhibition of prostaglandin biosynthesis.

We have re-investigated the time course of the release of bradykinin using the enhancement of oedema induced by a synthetic bradykinin potentiator ($BPP_{9a}$) as an indicator of the presence of bradykinin. The nonapeptide affects vascular permeability induced by bradykinin, but not that produced by other inflammatory mediators (Ferreira, 1965; Greene, Camargo, Krieger, Stewart & Ferreira, 1972).

Groups of eight to ten rats were used and the increase in hind paw volume caused by carrageenin (0.1 ml of 0.5% w/v) was estimated over 6 h by subtracting the volume of the contralateral paw which received an equal volume of saline. $BPP_{9a}$ (5 $\mu$g in 0.03 ml) was injected into both paws; it had no effect on normal paw volume but significantly increased the oedema when given at 0, 0.5, 1, 4 and 6 h after carrageenin. This enhancement was also seen in animals treated with indomethacin (10 mg/kg i.p.). Soya bean trypsin inhibitor (500 $\mu$g), which prevents bradykinin formation, abolished potentiation.

Potentiation of carrageenin oedema by prostaglandin $E_1$ was also studied in rats treated or not treated with indomethacin (10 mg/kg). A significant increase in paw oedema was observed in both groups of animals when prostaglandin $E_1$ (0.5 $\mu$g) was given, either 0.25 h before carrageenin or 0, 0.5, 1, 4 and 6 h afterwards. The increase was much greater in those animals in which oedema had been reduced by indomethacin.

These results indicate (a) that bradykinin is being formed during all of the first 6 h of carrageenin oedema and (b) that there is no tachyphylaxis to the potentiating action of prostaglandins on the effects of the other mediators.

These results re-inforce our previous conclusion that the late phase of carrageenin oedema results mainly from the potentiating action of prostaglandins on the effects of other mediators, especially bradykinin.

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## The reduction of prostaglandin $E_2$ to prostaglandin $F_{2\alpha}$ by various animal tissues

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The conversion of prostaglandin $E_2$ ($PGE_2$) to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by an enzyme in sheep red blood cells has recently been described (Hensby, 1974). This type of metabolism, namely reduction of the 9-oxo group, has previously only been described in a few instances. These include guinea-pig liver and urine (Hamberg & Samuelsson, 1969; Hamberg & Israelsson, 1970), various rat organs (Leslie & Levine, 1973), human urine (Hamberg & Wilson, 1972) and baker's yeast (Schneider & Murray, 1973). This type of metabolism is of interest because of the many markedly different pharmacological actions of $PGE_2$ and $PGF_{2\alpha}$. The metabolism of $PGE_2$ by tissue homogenates of heart, liver and kidney from a variety of animal species, namely guinea-pig, rabbit, horse, sheep, dog and pig have now been studied.

Tissues were removed and used as soon as possible after death (being stored on ice if transport required). Homogenates were prepared by chopping the tissues into small pieces and homogenizing in 3 volumes of ice-cold 0.1 M phosphate buffer (pH 7.4). The homogenate was centrifuged at 2,400 *g* for 30 min and the resulting supernatant was carefully decanted off. This was incubated at 37°C with $PGE_2$ at a substrate concentration of 14 $\mu$M (sp. act. 35.2 Ci/mole) and NAD (10 mM) plus NADH (10 mM) for 2 hours.

The products of the incubation were converted to methyl esters after extraction and separated on Lipidex 5000 gel columns of 29-30 ml bed volume (Brash & Jones, 1974). The eluting solvent was a heptane, chloroform mixture 80 : 20 (v/v) and the room temperature 20 ± 1°C. Fractions (3.0 ml) were collected and the aliquot assayed by scintillation counting to enable the elution profile of the column to be obtained. Where $PGF_{2\alpha}$