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Effect of central prostaglandins on carrageenan-induced pedal oedema in rats

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The possible modulatory effect of central prostaglandins (PGs) on carrageenan-induced pedal inflammation, was investigated in rats. Intracerebroventricularly (i.c.v.) administered arachidonic acid, the PG precursor, produced a statistically insignificant increase in the inflammatory response, though PG synthesis inhibitors, administered by the same route, markedly attenuated the oedema. Centrally administered PGE_2 had a significant pro-inflammatory effect, whereas $PGF_{2\alpha}$ exerted an anti-inflammatory action. The results indicate that central PGs may modulate peripheral inflammation and that, at least partly, the anti-inflammatory activity of PG synthesis-inhibiting non-steroidal anti-inflammatory agents may involve central PGs, as has been proposed for their analgesic effect.

The role of peripheral prostaglandins (PGs) in the modulation of peripheral inflammation is well accepted (Ferreira & Vane 1979). Using the carrageenan model of acute inflammation in rats, Ferreira (1979) postulated that inflammatory hyperalgesia had two components, one due to release of peripheral PGs while the other involved participation of central PGs. He maintained that the analgesic action of aspirin-like agents was, at least partly, due to inhibition of synthesis of central PGs. It was argued that PGs are released in the central nervous system parallel to their release at the inflammatory site. The centrally released PGs were thought to be responsible for fever accompanying inflammation as well as for accentuation of the local hyperalgesia. Since the hyperalgesia induced by carrageenan is dependent on the extent of the inflammation induced by the phlogistic agent, it was considered worthwhile to investigate whether central PGs could modulate the inflammatory process.

Materials and methods

The studies were on inbred strains of albino rats (120–180 g), of either sex, obtained from the Institute animal house. The rats were housed in colony cages at an ambient temperature of 25 ± 2 °C and fed on standard Hind Lever chow. Experiments were conducted between 9 am and 2 pm. Pedal inflammation was induced by injecting 0·1 ml of 1% carrageenan suspension in 0·9% NaCl (saline) below the plantar aponeurosis (Winter et al 1962). The index of inflammation was the increase in paw volume after administration of the phlogistic agent. The paw volume, up to the ankle joint, was measured by means of a mercury plethysmograph, before and at hourly intervals, for 4 h after carrageenan administration, and has been expressed as units, each representing 1 cm (volume = 0·075 ml) length of displaced mercury.

Intracerebroventricular (i.c.v.) cannulation of the right lateral ventricle was performed in pentobarbitone sodium (40 mg kg^{-1} i.p.) anaesthetized rats (Feldberg & Lotti 1967). Experiments were conducted a week after insertion of indwelling cannulae. All the drugs were administered i.c.v., dissolved in 10 µl of artificial cerebrospinal fluid (csf). Control animals received equivalent volume of artificial csf via the same route.

The drugs used, with doses and pretreatment times given in parentheses, were: arachidonic acid (50 µg, 60 min), sodium salicylate (30 µg, 30 min), diclofenac sodium (50 µg, 60 min), PGE_2 (20 µg, 15 min) and $PGF_{2\alpha}$ (20 µg, 15 min). The doses and pretreatment times were based on earlier studies from this laboratory.

Results and discussion

The results are summarized in Fig. 1. Arachidonic acid, the PG precursor, produced slight and statistically

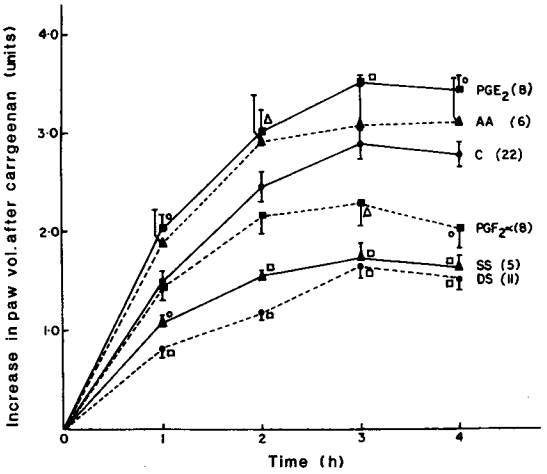

FIG. 1. Effect of i.c.v. administered arachidonic acid (AA), $PGF_{2\alpha}$, PGE_2, sodium salicylate (SS) and diclofenac sodium (DS) on carrageenan-induced pedal edema; C: Control. Vertical lines indicate s.e.; numbers in parentheses denote n. *P* values; △ < 0·05; ○ < 0·01; □ < 0·001, in relation to control.

* Correspondence.

non-significant increase in the degree of carrageenan-induced pedal inflammation. On the contrary, the PG synthesis inhibitors, sodium salicylate and diclofenac, markedly attenuated the inflammatory reponse throughout the 4 h of observation. PGE_2 significantly increased the pedal oedema over the period, whereas $PGF_{2\alpha}$ decreased the intensity of the inflammation which was statistically significant at 3 and 4 h post-carrageenan.

None of the drugs used, had any discernible effect on carrageenan oedema, after i.p. administration in the doses used.

Unlike the peripheral influences modulating inflammation, little is known about the role of the cns in modulating the cascade of events culminating in inflammation (Bonta 1978). Schizophrenics are known to have a low incidence of rheumatoid arthritis and show reduced inflammatory response to injury and infection (Horrobin 1977). Imposing evidence, albeit indirect, has been forwarded to suggest that schizophrenia is a PG deficiency disease (Horrobin 1977). Since the carrageenan model of acute inflammation has been increasingly used to screen agents for putative anti-rheumatoid activity, the observed anti-inflammatory effect of centrally administered PG synthesis inhibitors is intriguing. It also suggests that at least part of the anti-inflammatory effect of aspirin-like drugs may be due to inhibition of central PGs, as has been suggested for their analgesic action (Ferreira 1979). However, the absence of a significant anti-inflammatory effect of paracetamol, has been ascribed to its selective inhibitory effect on central PG synthesis (Flower & Vane 1972). Paracetamol could not be used in the present study because of solubility problems in artificial csf. There is no evidence to suggest that the cyclo-oxygenase enzyme system in the cns is different from that in the periphery. As such, the observed inflammation attenuating effect of PG synthesis inhibitors, on central administration, needs elaboration.

Arachidonic acid, the PG precursor, had insignificant pro-inflammatory action. Administered exogenously, it has been shown to be a poor precursor of endogenous PGs in the cns (Wolfe et al 1976). Attempts to bring rat brain PGs to assayable limits, by administering arachidonic acid, invariably ended in failure (Bhattacharya 1982).

The observed pro- and anti-inflammatory effects of PGE_2 and $PGF_{2\alpha}$ are consistent with reports pertaining to their peripheral administration. PGs of the E series have been reported to be predominantly pro-inflammatory in nature, whereas $PGF_{2\alpha}$ is known to exert anti-inflammatory effect. Thus, PGEs are suggested to initiate and sustain inflammation, while the PGs of the F series are thought to be involved in the termination of the inflammatory process (Ferreira & Vane 1979). $PGF_{2\alpha}$ has been reported to inhibit the peripheral pro-inflammatory effect of PGE_1 (Juan & Lembeck 1977). The mechanism of the pro- and anti-inflammatory effects of PGE_2 and $PGF_{2\alpha}$, respectively, on central administration, is not apparent. Further studies are required to elaborate this point. However, it is now accepted that PGs function as modulators of central synaptic transmission (Wolfe 1975). Recent studies have shown that the central noradrenergic neurotransmitter system exerts an inflammation inhibiting effect, possibly by influencing the peripheral vascular system (Das et al 1983). Since PGs of the E and F series are known to inhibit and enhance, respectively, release of the transmitter from central noradrenergic neurons (Wolfe 1975), it is possible that the observed effects of PGE_2 and $PGF_{2\alpha}$ are secondary to modulation of noradrenergic neurotransmission.

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