Arachidonic acid-induced paw oedema in the rat

J. COTTNEY, A.J. LEWIS & D.J. NELSON

Scientific Development Group, Organon Laboratories Limited, Newhouse, Lanarkshire, ML1 5SH

Arachidonic acid, a prostaglandin percursor, has previously been demonstrated to produce a small but significant, inflammatory oedema when administered by subplantar injection into the hind paw of the rat (Bekemeier, Giessler & Hirschelmann, 1974; Lewis, Nelson & Sugrue, 1975). In addition, when administered into the rat hindpaw in combination with carrageenan or kaolin, arachidonic acid is capable of potentiating the effects of these irritants by a mechanism thought to require conversion of the arachidonic acid to prostaglandins (Lewis *et al.*, 1975).

We have further examined the response produced in the rat hind paw by subplantar administration of arachidonic acid alone in an attempt to establish whether the resulting oedema is a consequence of the conversion of arachidonic acid to prostaglandins which are themselves pro-inflammatory (Glenn, Bowman & Rohloff, 1972).

Male Wistar rats (CE/CFHB, Carworth Europe) weighing between 80–100 g were used in groups of ten for these experiments. Arachidonic acid (Sigma) was dissolved in absolute ethanol before dilution with 0.9% w/v sodium chloride solution and was injected via the subplantar route to the left hind paw. The contralateral paw received an equal volume (0.1 ml) of vehicle. The paw diameters were measured by means of a paw meter (Bonta & Noordhoek, 1973) at regular intervals and paw swelling was calculated as the difference in paw diameters of the archidonic acid treated paw and the control paw. Arachidonic acid (10–250 μg/paw) produced a rapid, dose related swelling maximal between 15 and 30 min (40–50% increase for 100 μg/paw at 15 min) which persisted for as long as 6 hours.

The prostaglandin synthetase inhibitors, indomethacin (1–10 mg/kg) and phenylbutazone (10–100 mg/kg) did not significantly influence the early phase (0–1 h) of this swelling when administered orally in 5% mulgofen 60 min before the injection of 100 μg arachidonic acid. Indomethacin, but not phenylbutazone, partly suppressed the oedema between 1.5 and 3 hours. Major conversion of arachidonic acid to the prostaglandins is therefore unlikely to be responsible for the paw oedema response. An examination of the role played by other likely mediators in this response was then undertaken.

Neither of the histamine antagonists, mepyramine (2.5 mg/kg) and triproline (50 mg/kg) nor the 5-hydroxytryptamine (5-HT) antagonist, methysergide (2.5 mg/kg s.c.) 30 min prior to the injection of arachidonic acid, affected the course of the paw oedema. However, a combination of triprolidine (50 mg/kg) and methysergide (2.5 mg/kg) administered s.c. 30 min prior to arachidonic acid significantly suppressed the early stages of this oedema (0–2 h) This suggests that histamine and 5-HT are released during these early phases of the inflammation.

Pretreatment with either ellagic acid (2×10^{-4} M administered i.v. at 30, 25 and 20 min prior to arachidonic acid) or soybean trypsin inhibitor (SBTI; 80 mg/kg administered i.p. at 4, 2 and 0 h prior to arachidonic acid) both reduced the oedema from 0 to 4 hours. Both ellagic acid and SBTI have been reported to reduce kinin production, ellagic acid by depleting kininogen stores (Gautvik & Rugstad, 1967) and SBTI, by inhibiting kinin formation from kininogen (Maling, Webster, Williams, Saul & Anderson, 1974). Thus arachidonic acid-induced oedema also appears to involve kinin formation.

The combination of ellagic acid and triproline and methysergide did not completely suppress the arachidonic acid oedema, however, and consequently other factors in addition to histamine, 5-HT and kinins, would appear to be implicated in the inflammatory oedema produced by this fatty acid.

References

BEKEMEIER, H , GIESSLER, A.J. & HIRSCHELMANN, R. (1974). Prostaglandins and inflammation. *Pol. J. Pharmacol.*, **26**, 5–23.

BONTA, I.L. & NOORDHOEK, J. (1973). Anti-inflammatory mechanism in inflamed tissue factor. *Agents Actions*, **3**, 348–356.

GAUTVIK, K.M. & RUGSTAD, H.E. (1967). Kinin formation and kininogen depletion in rats after intravenous injection of ellagic acid. *Br. J. Pharmac. Chemother.*, **31**, 390–400.

GLENN, E.M., BOWMAN, B.J. & ROHLOFF, N.A. (1972). Proinflammatory effects of certain prostaglandins. In *Prostaglandins in Cellular Biology*, ed., Ramwell, P.W. & Pharriss, B.B., pp. 329–344. New York: Plenum Press.

LEWIS, A.J., NELSON, D.J. & SUGRUE, M.F. (1975). On the ability of prostaglandin E_1 and arachidonic acid to modulate experimentally induced oedema in the rat paw. *Br. J. Pharmac.*, **55**, 51–56.

MALING, H.M., WEBSTER, M.E., WILLIAMS, M.A., SAUL, W. & ANDERSON, W. (1974). Inflammation induced by histamine, 5-hydroxytryptamine, bradykinin and compound 48/80 in the rat; antagonists and mechanisms of action. *J. Pharmac. exp. Ther.*, **191**, 300–310.