ANTI-INFLAMMATORY STEROIDS INHIBIT PHOSPHOLIPASE A_2 ACTIVITY

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In this investigation steroid anti-inflammatory drugs have been found to inhibit the enzyme phospholipase A_2 in the perfused rat kidney. Prostaglandins have been implicated in the pathogenesis of inflammation. The prostaglandin precursor, arachidonic acid, occurs mainly in the 2 position of cellular phospholipids and is released by the action of phospholipase A_2. A single rat kidney was isolated and perfused as described by Armstrong et al (1976). Phospholipase A_2 was measured using a double-isotope assay 2-([9,10^{3}H] - Oleoyl) Phosphatidyl Choline and [1 - ^{14}C] Oleic acid (0.1μ Ci total) were injected into the renal artery. The perfusate was collected for 5 min. The labelled fatty acids were extracted with 50ml n-hexane. The solvent was evaporated to dryness and the $^3H/^{14}C$ ratio estimated after liquid scintillation counting. The formation of prostaglandins E_2 and $F_{2\alpha}$ was measured by cascade superfusion of the rat stomach strip and rat colon (Gilmore, et al, 1968). The perfused kidney had a steady basal hydrolysis of radio-labelled phospholipid (2-4%) which remained constant from 30 min to 5h after commencement of perfusion. Infusion of dexamethasone, betamethasone, prednisolone or hydrocortisone produced a concentration-dependent, time-dependent inhibition of phospholipase A_2 activity and a corresponding decrease in prostaglandin production. After 90 min of steroid infusion the ID_{50} values for inhibition of Phospholipase A_2 were; dexamethasone (0.8μg/ml), betamethasone (0.9 μg/ml), prednisolone (1.5μg/ml) and hydrocortisone (12μg/ml). Progesterone (50μg/ml) had no effect on phospholipase A_2. Simultaneous administration of progesterone (0.1 - 5μg/ml) competitively reduced the inhibitory effects of the anti-inflammatory steroids. The competitive effect of progesterone corroborates the findings of Tjurufuji et al (1979).

These investigators suggested the involvement of a glucocorticoid receptor in the anti-inflammatory activity of dexamethasone. The inhibition of phospholipase A_2 in the isolated perfused rat kidney by dexamethasone, betamethasone, prednisolone and hydrocortisone was similar to their relative anti-inflammatory potencies (Nijkamp et al, 1976). Thus their anti-inflammatory activity could be attributed to the reduction in the release of arachidonic acid, the Prostaglandin precursor.

Armstrong, J.M. et al (1976) Nature 260: 582 - 586
Gilmore N et al (1968) Nature 218: 1135 - 1138
Nijkamp F.P. et al (1976) Nature 263: 479 - 482
Tjurifuji S. et al (1979) Nature 280: 408 - 410