BAEe activity which was restored after replacement of oestrogen (0.5 mg oestradiol undecylate x 4 doses/7 day interval) and unaffected by androgen (5 mg testosterone oenanthate x 4 doses/7 day interval).

Morphologically mature glandular units in rodents consist of acini, intercalated ducts, secretory tubules and striated tubules. Postnatal development of glandular elements other than the acinus shows no sex-linked variation in the hamster. Ultrastructurally, sex hormone related differences are only observed in the granule population of the acinar cells. In the female, mainly one type of cell is seen with a single population of granules which possess a central pale area and a peripheral dense region. In contrast, the male has three cell types, the predominant containing granules with a central dense core and an outer pale section. In the ovariectomized females the fine structural appearance of the granules changes to that observed in the male, but the *female* type of granules return after replacement of oestrogen.

Androgens specifically influence enzyme induction and formation of granules in the secretory tubules of the mouse submaxillary gland. In the hamster in contrast the sex-hormone related changes in the acinar cell granules and in the activity of the kallikrein-like enzymes seems to be mediated by oestrogens. Such changes are probably regulated by genes specifically controlled by androgen or oestrogen.

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Effect of oestrogens and progesterone alone and in combination on the female rat plasma kininogen concentrations

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Previous work in this laboratory (McCormick & Senior, 1973) has confirmed the observations of Weigerhausen, Kläusch, Hennighausen & Sosat (1967) that the concentration of plasma kininogen rises with advancing gestation in the rat. McCormick & Senior (1971) have also shown that oestrogens in optimal doses raise the concentration of plasma kininogen in the female rat, and progesterone in the doses studied had no effect.

This communication describes experiments to study the effect of oestrogens and progesterone alone and in combination on non-pregnant female rats in an attempt to elucidate this phenomenon further.

All drugs were administered daily for five days to mature, virgin, female rats by the subcutaneous route. The concentrations of plasma kininogen were determined using the micromethod of Diniz & Carvahlo (1963).

β-oestradiol (in doses from 1 to 50 μg/kg/day) and a soluble synthetic oestrogen, FI6173 (2,4,dimethyl-5,5-diphenyl pent-4-enoic acid sodium salt) (in doses from 10-500 μg/kg/day) were used.

With both oestrogens a dose response effect was obtained with maximum significant increase in plasma kininogen concentrations occurring at 5 μg/kg for β-oestradiol and 50 μg/kg for FI6173. Progesterone had no effect on kinin precursor concentrations at doses of 0.5, 2.5 and 5 mg/kg; however, a significant decrease was obtained with 10 mg/kg. β-oestradiol and progesterone were administered in arachus oil.

Two dose levels of oestrogens were used (5 μg/kg and 10 μg/kg for β-oestradiol and 50 μg/kg and 250 μg/kg for FI6173) in conjunction with varying doses of progesterone (0.5, 2.5, 5 and 10 mg/kg). In all cases, the significant increase in kininogen concentrations produced by the oestrogens was reduced by, and in proportion to, the dose of progesterone. Progesterone had a more marked effect when in conjunction with the lower dose of each oestrogen.

The results show that the two oestrogens used increase the plasma kininogen concentration of the non-pregnant female rat in proportion to the dose used. A high dose of progesterone is required to produce a significant decrease in plasma kininogen concentrations.

It appears that progesterone will reduce the increase in kinin precursor produced by the

oestrogen alone and the extent of this reduction appears to be related to the ratio of oestrogen to progesterone.

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Potentiation by prostaglandin E_1 and arachidonic acid of oedema in the rat paw induced by various phlogogenic agents

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Although prostaglandins have been implicated as mediators of inflammation (Vane, 1970) the nature of their involvement remains to be elucidated. In light of the findings of Ferreira (1972) that exogenous prostaglandins can potentiate the pain-producing effect of exogenous bradykinin and histamine in humans, it was of interest to determine if the ability of various phlogogenic agents to induce inflammation in the rat paw could be potentiated by prostaglandin E_1 (PGE_1) and arachidonic acid (A.A.).

Male Wistar (CE/CFHB) rats weighing 80-100 g were divided into three groups, each containing 10 animals. Groups of the animals received either: (a) a submaximal dose of the phlogogenic agent, (b) PGE_1 (100 ng) or A.A. (100 μg), or (c) a combination of the phlogogenic agent and either PGE_1 (100 ng) or A.A. (100 μg). Injections were via the subplantar route into the right hind paw. The contralateral paw received an equal volume of vehicle (0.05-0.1 ml). The mean difference between right and left paw volumes for each group, as measured by mercury displacement plethysmometry, was determined at the time of maximal oedema, namely 0.5 h for PGE_1 treated groups and 1.5 h for A.A. treated groups. To quantify the degree of potentiation, the inflammations ensuing after separately administered phlogogenic agent and either PGE_1 or A.A. were summated. This value was subtracted from the oedema observed when the agent and either PGE_1 or A.A. were administered concomitantly. The difference was expressed as a percentage of the summated oedema produced by the agent and either PGE_1 or A.A. given separately.

PGE_1 did not potentiate the summated responses to serotonin (1 μg), histamine (10 μg), compound 48/80 (1 μg) or dextran (6 μg). However, PGE_1 did enhance the summated response to carrageenan (1 mg) by 83 ± 17%, kaolin (10 mg) by 80 ± 16%, bradykinin (4.5 μg) by 110 ± 25% and trypsin (50 μg) by 38 ± 8%. A.A. potentiated the summated response to carrageenan (1 mg) by 25 ± 5% and kaolin (10 mg) by 69 ± 11% but did not enhance the action of serotonin (1 μg), histamine (10 μg), compound 48/80 (1 μg), dextran (6 μg), bradykinin (4.5 μg) or trypsin (50 μg).

Leucocytes have been implicated in carrageenan- (Di Rosa, Papadimitriou & Willoughby, 1971), but not bradykinin-induced oedema (Ward, 1972). Since leucocytes constitute a source of prostaglandin synthetase (Higgs & Youlten, 1972), the inability of A.A. to potentiate the response to bradykinin may result from inadequate conversion of A.A. to prostaglandins. Inflammation induced by carrageenan and kaolin, but not by serotonin, histamine, dextran or compound 48/80, is potentiated by exogenous PGE_1 and A.A. Non-steroidal anti-inflammatory drugs, such as indomethacin, are potent inhibitors of carrageenan-induced oedema whilst being less effective inhibitors of inflammation induced by serotonin or dextran (Winter, 1964). Should inhibition of prostaglandin synthetase constitute the mechanism of action of non-steroidal anti-inflammatory drugs (Vane, 1970), prostaglandins would not appear to be involved in the mediation of serotonin and dextran oedema. Hence, the results of this study suggest a correlation between the role of prostaglandins in experimentally induced oedemas and the ability of PGE_1 and A.A. to potentiate such oedemas.

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