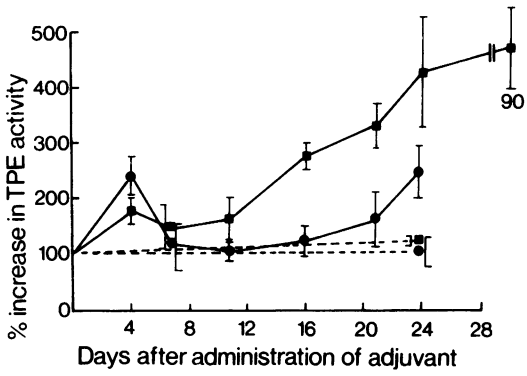

Figure 1 Trypsin-protein-esterase (TPE) values of the plasma of arthritic rats ■——■ and arthritic rats treated with cortisol ●——●. Dotted lines represent non-arthritic control animals. Each result represents the mean of five animals and vertical lines indicate s.e. mean.

measuring their trypsin-protein esterase (TPE) activity (Ganrot, 1973).

In this communication we report on the action of cortisol on the plasma levels of α_1-macroglobulin and α_2-acute phase protein in the normal and adjuvant arthritic rat.

Adjuvant arthritis was induced in male, Wistar strain rats (180–200 g body weight) (Parrott & Lewis, 1974). Some normal and some arthritic rats were injected daily, subcutaneously, with cortisol acetate in saline (5 mg/kg body weight) over the experimental period. The controls were injected with saline. α_1-macroglobulin and α_2-acute phase globulin were assayed simultaneously by measuring the TPE activity of plasma.

The results show that TPE plasma levels were elevated by inflammation but that cortisol treatment depressed these levels towards that of the non-arthritic controls. Cortisol had no significant effect on non-Arthritic rat plasma TPE levels.

Cortisol stimulates α_1-antitrypsin levels in the blood of both normal and arthritic rats (Parrott & Lewis, 1976) but clearly it has no effect on α_1-macroglobulin or α_2-acute phase globulin levels apart from depressing acute phase antiproteases through its anti-inflammatory action.

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Potentiation of anaphylactic bronchoconstriction by non-steroidal anti-inflammatory agents

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Non-steroidal anti-inflammatory agents have been reported to enhance mediator release from both human and guinea-pig sensitized lung challenged *in vitro* (Walker, 1972; Engineer, Piper & Sirois, 1976). We have extended these observations to the *in vivo* situation and report here the effect of non-steroidal anti-inflammatory agents on anaphylactic bronchoconstriction in the guinea-pig.

Guinea-pigs were sensitized either passively or actively. Passive sensitization was by intravenous injection of 0.5 ml of a 1/50 dilution of serum prepared according to the method of Davies & Johnston (1971) and were challenged 24 h later. Active sensitization was by the intraperitoneal and subcutaneous injection of ovalbumen (100 mg/kg) with antigen challenge three weeks later. Anaphylactic bronchoconstriction was measured according to the method of Collier & James (1967). Inhibitory compounds and antigen (ovalbumen) were administered intravenously, the compounds being given 5 min before antigen.

Sodium meclofenamate (1 mg/kg) significantly potentiated anaphylactic bronchoconstriction in passively sensitized guinea-pigs when submaximal doses of antigen (0.12–0.60 mg/kg) were used for challenge. When animals were challenged with a maximal dose of antigen (15 mg/kg), sodium meclofenamate had no significant effect. In animals challenged with a maximal dose of antigen in which the histamine-induced component of bronchoconstriction had been suppressed by the administration of mepyramine (2 mg/kg), sodium meclofenamate potentiated the reaction, returning the bronchoconstriction to the level of that seen in control animals.

In animals treated in this way however, mepyramine plus meclofenamate significantly inhibited the reaction over the first minute following antigen challenge, the period of the reaction identified by Collier & James (1967) as being mediated by kinins. Similar results were obtained for flufenamic acid (5 mg/kg).

In actively sensitized guinea-pigs, similar results were obtained, although there were quantitative differences. Thus, mepyramine was less effective in blocking bronchoconstriction following challenge with antigen (0.6 mg/kg of ovalbumen) in active than passively sensitized animals. Moreover, whereas in passively sensitized guinea-pigs mepyramine inhibited over the whole of the 10 min period for which the reaction was followed, in actively sensitized animals mepyramine inhibited the reaction only over the initial 4–5 minutes. Sodium meclofenamate had no effect when given alone but potentiated the reaction in mepyramine treated animals; again, however, the initial period of bronchoconstriction was inhibited in animals given mepyramine plus meclofenamate.

These results confirm the potentiation of mediator release by non-steroidal anti-inflammatory agents and have shown its importance in an *in vivo* situation. From the results obtained, it appears that sodium meclofenamate potentiated the SRS-A mediated portion of anaphylactic bronchoconstriction, probably through an effect upon the synthesis of prostaglandins thought to play a modulatory role in the control of mediator release (Walker, 1972). Differences were observed between the relative importance of the mediators in anaphylactic bronchoconstriction in actively and passively sensitized animals, and it appears that histamine is less important in actively sensitized animals.

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Effects of activation of H_1- and H_2-receptors on central cardiovascular structures in cats and on behaviour in chickens

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Intracerebroventricular administration of histamine increased blood pressure, heart rate and amplified sympathetic discharges. Intracerebroventricular administrations of mepyramine but not of metiamide have been reported to reduce this effect which was therefore suggested to be mediated by activation of H_1-receptors (Finch & Hicks, 1976).

In chloralose-anaesthetized cats, histamine, 4-methylhistamine, 2-(2-aminoethyl) pyridine and betahistine were administered into the lateral ventricle of the brain. Histamine (2–10 μg/kg) induced a rise in blood pressure which was reduced by mepyramine indicating the involvement of H_1-receptors. 2-(2 aminoethyl) pyridine, and betahistine, two stimulants of H_1-receptors, induced hypertension and tachycardia. The pressor effect reached 35 mmHg after 100 μg/kg of 2-(2 aminoethyl) pyridine and 15 mmHg after 200 μg/kg of betahistine.

These effects were suppressed by an intraventricular administration of mepyramine (100 μg/kg) but not of metiamide (50 μg/kg). High doses of 4-methylhistamine (100 μg/kg), a stimulant of H_2-receptors, injected into the lateral ventricle of the brain, induced a brief increase in blood pressure (15–20 mmHg). At higher doses, this effect was followed by a hypotension, possibly due to leakage into the systemic circulation. The rise in blood pressure was abolished by an intracerebroventricular injection of metiamide (100 μg/kg) and of mepyramine (50 μg/kg).

Histamine in newborn chickens induced sleep characterized by a loss of the righting reflex. The duration of sleep was 12 min after 50 mg/kg, i.m. of the drug. 4-Methylhistamine (50 mg/kg, i.m.) induced sleep for 6 min, but 2-(2 aminoethyl) pyridine and betahistine (100 mg/kg, i.m.) failed to abolish the righting reflex.