Inhibition of eosinophil chemotaxis by the antagonist of slow reacting substance of anaphylaxis — compound FPL 55712*

The antigen challenge of sensitized lung and skin leads to the release of a number of pharmacological mediators which include histamine, a slow reacting substance of anaphylaxis (SRS-A) and an eosinophil chemotactic factor of anaphylaxis (ECF-A) (Brocklehurst, 1960; Kay, Stechschulte & Austen, 1971; Jones & Kay, 1974). ECF-A selectively attracts eosinophils from a mixed leucocyte population (Kay, Shin & Austen, 1973) has an estimated molecular size of between 500 and 1000 and probably has a peptide-like structure (Kay, Stechschulte & others, 1971).

In a recent report it was shown that the compound FPL 55712* is a potent inhibitor of SRS-A whereas it had relatively little antagonistic effect on the ileum-contracting activity of histamine and other pharmacological agents (Augstein, Farmer & others, 1973). In the present study we have tested the capacity of FPL 55712 to inhibit ECF-A activity. In addition the antiallergic compounds hydrocortisone and disodium cromoglycate have been tested for inhibition of ECF-A-induced eosinophil chemotaxis, since both these agents are associated with a reduction in the number of circulating eosinophils when administered *in vivo* (Thorn, Forsham & others, 1948; Easton, 1973).

A partially purified preparation of guinea-pig ECF-A was prepared as previously described (Kay & others, 1973). Chemotaxis was measured by a modification of the Millipore technique of Boyden using guinea-pig eosinophils prepared from the peritoneal cavity of animals which had received multiple injections of horse serum (Kay, 1970).

Solutions of FPL 55712, disodium cromoglycate and hydrocortisone were freshly prepared by dissolving the compounds in distilled water. One part of increasing

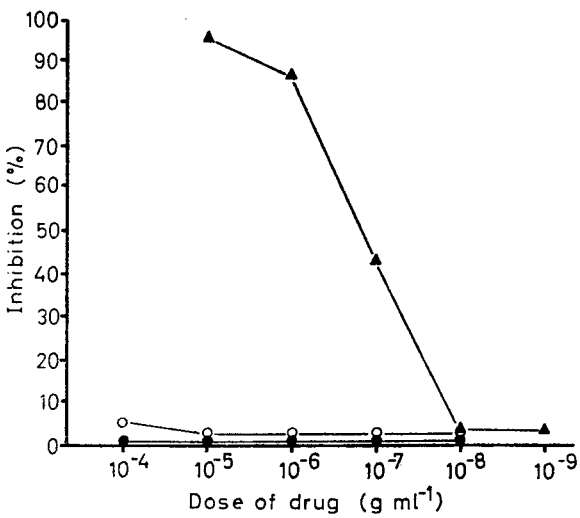

FIG. 1. The graph shows the percent inhibition of the chemotactic response of guinea-pig eosinophils towards partially purified guinea-pig ECF-A by increasing concentrations of FPL 55712 (▲ — ▲), disodium cromoglycate (○ — ○), and hydrocortisone (● — ●).

* Sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-chromene-2-carboxylate.

dilutions of the compound were added to nine parts of ECF-A in Tyrode solution. The results were expressed as the percent inhibition of eosinophil chemotaxis as compared with the same volume of ECF-A containing one part of distilled water. As shown in Fig. 1, FPL 55712 inhibited ECF-A in a dose-dependent fashion and had an IC50 of 0·2 μg ml^{-1} (3·8 $\times$ 10^{-7}M). Neither hydrocortisone nor disodium cromoglycate inhibited the activity of ECF-A at concentrations of up to 100 μg ml^{-1} (2·8 $\times$ 10^{-4} and 1·9 $\times$ 10^{-4}M respectively). These experiments were performed three times and gave similar results.

We were also able to confirm both the antagonistic effect of FPL 55712 on the ileum-contracting activity of guinea-pig SRS-A, and its negligible effect on histamine.

Thus the present report suggests that the reduction in the number of circulating eosinophils *in vivo* associated with the administration of corticosteroids and disodium cromoglycate is unlikely to be due to their direct effect on this cell. The inhibitory effect of FPL 55712 on ECF-A-induced chemotaxis of eosinophils could be a result of an alteration of the ECF-A molecule itself or on the recognition by the eosinophil of the chemotactic stimulus. Thus the unique action of FPL 55712 may serve as a useful adjunct for further study on the mechanism of ECF-A-induced chemotaxis of eosinophils.

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