The Anti-Allergic Effects of FPL 52694

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Abstract

The substituted chromone carboxylic acid FPL 52694 inhibited models of **IgE-mediated** immediate hypersensitivity reactions in the rat by a mechanism similar to that of sodium cromoglycate. The compound was more potent than sodium cromoglycate but unlike cromoglycate was active following oral administration.

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It has been reported that FPL 52694 (5-[2-hydroxy-propoxy]-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid sodium salt) inhibits the secretion of gastric acid in volunteers [1] and animals [2]. It has been suggested that the suppression of gastric acid secretion following infusion with pentagastrin is due to the ability of the compound to inhibit histamine release within the gastric mucosa [2]. This communication presents the evidence showing that FPL 52694 inhibits mediator release from mast cells challenged with antigen or antibody to IgE, and that the mechanism of mast cell stabilisation is similar to that for sodium cromoglycate.

For a number of years, the immediate hypersensitivity reaction to egg albumin in rats passively sensitised with serum containing IgE antibodies to egg albumin, the passive cutaneous anaphylaxis test (PCA) [3], has been used as a screen to evaluate anti-allergy compounds [4]. FPL 52694 administered intravenously, 1 min before antigen challenge, inhibited the PCA reaction in a dose-dependent manner. Results from two experiments showed that FPL 52694 was approximately twice as potent as sodium cromoglycate, having an ED₅₀ value of 0.8 mg/kg. However, unlike sodium cromoglycate, FPL 52694 was shown to inhibit the PCA reaction in rats when administered orally 7 min before antigen challenge (50% inhibition at 20 mg/kg) or when administered directly into the duodenum of anaesthetised laparotomised rats 7 min before antigen challenge (50% inhibition at 12.5 mg/kg, mean of two experiments).

Several workers [5–9] have reported the beneficial effects of sodium cromoglycate, administered orally, in patients with food allergy, and from the work of Paganelli et al. [10] it has been suggested that sodium cromoglycate was inhibiting local intestinal anaphylaxis, preventing an increase in intestinal permeability. We have examined several chromones in the model of intestinal anaphylaxis described by Byars and Ferraresi [11]. Rats were sensitised to egg albumin [3] and challenged 4 weeks later by administering antigen (1 mg) intraduodenally to anaesthetised laparotomised animals. A change in capillary permeability was measured by injecting intravenously, 15 min before antigen challenge, 125-iodinated-Bovine serum albumin.

15 min after antigen challenge, the radioactive content of the intestine was measured. The increase in capillary permeability following antigen challenge was inhibited by the administration of sodium cromoglycate, intraduodenally, but results were highly variable and inhibition was only observed at high doses (400 mg/kg, administered simultaneously with antigen).

However, in a direct comparison with sodium cromoglycate, FPL 52694 was shown to be at least four times more potent than cromoglycate in this model of intestinal anaphylaxis.

Compound 48/80 administered intravenously in rats causes the widespread degranulation of mast cells which can be quantitated by staining the subcutaneous connective tissue with toluidine blue [12]. The degree of degranulation can be inhibited by injecting

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Dose FPL 52694, mg/kg

Fig. 1 Inhibition of subcutaneous mast cell degranulation induced by Compound 48/80 (0.5 mg kg⁻¹ i.v.) in male Sprague Dawley rats (100 g; n = 6).

FPL 52694, intravenously, 1 min before Compound 48/80. As shown in figure 1, a bell-shaped dose response is observed similar to that found for sodium cromoglycate [13].

FPL 52694 was compared with sodium cromoglycate for its ability to inhibit degranulation of unpurified rat peritoneal mast cells challenged in vitro with anti-rat IgE (Miles) as previously described [14]. By comparing the concentrations required to give half maximum inhibition, FPL 52694 was shown to be 15.4 times more potent than sodium cromoglycate in blocking histamine release (range 14.3–19.9 in three experiments). Typical dose response curves are shown in figure 2a.

Sodium cromoglycate has been shown to induce the phosphorylation of a 78,000-molecular weight protein in rat peritoneal mast cells, in the absence of challenge [15], and induction of this phosphorylation event correlates well with the ability of anti-allergic chromones to inhibit histamine release [14]. Phosphorylation of this same protein also occurs late in the challenge sequence and it has been proposed that this represents the natural feedback mechanism which restabilises the mast cell [16]. Sodium cromoglycate thus appears to inhibit mediator release by inducing this natural switch-off mechanism. Using the methodology previously reported [14], FPL 52694 also induced phosphorylation of this 78,000-molecular weight protein (fig. 2b), at similar concentrations to those required to inhibit histamine release.

In summary, FPL 52694 has been shown to inhibit type I immediate hypersensitivity reactions in the skin and intestine of rat. Further, this compound inhibits degranulation and mediator release from rat mast

Fig. 2. a Inhibition of histamine release induced by anti-rat IgE (1/2,000 dilution, Miles). Drugs were added at the time of challenge. The unblocked release was 21% of total histamine. b Phosphorylation of the 78,000 molecular weight protein after a 30-second incubation of [32P]-orthophosphate loaded purified mast cells with compound. Proteins were fractionated by SDS polyacrylamide gel electrophoresis and the peak height on a densitometric scan of the autoradiograph used as a measurement of phosphorylation. cells by a similar mechanism to that of sodium cromoglycate. The compound appears to be more potent than sodium cromoglycate and is absorbed after oral administration. It is possible that the mast cell-stabilising properties of FPL 52694 account for the ability of the compound to inhibit gastric acid secretion in animals and man, by preventing histamine release from cells within the gastric mucosa.

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