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Inhibitory effects of prostaglandin EP₄ receptors on human eosinophils

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Background

The accumulation of eosinophils in lung tissue is a hallmark of asthma, and it is believed that eosinophils play a crucial pathogenic role in allergic inflammation. Prostaglandin (PG) E₂ exerts anti-inflammatory and broncho-protective mechanisms in asthma, but the underlying mechanisms have remained unclear. We have shown previously that PGE₂ and the EP₂ receptor agonist butaprost inhibit eosinophil trafficking in vitro and in vivo.

Methods

Human eosinophils were purified by negative magnetic selection from peripheral blood. Cell migration was determined in microBoyden chemotaxis chambers. Ca²⁺ flux and expression of cell surface markers was recorded by flow cytometry. EP₄ receptor expression was demonstrated by immunostaining.

Results

The chemotaxis of eosinophils towards eotaxin and C5a was attenuated by the EP₄ agonist ONO-AE1-329, and the EP₄ antagonists ONO-AE3-208 and GW627368x partially reversed the inhibitory effect of PGE₂ on eosinophil migration. ONO-AE1-329, and also PGE₂, but not butaprost inhibited the Ca²⁺ flux and the production of reactive oxygen species in eosinophils. ONO-AE1-329 also inhibited eosinophil degranulation and the up-regulation of the adhesion molecule CD11b. Selective kinase inhibitors revealed that the inhibitory effect of EP₄ stimulation on eosinophil migration depended upon activation of phosphatidylinositol 3-kinase and protein kinase C, but not cAMP. Immunostaining showed that human eosinophils express EP₄ receptors and that EP₄ receptor expression in the murine lungs is prominent in airway epithelium, and after allergen challenge, in peribronchial infiltrating leukocytes.

Conclusion

These data show that EP₄ receptor agonists potently inhibit eosinophil trafficking and activation, and might hence be a useful therapeutic option in eosinophilic diseases.