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Meeting abstract

Inhibitory effects of prostaglandin EP_4 receptors on human eosinophils

Petra Luschnig-Schratl, Eva M Sturm, Viktória Kónya, Rufina Schuligoi and Ákos Heinemann*

Address: Institute of Experimental and Clinical Pharmacology, Medical University of Graz, 8010 Graz, Austria

Email: Ákos Heinemann* - akos.heinemann@medunigraz.at

* Corresponding author

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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) E_2 exerts anti-inflammatory and bronchoprotective mechanisms in asthma, but the underlying mechanisms have remained unclear. We have shown previously that PGE_2 and the EP_2 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. Ca^{2+} flux and expression of cell surface markers was recorded by flow cytometry. EP_4 receptor expression was demonstrated by immunostaining.

Results

The chemotaxis of eosinophils towards eotaxin and C5a was attenuated by the EP_4 agonist ONO-AE1-329, and the EP_4 antagonists ONO-AE3-208 and GW627368x partially reversed the inhibitory effect of PGE_2 on eosinophil migration. ONO-AE1-329, and also PGE_2, but not butaprost, inhibited the Ca^{2+} 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 EP_4 stimulation on eosinophil migration depended upon activation of phosphatidylinositol 3-kinase and protein kinase C, but not cAMP. Immunostaining showed that human eosinophils express EP_4 receptors and that EP_4 receptor expression in the murine lungs is prominent in airway epithelium, and after allergen challenge, in peribronchial infiltrating leukocytes.

Conclusion

These data show that EP_4 receptor agonists potently inhibit eosinophil trafficking and activation, and might hence be a useful therapeutic option in eosinophilic diseases.