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Meeting abstract

Effects of PGH_2 and PGD_2 on CRTH2 and DP receptors in primary cells and co-expressed in HEK293 cells

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Prostaglandin (PG) D_2 is a PGH_2 metabolite deriving from the cyclooxygenase pathway and the major prostanoid released from activated human mast cells. The biological effects of PGD_2 are mediated by the G protein-coupled receptors (GPCRs) D-type prostanoid receptor (DP) and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). Eosinophils, important effector cells in allergy, express both receptors. Activation of CRTH2 has been shown to result in pro-inflammatory responses, while the role of DP in allergic inflammation is still unclear. In this study we show that PGH_2 selectively stimulates human peripheral blood eosinophils and basophils, but not neutrophils, and this effect is prevented by the CRTH2 receptor antagonist, Cay10471. In chemotaxis assays, eosinophils showed a pronounced migratory response towards PGH_2, while eosinophil degranulation was inhibited by PGH_2. Moreover, collagen-induced platelet aggregation was inhibited by PGH_2 in platelet-rich plasma, which was abrogated in the presence of the DP antagonist, BWA868c. HEK293 cells transfected with either human CRTH2 or DP responded with Ca^{2+} flux, while untransfected HEK293 cells showed no response. These data indicate that PGH_2 causes activation of the PGD_2 receptors, CRTH2 and DP, even in the absence of functional PGD synthase. In further experiments, CRTH2 and DP receptors were stably co-expressed in HEK293 cells as a tool to explore receptor signalling and to investigate possible receptor heterodimerization. Data will be shown that demonstrate possible combinatorial effects of CRTH2 and DP to selective and non-selective agonists and antagonists in Ca^{2+} signalling assays.