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THE CYSTEINYL LEUKOTRIENE D_4 ENHANCES THE CELLULAR RESPONSE TO HISTAMINE IN HUMAN DETRUSOR SMOOTH MUSCLE CELLS

Aims of Study

Mast cells release upon activation potent smooth muscle spasmogens including cysteinyl containing leukotrienes and histamine. The presence of cysteinyl-leukotriene D_4 (LTD_4) receptors in human detrusor smooth muscle cells (DSMC) [1] and increased level of leukotriene E_4 in urine from patients with Interstitial Cystitis (IC) and detrusor mastocytosis [2] have been shown recently. Exaggerated cellular histamine reactivity is associated with a variety of pathological conditions, in particular astmatic disease. The aim of the study was to investigate whether histamine induces the production of prostaglandin E_2 (PGE_2) in cultured DSMC and whether this production is enhanced by LTD_4.

Methods

Histamine responsiveness was determined by measuring histamine-induced release of PGE_2 production in cultured human detrusor smooth muscle cells. Using explant technique DSMC were isolated and cultured as previously described [1]. Only primary cultures were used for experiments. DSMC were seeded in 24-wells plates and used when confluent. For PGE_2 determinations cells were maintained in serum free medium for 24 hours and challenged by histamine (0.1 – 100 μM) with and without addition of either 10 nM or 50 nM LTD_4 for 5 min. Supernatants were collected after 12 hours. PGE_2 production was measured using a commercially available enzyme linked immuno asay (ELISA). All determinations were performed in dublicate and normalized to protein concentration in each well.

Results

Histamine (0.1 – 100 μM) induced a dose-dependent increase in PGE_2 production in human DSMC. Stimulation of DSMC with low concentration (10 nM) LTD_4 failed to induce PGE_2 release. However, higher LTD_4 concentration (50 nM) caused a small but statistically significant increase in PGE_2. Preincubation with the low concentration of LTD_4 (10 nM) strongly enhanced the PGE_2 release in DSMC when challenged with histamine (0.1 – 100 μM). However, when DMSC where preincubated with the high (50 nM) concentration of LTD_4 a lower response to histamine was observed.

Conclusions

We here show for the first time that histamine induce the production of PGE_2 in cultured DSMC and that LTD_4 enhances the production of PGE_2 induced by histamine. This could play a pathophysiological role in IC where both LTD_4 and histamine are involved as inflammatory mediators. Recently, the leukotriene antagonist Montelukast for the treatment of IC have shown promising results [3]. The results of this study indicate a role for antihistamines and/or COX-2 inhibitors in combination with leukotriene antagonists for the treatment of Interstitial Cystitis.

Reference List

1. The action of cysteinyl-leukotrienes on intracellular calcium mobilization in human detrusor myocytes. BJU.Int. 2001;87:690-96.

2. Increased urinary leukotriene E4 and eosinophil protein X excretion in patients with interstitial cystitis. J.Urol. 2001;166:2121-25.

3. The cysteinyl leukotriene D4 receptor antagonist montelukast for the treatment of interstitial cystitis. J.Urol. 2001;166:1734-37.