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Calcium Release- Activated Calcium Channels as a Target in Treatment of Allergic Asthma

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Abstract : Bronchial asthma is characterized by increased bronchoconstrictor responses to provoking agonists, airway inflammation and remodeling. All these processes involve Ca2+ influx through Ca2+-release-activated Ca2+ channels (CRAC) that are widely expressed in immune, respiratory epithelium and airway smooth muscle (ASM) cells. Our previous study pointed on possible therapeutic potency of CRAC blockers using experimental guinea pigs asthma model. Presented work analyzed complex anti-asthmatic effect of long-term administered CRAC blocker, including impact on allergic inflammation, airways hyperreactivity, and remodeling and mucociliary clearance. Ovalbumin-induced allergic inflammation of the airways according to Franova et al. was followed by 14 days lasted administration of CRAC blocker (3-fluoropyridine-4-carboxylic acid, FPCA) in the dose 1.5 mg/kg bw. For comparative purposes salbutamol, budesonide and saline were applied to control groups. The anti-inflammatory effect of FPCA was estimated by serum and bronchoalveolar lavage fluid (BALF) changes in IL-4, IL-5, IL-13 and TNF-α analyzed by Bio-Plex® assay as well as immunohistochemical staining focused on assessment of tryptase and c-Fos positivity in pulmonary samples. The in vivo airway hyperreactivity was evaluated by Pennock et al. and by organ tissue bath methods in vitro. The immunohistochemical changes in ASM actin and collagen III layer as well as mucin secretion evaluated anti-remodeling effect of FPCA. The measurement of ciliary beat frequency (CBF) in vitro using LabVIEW™ Software determined impact on mucociliary clearance. Long-term administration of FPCA to sensitized animals resulted in: i. Significant decrease in cytokine levels, tryptase and c-Fos positivity similar to budesonide effect; ii.Meaningful decrease in basal and bronchoconstrictors-induced in vivo and in vitro airway hyperreactivity comparable to salbutamol; iii. Significant inhibition of airway remodeling parameters; iv. Insignificant changes in CBF. All these findings confirmed complex anti-asthmatic effect of CRAC channels blocker and evidenced these structures as the rational target in the treatment of allergic bronchial asthma.

Keywords : allergic asthma, CRAC channels, cytokines, respiratory epithelium
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