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The effect of β_2 -adrenoceptor agonists and steroids on induced airway inflammation and bronchial responsiveness

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Abstract

Acute exposure of healthy subjects in a swine barn induces an intense airway inflammation and increased bronchial responsiveness. Dust collected in swine houses is a potent stimulus for release of pro-inflammatory cytokines from cells *in vitro*. The main aim of this thesis was to elucidate the effects of long-acting β_2 -agonists and glucocorticosteroids on inflammatory mechanisms *in vivo* and *in vitro* using organic dust as pro-inflammatory stimulus.

In the first study, formoterol and salmeterol were shown to induce enhancement of IL-6 and IL-8 release from non-stimulated primary bronchial epithelial cells (PBEC) and A549 cells *in vitro*. The β_2 -agonists also added to the effect of organic dust. This enhanced release was blocked by a β -blocker in PBEC, but not in A549 cells. The results indicate different mechanisms of β_2 -agonists action in bronchial and alveolar epithelial cells, and that A549 cells do not possess functional β_2 -adrenoceptors.

In the second study formoterol was shown to add to the dust-induced IL-6, but not IL-8 release from PBEC. Budesonide attenuated the release of both cytokines in a dose-response manner. This inhibiting effect was sustained but not reinforced by formoterol. No synergistic effect between formoterol and budesonide was found.

In the third study the effect of formoterol and budesonide on chemokine/cytokine release, chemokine receptor expression and chemotaxis in isolated human neutrophils *in vitro* was evaluated. Formoterol enhanced and budesonide inhibited IL-6, IL-8, and GRO- α release from LPS-stimulated neutrophils. Formoterol upregulated both CXCR1 and CXCR2 expression, whereas budesonide upregulated the expression of CXCR2 only. Despite the effects on chemokine release and drug-induced up-regulation of chemokine receptors, no influence on neutrophil chemotaxis could be demonstrated by the β_2 -agonist or the glucocorticosteroid.

In the fourth study, 12 healthy subjects were exposed to organic dust in a swine barn. In this cross-over designed study, we found that one single dose of salmeterol partially protected against the increased responsiveness to methacholine. Salmeterol did not influence the inflammatory response to dust exposure. One week pre-treatment with fluticasone or ibuprofen had no effect on the airway responses and did not alter the effect of salmeterol. In addition, a retrospective analysis of pooled data from four previous studies was performed. We concluded that exposure leads to an enhancement of bronchial responsiveness to a certain maximal level which is similar in all subjects, and almost totally unrelated to pre-exposure level of bronchial responsiveness.

In conclusion, although β_2 -agonists and glucocorticosteroids influence the release of pro-inflammatory cytokines/chemokines and up-regulate chemokine receptors *in vitro*, these drugs did not influence the investigated inflammatory parameters *in vivo*. As the increase in bronchial responsiveness following organic dust exposure is strongly related to pre-exposure bronchial responsiveness, interventions altering bronchial responsiveness have to be compared between groups with similar pre-challenge bronchial responsiveness or in a cross-over design. No additive/synergistic effects between β_2 -agonists and steroids were found.