Asthma, hypersensitivity pneumonitis and cough

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Influence of selective phosphodiestarease 4 and 5 inhibitors on airway reactivity, inflammation, and apoptosis in ovalbumin-sensitized guinea pigs.

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Introduction/question: Chronic obstructive diseases associated with inflammation and cough have been treated with bronchodilating and anti-inflammatory drugs for decades. An inhibition of phosphodiesterases (PDE) can lead to both of these effects, with further effects on immune cell survival and apoptosis. In chronic obstructive pulmonary disease (COPD), roflumilast, a selective PDE4 inhibitor, has been recently approved for the pharmacotherapy. The aim of this study was to evaluate the effects of long-term administration of roflumilast and tadalafil (PDE5 inhibitor) on airway reactivity and markers of inflammation and apoptosis in the model of experimentally induced allergic inflammation in guinea pigs.

Material and methods: Male adult guinea pigs were used in the study. Control group was left without sensitization. The latter 6 groups have been sensitized with ovalbumin for 14 days and thereafter treated for 7 days with roflumilast (1.0 mg/kg i.p. and inh.), tadalafil (1.0 mg/kg i.p.), dexamethasone (1.0 mg/kg i.p.), or salbutamol (1.0 mg/kg inh.), or with vehicule (*aqua pro injectione*, i.p., 3 mL/kg), respectively.

Results: Both roflumilast and tadalafil reduced specific airway resistance (as a marker of *in vivo* airway reactivity) after nebulization of histamine measured in double chamber whole body plethysmograph. These changes have been confirmed in *in vitro* conditions using organ bath method with significant decrease of tracheal and lung smooth muscle contractility after cumulative doses of acetylcholine and histamine. Furthermore, the suppression of hematological markers (total white blood cells count and relative eosinophil count in blood and bronchoalveolar lavage fluid, BALF), changes in the concentrations of several immunological markers of inflammation in lung homogenate (decrease in IL-4, IL-5, TNFα, NF-κB), and apoptosis (suppression of inflammatory cells viability in BALF, changes in the number of TUNEL positive cells in lungs, increase in kaspase-3 and annexin V, changes in Bak, Bax and Bad pro-apoptotic proteins in lung homogenate), in animals treated with roflumilast and tadalafil were observed, which were comparable or stronger than in animals treated with dexamethasone or salbutamol.

Conclusions: Our results suggest beneficial effects of selective PDE4 and PDE5 inhibitors in this model of allergic inflammation with significant influence on apoptosis.

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