International Conference "ADVANCES IN PNEUMOLOGY"
Poznań, 6 – 7 June, 2008

INFLUENCE OF SELECTIVE INHIBITORS OF PHOSPHODIESTERASE-3 AND PHOSPHODIESTERASE-4 ON COUGH AND AIRWAY REACTIVITY

J. Mokry[1], D. Mokra[2], G. Nosalova[1], M. Beharkova[1], and Z. Feherova[1]

[1]Department of Pharmacology, [2]Department of Physiology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia; mokry@jfmed.uniba.sk

Introduction: Nowadays, there are several groups of drugs used in the therapy of cough. As their administration is often associated with occurrence of adverse effects, new alternatives and pharmacological targets are evaluated in experimental and clinical conditions. One of the ways is suppression of inflammation in patients with airway diseases associated with cough and airway hyperresponsiveness. In this, selective inhibition of special isoforms of phosphodiesterase (PDE) could be of benefit. The aim of this study was to assess the influence of selective inhibitors of PDE3 and PDE4 on cough and airway reactivity. **Methods:** Cough and airway reactivity were evaluated in non-anaesthetized guinea pigs in double-chamber whole body plethysmograph. The cough was evoked by inhalation of citric acid aerosol (AC; 0.6 mol/l) and trained observer visually counted and recorded number of coughs during AC nebulization (2 min) as well as after finishing the nebulization (2 min). As a marker of i*n vivo* airway reactivity specific airway resistance was measured after 2 min lasting nebulization of AC and histamine aerosol (10^{-6} mol/l). *In vitro* airway reactivity was measured in organ chambers. Tissue strips from trachea and lungs were exposed to cumulative doses of histamine and acetylcholine (10^{-8}-10^{-3} mol/l) and contractile responses were recorded. In blood, count and differential count of white blood cells were evaluated. All parameters were measured in healthy as well as in ovalbumin-sensitized guinea pigs before and after intra-peritoneal administration of cilostazol (selective PDE3 inhibitor) or citalopram (selective PDE4 inhibitor) at a dose of 1 mg/ kg. **Results:** Sensitization of guinea pigs with ovalbumin significantly increased number of cough efforts as well as specific airway resistance. *In vitro* studies confirmed significantly increased tracheal and lung tissue reactivity to histamine and acetylcholine. Pre-treatment with cilostazol decreased number of cough efforts only in healthy guinea pigs, whereas citalopram significantly suppressed cough in both healthy and ovalbumin-sensitized animals. Both selective PDE inhibitors decreased *in vivo* and *in vitro* airway reactivity, with more significant decrease observed after cilostazol in sensitized animals and after citalopram in healthy animals. Sensitization with ovalbumin led to significant increase of white blood cells count in blood, with predominant increase in percentual representation of neutrophils, monocytes and eosinophils. Both cilostazol and citalopram decreased the count of monocytes and neutrophils, confirming their anti-inflammatory potential. **Conclusions:** Administration of selective PDE inhibitors (PDE3 and PDE4) may participate in influencing the cough and airway reactivity in the model of ovalbumin-sensitized guinea pigs. However, their therapeutic potential as antitussive and anti-inflammatory drugs needs to be more corroborated. Nevertheless, advantageous could be simultaneous inhibition of PDE3 and PDE4, as both of them are involved in the pathomechanisms of inflammatory airway disease associated with airway hyperresponsiveness and cough.

Supported by Grants VEGA No. 1/0072/08, No. 1/3375/06, Grant of Ministry of Health No. 2005/13-MFN-05, and Grant ESF SOP LZ 2005/NP1-027 - 11230100433.