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RAPID CORTICOSTEROID EFFECT ON LONG-ACTING β_2-AGONIST DISPOSAL BY SMOOTH MUSCLE CELLS IN THE AIRWAY: A NEW PARADIGM OF INHALED COMBINATION THERAPY

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WINNING ABSTRACT: Organic cation transporters (OCTs) have an important role in tissue distribution and elimination of cationic drugs. To assess airway disposal of cationic bronchodilators, human airway cells and tissues obtained from organ donors were evaluated for drug transporter expression by quantitative RT-PCR and immunofluorescence. For *in vitro* functional studies, [^{3}H]-formoterol (FORM) and [^{3}H]-salmeterol (SALM) uptake by bronchial and vascular smooth muscle cells (SMC) was measured. RT-PCR analysis indicated high mRNA levels for the corticosteroid-sensitive OCT3 in bronchial and vascular SMC. Immunofluorescence staining of airway sections confirmed OCT3 expression in these cells. In bronchial SMC, uptake of the cationic FORM was inhibited with OCT inhibitors. Corticosteroids also inhibited FORM uptake through a rapid (within 15 min) nongenomic action, with the following rank order for inhibitory potency: corticosterone >budesonide >fluticasone (IC_{50}: 0.48±0.09, 1.88±0.24, 4.48±0.31 μmol·l^{-1}, respectively). The corticosteroid-induced inhibition was significantly higher in vascular than bronchial SMC (40.5±1.3% vs. 27.4±3.1%, respectively; $p<0.05$). In comparison to FORM, uptake of the noncharged lipophilic SALM was about 10-fold higher (28.4±1.7 vs. 327.5±13.7 pmol·mg^{-1} protein/15 min; $p<0.05$), and insensitive to all OCT inhibitors and corticosteroids. Our findings suggest that corticosteroids, through OCT3 inhibition, rapidly interfere with the disposal of cationic bronchodilators in the airway. This novel immediate interaction supports the use of such combinations in the pharmacotherapy of asthma.

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MY JOB AND THE UNIT IN WHICH I WORK

I work in the pulmonology dept at the Semmelweis University School of Medicine, Budapest, Hungary. Our university hospitals have 2,300 beds and admit ~112,000 patients annually. The outpatient depts care for ~2.1 million patients each year. Our university has more than 230-yrs tradition of academic excellence and commitment to the education of physicians. In fact, we were the first Hungarian university to offer international courses at the Medical School in German and English ~20 yrs ago. Research programmes at the pre-clinical and clinical depts are sponsored by the university, the Ministry of Education, the Hungarian Academy of Sciences, and by many national and international grants. Currently, I hold a faculty position at the rank of Associate Professor at the Dept of Pulmonology. Our dept combines state-of-the-art clinical care with training and research programmes in pulmonary medicine, critical care and sleep disorders, and biomedical research to serve patients with respiratory and critical illnesses. Although we have experience in managing the entire spectrum of lung disease and critical care, we have special interests in asthma and chronic obstructive pulmonary disease (COPD), lung cancer, tuberculosis, pulmonary hypertension and the study and treatment of sleep disorders.

MY WINNING POSTER AS PART OF MY RESEARCH

My research activities include national and international collaborations. Having completed my training in pulmonary medicine at Semmelweis University in 1999, I received an award from the Hungarian Respiratory Society to join the asthma research programme at the Division of Pulmonary and Critical Care at the University of Miami School of Medicine, Miami, USA. In order to develop an academic research career with special emphasis on airway biology, I was assigned to the Cell And Molecular Biology Research Laboratory. Funding for my research was granted by a number of national and international awards and fellowships. In 2001, in addition to

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research funding, I was named as an Outstanding Fellow of the American Heart Association Florida/Puerto Rico Affiliate. In 2005, I was awarded the 3-yr Bolyai Fellowship of Hungarian Academy of Sciences. At present, I split my time between the pulmonary dept in Hungary and the Airway Biology Research Laboratory at the University of Miami.

My research interest focuses on the airway actions of inhaled corticosteroids, which are the most effective drugs to suppress airway inflammation in asthma. In addition to their transcriptional effects, recent studies add a new dimension to corticosteroid pharmacology by demonstrating actions that manifest within seconds or minutes [1]. The potential targets for these rapid actions include the airway epithelium, the bronchial musculature, and blood vessels supplying the airway wall; however, the underlying molecular mechanisms remain to be fully elucidated. My studies try to identify specific cellular drug transport mechanisms, *i.e.* organic cation transporters [2], as possible targets for nongenomic corticosteroid actions [3]. By inhibiting the elimination of organic cations in the airway tissue, inhaled corticosteroids may rapidly influence the actions of a large array of molecules of physiological (*e.g.* acetylcholine, noradrenaline) and pharmacological (*e.g.* β_2-adrenergic agonists, anticholinergics) importance. My research provides insights into the mechanisms by which inhaled corticosteroids could rapidly regulate airway functions, such as the tracheobronchial blood flow, and reveal an immediate interplay of corticosteroids and β_2-agonists for which previously only genomic interactions had been shown [4].

MY RESEARCH AS PART OF MY WORKING GROUP/ RESEARCH TEAM

In Hungary, my initial research studies on the pharmacotherapy of obstructive airway diseases were mentored by Professor Endre Vastag, who is an internationally recognised expert of mucociliary clearance and COPD. After joining the research programme at the University of Miami, I had the opportunity to collaborate with many faculty clinicians, clinician-scientists and basic scientists: Professor Adam Wanner (in tracheobronchial circulation and asthma pathogenesis), Prof. Matthias Salathe (in airway ciliary beating and mucus secretion regulation), and Dr Gregory Conner (in airway cell biology and mucus secretion of normal and diseased airways). The goal of our current active collaboration is to identify the role of airway pH abnormalities in the pathomechanism and the pharmacotherapy of inflammatory airway diseases, such as bronchial asthma. We are also investigating the cellular mechanisms of corticosteroid and β_2-agonist interactions. In addition to studies with model systems (*i.e.* air–liquid interface cultures of airway epithelial cells for drug transport measurements), Professor Wanner directs *in vivo* experiments in healthy and asthmatic subjects to explore the clinical relevance of our findings.

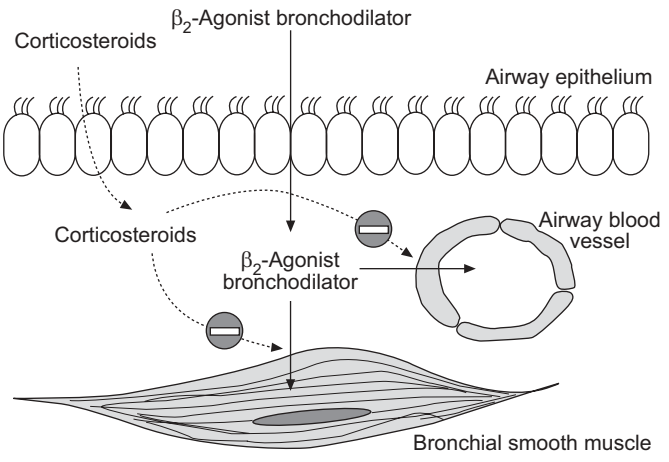

FIGURE 1. Schematic diagram showing rapid corticosteroid action on the disposal of cationic/hydrophilic β_2-agonist bronchodilator (*i.e.* formoterol) disposal in the airway.

THE IMPACT OF MY WORK ON CLINICAL OR RESEARCH PRACTICE

Inhaled corticosteroids, in addition to suppressing asthma-associated airway inflammation, have been suggested to improve β_2-adrenergic bronchodilation. In a series of *in vitro* experiments, we report a novel immediate form of interaction of corticosteroids and β_2-agonists to further explore the beneficial effects of combined inhalation therapy. We suggest that increased airway tissue retention of inhaled bronchodilators due to the corticosteroid-sensitive drug disposal mechanism could acutely improve responses to cationic β_2-agonist bronchodilators (*i.e.* formoterol), but not to lipophilic ones (*i.e.* salmeterol; fig. 1). The study demonstrates an immediate interplay of corticosteroids and β_2-agonists, for which only genomic interactions were previously shown. Nevertheless, whether inhaled corticosteroids potentiate β_2-adrenergic responses by inhibiting airway drug disposal mechanisms remains to be explored *in vivo*.

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