Supported by grants from the Cloëtta Research Foundation to A.O. and the Swiss National Science Foundation No 31-59511.99 to A.O. and No 31-61505.00 to F.J.F..

PULMONARY PHARMACOLOGY (653.1-653.10)

653.1

Computer simulations of asthma

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The incidence of asthma is increasing throughout the world, especially among children, to the extent that it has become a medical issue of serious global concern. Appropriately, numerous pharmacologic drugs and clinical protocols for the treatment and prophylaxis of the disease have been reported. From a scientific perspective, a review of the literature suggests that the targeted delivery of an aerosol would, in a real sense, enhance the efficacy of an inhaled medicine. Therefore, in accordance with published data we have developed a mathematical description of disease-induced effects of disease on airway morphology. A morphological algorithm defining the heterogeneity of asthma has been integrated with a computer code that formulates the behavior and fate of inhaled drugs. In this work, predicted drug particle deposition patterns have been compared with SPECT images from experiments with healthy human subjects (controls) and asthmatic patients. The asthma drug delivery model simulations agree with observations from human testing. The results indicate that mathematical modeling provides a technical foundation for addressing effects of disease on the administration of aerosolized drugs, and suggest that modeling should be used in a complementary manner with future inhalation therapy protocols.

[Disclaimer: This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.]

653.2

Mechanical and bioelectic responses of guinea-pig airways to mucosal hyperosmolar (HO) and isosmolar (IO) solutions

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Asthmatics experience obstruction during exercise, due to an increase in the osmolarity of the airway surface liquid, and after inhalation of HO aerosols. The mechanism of the response to changes in osmolarity was examined by comparing the effects of mucosal HO (osmolyte added to Krebs solution) and IO (osmolyte added to water) solutions on mechanical responses of serosal methacholine ($3x10^{-7}$ M)-contracted perfused trachea (PT) and short circuit current (Isc) responses of the epithelium. HO D-mannitol (D-M), NMDG-gluconate (N-G), urea (U), NaCl or KCl caused relaxation of the PT. Perfusion with IO solutions of these osmolytes caused variable responses (contraction, contraction/relaxation, no response, or, rarely, relaxation), but subsequent HO addition of the same osmolyte to the IO perfusate always triggered relaxation. HO D-M, N-G and U decreased Isc, whereas HO NaCl and KCl increased Isc. IO solutions of the three ionic osmolytes, N-G, NaCl and KCl, decreased Isc, but subsequent HO addition of these osmolytes stimulated Isc responses similar to those obtained after adding them to Krebs solution. Thus, the mechanical responses to HO or IO osmolyte solutions were independent of the ionic nature or permeance of the solute. Relaxation was associated with an increase in osmolarity. The bioelectric effects of IO solutions of osmolytes were similar, but those of HO solutions were agent-specific. Funding: NIOSH

653.3

Losartan Reduces Norepinephrine and Thromboxane A2-Induced Pulmonary Vascular Responses in the Rat

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Angiotensin II (Ang II) type 1 (AT1) receptor antagonists such as losartan (LOS) are used in the treatment of hypertension and heart failure and are reported to interact with thromboxane (TXA2) receptor. The present study compares the effects of LOS on responses to the TXA2 mimic U46619, Ang II, and norepinephrine (NE), in the rat pulmonary vascular bed. Cardiac output was measured by the thermodilution technique and pulmonary arterial and wedge pressures were measured. Intravenous (iv) injections of Ang II, U46619, and NE caused dose-related increases in PAP. Administration of LOS in a dose of 10 mg/kg iv decreased responses to U46619 and NE and abolished responses to Ang II. At the dose 10 mg/kg, LOS inhibited U46619-induced platelet aggregation in rat platelet rich plasma. However, LOS in a dose of 1 mg/kg iv, reduced responses to NE, markedly attenuated responses to Ang II, but did not alter responses to U46619. Daltroban, a TXA2 antagonist, reduced responses to U46619 without altering responses to Ang II and NE. The alpha-receptor antagonist, phentolamine, reduced responses to NE without altering responses to U46619 and Ang II. These results show that LOS at high doses antagonizes TXA2 and NE responses, suggesting that depending on dose, LOS can interact with TXA2, AT1, and alpha receptors with the highest affinity for AT1 receptors and the lowest affinity for TXA2 receptors in the rat pulmonary vascular bed.

653.4

Hyperosmolar (HO) solution-induced bioelectric and mechanical responses of guinea-pig isolated, perfused trachea (IPT): effects of MAPK inhibitors

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Exercise causes evaporative water loss in airway surface liquid and airway obstruction in asthmatics. Mucosal application of HO solution to the IPT elicits transepithelial potential difference (Vt) changes preceding epithelium-dependent smooth muscle relaxation mediated by epithelium-derived relaxing factor (EpDRF). We examined the relationship between mucosal HO D-mannitol(D-M)-induced Vt and mechanical responses (changes in inlet - outlet pressure difference; ΔP) in IPT and examined the possible role of MAPK signaling with mucosally-applied P38, JNK and ERK inhibitors. HO D-M solutions (D-M added to Krebs perfusion solution, 2.7-266.8 mosM) hyperpolarized Vt below 80 mosM, but depolarized Vt at higher concentrations. Maximum relaxation occurred at ~80 mosM, and there was coincidence in the Vt and relaxation dose-response curves to that point. The JNK inhibitor II, SP 600125 (30 μM), inhibited Vt responses to HO D-M but had no effect on relaxation responses to 30 mosM D-M. The ERK inhibitor, PD 98059 (50 μM), had no effect on D-M-induced Vt and relaxation responses. The P38 inhibitor, SKF 86002 (30 μM), had no effect on Vt responses but potentiated HO D-M-induced relaxation. The results indicate that the P38 pathway may be uniquely involved in regulating mechanical responses of the airways to mucosal HO challenge. Funding: NIOSH.

653.5

Effects of Cigarette Smoking on Nuclear Retinoic Acid Receptors in Guinea Pig Lung

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We have recently reported that mainstream and sidestream cigarette smoke exposure increases the retinol content in the lung of guinea pigs. Furthermore, the elevation of retinol was associated with elevated proliferation of alveolar type II cells. The molecular mechanism(s) leading to the elevation of retinol is not known and warrants exploration.

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Experimental Biology 2003®
San Diego, California
April 11–15, 2003

ABSTRACTS
PART II

Abstracts A456.1–A886.2

Official Publication of the Federation of American Societies for Experimental Biology
Volume 17, Number 5, March 17, 2003