P16.2.13
INFLUENZA A VIRUS ATTENUATES ET$_B$, BUT NOT ET$_A$, RECEPTOR-MEDIATED CONTRACTIONS TO ENDOTHELIN-1 IN MOUSE AIRWAYS.

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Respiratory tract viral infections are associated with airway epithelial cell damage and increased airway reactivity in both asthmatic and otherwise healthy individuals. Endothelin-1 (ET-1) is released from airway epithelial cells, is a potent airway smooth muscle spasmogen and may contribute to the pathophysiology of asthma. In the current study, the influence of respiratory tract viral infection on the density, distribution and contractile function of ET$_A$ and ET$_B$ receptors, which mediate the spasmogenic actions of ET-1, was investigated in murine airways. Male CBA/CaH mice (4 weeks) were anaesthetized (pentobarbitone, 50mg/kg, ip) and inoculated intranasally with 2000 egg infectious doses of influenza A/PR-8/34 virus (V mice) or 25µl sterile saline (control, C mice). All studies of tracheal smooth muscle (TSM) were performed two days post-inoculation. Quantitative autoradiographic studies using ^{125}I-ET-1 and selective ligands for ET$_A$ receptors (BQ123) and ET$_B$ receptors (sarafotoxinS6c, STX) revealed that TSM from C mice contained a mixture of ET$_A$ and ET$_B$ receptors in the ratio of 40 : 60 (±3, n=10). TSM from V mice contained fewer ET receptors (77 ± 2 % of C mice, n=10) due to a marked reduction in the density of ET$_B$ receptors (ratio of ET$_A$: ET$_B$ receptors in V mice; 56 : 21 ± 2). This is consistent with the findings that TSM from V mice was hyporesponsive to the ET$_B$ receptor-selective spasmogen STX (contraction induced by 100nM STX was 37 ± 5 %Cmax in V mice versus 85 ± 4 %Cmax in C mice; n=16, $P<0.05$; 100%Cmax = contraction induced by 10µM carbachol). ET$_A$ receptor-mediated contractions were similar in TSM of C and V mice. In summary, respiratory tract viral infection was associated with a marked reduction in the density and function of ET$_B$, but not ET$_A$ receptors in murine TSM.
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P16.2.14
ANAPHYLACTIC SHOCK AND CALCITONIN GENE-RELATED PEPTIDE-LIKE IMMUNOREACTIVITY (CGRP-Li) LEVELS IN PULMONARY TISSUES

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Evidence is accumulating that neuropeptides do participate as mediators or modulators in hyperreactive airway disorders. Recently we have shown that Calcitonin gene-related peptide (CGRP), localized in sensory nerves, makes the airways less sensitive to the action of various bronchoconstrictor agents including 5-HT, acetylcholine (ACh) and substance P (SP). However, in airways from sensitized guinea-pigs, this antibronchoconstrictor effect of CGRP is reduced by 60 to 80%. In the present study, we have tested for elevated or decreased levels of CGRP-Li in pulmonary tissues (trachea, bronchus, parenchyma) and plasma from untreated and ovalbumin (OA)-sensitized guinea-pigs before and after an OA challenge using a specific radioimmunoassay (RIA) technique. Sensitization was performed by injecting 100 mg i.p. and 100 mg s.c. on day 1 and a further 10 mg i.p. on day 8; animals were used two weeks later (days 21-22). Our results showed that the sensitization procedure did not alter the levels of CGRP-Li in pulmonary tissues and plasma of OA-sensitized guinea-pigs when compared to controls. However when sensitized guinea-pigs were challenged with a low dose of OA (1 mg i.p.) which caused only a minor anaphylactic reaction, a 2 fold increase in CGRP-Li levels in pulmonary tissues (e.g.:parenchyma, from 0.6 ± .05 to 1.2 ± 0.1 pmol/g) was observed one hour following the injection of OA. The levels of CGRP-Li slowly returned to baseline values within 3 to 4 hours. Significant changes in plasma CGRP-Li concentrations were also observed in challenged animals. These results indicate that tissues and plasma CGRP-Li levels are significantly altered during anaphylactic reaction which suggest an involvement of CGRP in hyperreactive airway disorders. (Supported by "l'Association Pulmonaire du Québec")

P16.2.15
A DOSE RESPONSE STUDY OF DISKHALER SALBUTAMOL TREATMENT IN ASTHMATIC PATIENTS

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In a balanced and randomized cross-over study, peak expiratory flow rate (PEFR) responses to inhaled salbutamol (400 µg, 200 µg and placebo by diskhaler and 200 µg by metered dose inhaler were assessed in asthmatic out-patients. The 12 patients, [20-60 years old, 8F/4M) were not on oral steroids, and abstained from β-agonist inhalation for 6h prior to each assessment. PEFR was measured pre and 10-15 minutes post inhalation. All patients gave informed consent and the study was approved by our Ethics Committee. Mean ±SD of first visit pre-treatment PEFR and percentage of predicted values were 337 ±87 (l/min) and 79% ±17%. There was no clinically or statistically significant difference in PEFR increments after the active treatments; respective mean (±SD) values being 44 (±44), 48 (±39), and 37 (±39) (Pairwise Mann-Whitney & t tests). Due to concerns about the safety of β-agonist inhalations, use of 400 rather than 200 µg doses of salbutamol via diskhaler needs reassessment.

P16.2.16
EFFECT OF NEUROPEPTIDE Y ON THE RELEASE OF CYCLO-OXYGENASE PRODUCTS INDUCED BY BRADYKININ FROM UNTREATED AND OVALBUMIN-SENSITIZED GUINEA-PIG PERFUSED LUNG.

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Recently, we have shown that Neuropeptide Y (NPY), localized in sympathetic nerves, inhibits response induced by several agonists (VIP, SP, 5-HT and NA) in isolated guinea pig trachea. When postjunctionally-mediated, this effect of NPY was found to be expressed especially with agents that generate prostaglandins concomitantly with inducing their response. However, this inhibitory action of NPY was lost when measured in airways from ovalbumin-sensitized guinea pigs (OA). The aim of the present study was to examine whether NPY was capable of regulating the release of cyclo-oxygenase products detected by radioimmunoassay, induced by inflammatory mediators from untreated and OA guinea pig perfused lung. Our results showed that infusion of NPY (2.4×10^{-9}M) through the lung inhibited the release of 6-Keto-PGF$_{1\alpha}$ (69.5%) and TxB$_2$ (30%) induced by intra arterial administration of BK (3µg) from untreated guinea pig perfused lung. However, in OA guinea pig, NPY did not affect the release of TxB$_2$ but slightly enhances the release of 6-Keto-PGF$_{1\alpha}$ induced by BK. Furthermore NPY inhibits the release of 6-Keto-PGF$_{1\alpha}$ (66.8%) and TxB$_2$ (40.6%) induced by intra arterial administration of ovalbumin (1µg). These results suggest that NPY may act as a regulatory agent of the release of cyclo-oxygenase products.
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P16.2.17
MUSCARINIC RECEPTOR ACTIVATION BY PENTAMIDINE ON AIRWAY SMOOTH MUSCLE.

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Pentamidine (P) is routinely used to reduce the incidence of pneumocystis carinii pneumonia in patients infected with human immunodeficiency virus, but has been described to induce pulmonary adverse effects such as cough. We have investigated the effects of P on the guinea-pig isolated main bronchus (GPB) and on the human isolated bronchus (HB).
Pentamidine induces a contraction in both preparation with pD_2 values of 9.6 ± 0.2 (n=8) and 9.7 ± 0.3 (n=8) in GPB and HB respectively. Maximal effects was however considerably lower than acetylcholine (37 ± 3% and 39 ± 4 % of maximal effect of acetylcholine). P-induced contractions were not modified by epithelium removal or hexamethonium. They were inhibited or abolished by atropine (10^{-9} to 10^{-7} M), or by very high concentrations of pirenzepine (10^{-6} to 10^{-5} M), or AFDX 116 (10^{-5} M).
Finally the effects of P on the GPB were modified neither by mepyramine or by indomethacin, nor by SR 48968, CP 96345, capsaicin, ruthenium red, phosphoramidon or sodium cromoglycate suggesting that histamine receptor stimulation, arachidonic acid derivative formation or tachykinin release are not involved in the effects of P.
In additional experiments, we have shown that P does not induce a beadycardia on the guinea-pig isolated atria. It can be concluded that the P-induced contraction involves M3 muscarinic receptor stimulation.

P16.2.18
TA 2005, A NEW LONG ACTING β-ADRENOCEPTOR AGONIST.

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TA 2005 is a new long acting β_2-adrenoceptor agonist (Voss, 1992). The potency of this compound is higher than the agonists currently on the market. The pD_2-value for metbaterline (3×10^{-6} M) precontracted guinea pig tracheal smooth muscle relaxation was 9.29 ± 0.11. The compound is a full agonist on the β_2- but a partial agonist on the β_1-adrenoceptor. The β_1/β_2-selectivity ratio was measured on different guinea pig heart tissues vs. trachea and was found to be 250. On guinea pig right atrial chronotropism a biphasic response was observed for TA 2005. Due to the high selectivity and potency a very clear β_2-adrenoceptor mediated response was demonstrated (pD_2 value of 8.54 ± 0.51) besides the β_1-response. Effects of TA 2005 on the heart were also measured in vivo in the Beagle dog. Inhalation of TA 2005 gives a rise in the heart rate. The aspecific β-adrenoceptor antagonist propranolol and the β_2-selective ICI 118.551 were both able to completely inhibit the response of TA 2005. Also atenolol, a β_1-selective antagonist could inhibit the TA 2005 response, although not completely. From these results it is hypothesized that β_2-adrenoceptors facilitate a β_1-response, possibly via presynaptic β_2-adrenoceptors on sympathic neurons in the dog heart.

H-P. Voss, D. Donnell and A. Bast. *Atypical molecular pharmacology of a new long acting β_2-adrenoceptor agonist, TA 2005.* Eur J. Pharmacol. - Molec. Pharmacol. Section 227, 403-409, 1992