European Respiratory Society
Annual Congress 2013

Abstract Number: 2501

Publication Number: P557

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Airway smooth muscle **Keyword 2:** Pharmacology **Keyword 3:** Asthma - mechanism

Title: The effect of adenosine on VEGF release from airway smooth muscle from subjects with asthma

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Body: Introduction Airway smooth muscle cells (ASM) from subjects with mild asthma secrete increased levels of VEGF and increased expression of adenosine A1 receptor in bronchial biopsies compared to healthy subjects. We hypothesised that VEGF release from ASM in asthma is mediated via adenosine A1 receptors. Objectives To examine the effect of adenosine on VEGF release in ASM derived from asthmatic subjects. Methods ASM from healthy (n=4) and mild asthmatic (n=3) subjects were treated with and without adenosine receptor agonists (0.01-100μM) targeting A1 (CPA), A2 (CV1808), A2a (CGS21680), A3 (IB-MECA) or non-selective (adenosine, NECA). ASM were also treated with 10μM NECA following pre-treatment with adenosine receptor antagonists (1-100nM). After 24hr, VEGF levels in cell-conditioned media were determined by ELISA. Results Constitutive levels of VEGF in ASM derived from asthmatics (275±34pg/ml/10^6 cells) were 1.7 fold greater than ASM derived from healthy subjects (159±34pg/ml/10^6 cells, $p<0.05$). Activation of each adenosine receptor subtype did not significantly alter basal VEGF release from ASM derived from healthy subjects. However, NECA and CGS21680 concentration dependently increased VEGF release by 1.8- and 2-fold respectively in ASM derived from mild asthmatics compared to unstimulated controls ($p<0.05$). Pre-treatment of ASM with adenosine receptor antagonists (1-100nM) followed by 10μM NECA revealed that the A2a and A2b receptor antagonist ZM241385 and PSB0788 respectively, both significantly inhibited NECA-induced VEGF release ($P<0.05$). Conclusions VEGF release induced by adenosine receptor activation in ASM derived from mild asthmatic subjects was mediated through A2a and A2b receptors.