European Respiratory Society
Annual Congress 2012

Abstract Number: 957

Publication Number: 2803

Abstract Group: 5.1. Airway Pharmacology and Treatment

Keyword 1: Animal models **Keyword 2:** Asthma - mechanism **Keyword 3:** Pharmacology

Title: Late asthmatic response is modulated by TRPA1 antagonists in ovalbumin-induced bronchoconstriction in anaesthetized guinea pigs

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Body: In animal models of asthma, ovalbumin (OVA) aerosol results in bronchoconstriction characterized by a histamine-related early asthmatic response (EAR) followed by a neuropeptide-related late asthmatic response (LAR) which can be modulated by transient receptor potential (TRP) channel A1 antagonists (Thorax. 2012, 67, 19-25). The aim of the study was to assess the potential of two TRPA1 antagonists on the EAR and LAR in OVA-induced bronchoconstriction in anaesthetized guinea pigs. Bronchoconstriction was induced by intra-tracheal administration of a single dose of OVA (50 µg/kg) and lung resistance recorded for 30 minutes. The animals were pre-treated with pyrilamine (2 mg/kg i.v.) or its vehicle (saline) 10 min before OVA. The TRPA1 antagonists HC-030031 and A-967079 or their vehicle (0.5 % methylcellulose) were administered i.p. 1 h before OVA. Without pyrilamine pre-treatment, OVA induced a fast increase in lung resistance (max. 60 ± 13 ml overflow after 1 min) which was not reduced by the TRPA1 antagonists. Under pyrilamine pre-treatment, OVA induced a slow increase in lung resistance (max. 33 ± 10 ml overflow at the end of the recording). HC-030031 (1 µg/kg – 1 mg/kg) dose-dependently inhibited the non-histamine-related OVA- induced bronchoconstriction (ED_{50} = 0.01 mg/kg) with a maximum bronchoprotection of 76 % at 0.03 mg/kg ($p<0.05$). A-967079 (1 µg/kg – 1 mg/kg) displayed the same profile as HC-030031 (ED_{50} = 0.01 mg/kg) with a maximum bronchoprotection of 78 % at 0.03 mg/kg ($p<0.05$). This study shows that the EAR is histamine related, while the LAR is modulated by the TRPA1 channel in OVA-induced bronchoconstriction in anaesthetized guinea pigs.