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Challenge with hyperosmolar mannitol induces mast cell activation in isolated human small airways: a model of exercise-induced bronchoconstriction

BACKGROUND: Exercise-induced bronchoconstriction (EIB) is believed to occur by loss of water from the airway lining fluid causing a local increase of osmolarity that triggers mast cell activation. This can be mimicked in patients by inhalation of mannitol. The mechanism involved, however, remains unclear.

AIM: Our aim was to develop a model using isolated human bronchi in order to study the effect of hyperosmolar bronchoconstriction.

METHODS: Small bronchi (inner diameter of 0.5-2 mm) were isolated from macroscopically healthy human lung tissue specimens obtained from patients undergoing surgery (n=23). The segment were incubated overnight and mounted in a tissue organ bath to measure smooth muscle contractions evoked by challenge with hyperosmolar mannitol in relation to contractions generated by 60 mMof potassium chloride.

RESULTS: A protocol was developed to investigate hyperosmolar mannitol-induced bronchoconstriction (E_{max}: 43.0± 3.2%). The constriction could be completely prevented using a combination of receptor antagonists blocking the TP, H_1 and $CysLT_1$ receptors (SQ-29,548, mepyramine and montelukast, respectively; $p<0.05$), or by pretreatment with the mast cell stabilizer cromolyn (100 µM). In contrast, global inhibition of the cyclooxygenase enzymes using indomethacin enhanced the bronchoconstriction (E_{max}: 65.6 ± 5.6%; $p<0.05$). Likewise, treatment with either EP_2 (PF-04418948) or EP_4 (ONO-AE3-208) receptor antagonists also enhanced the mannitol-induced bronchoconstriction (E_{max}: 67.4 ± 5.2 and 66.0 ± 4.0, respectively; $p<0.05$).

CONCLUSION: When isolated human bronchiare exposed to mannitol a bronchoconstriction occurs that is mediated by release of typical mast cell mediators. The increased effect during cyclooxygenase inhibition suggests a production of prostanoids that counteracts the mannitol-induced broncho constriction. These prostanoids acts on both EP_2 and EP_4 receptors possibly inducing both mast cell inhibition and bronchorelaxation, as observed previously for exogenous PGE_2 (1). This first *ex vivo* protocol of hyperosmolar mast cell activation in isolated human bronchi can be used for further mechanistic studies of EIB.

1. Säfholm J. et al. (2015) J Allergy ClinImmunol. doi: 10.1016/j.jaci.2015.04.002