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

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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 mM of 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, H₁ and CysLT₁ 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 bronchi are 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 bronchoconstriction. These prostanoids acts on both $EP_2$ and $EP_4$ receptors possibly inducing both mast cell inhibition and bronchorelaxation, as observed previously for exogenous PGE₂ (1). This first ex vivo protocol of hyperosmolar mast cell activation in isolated human bronchi can be used for further mechanistic studies of EIB.
