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Title: Activation of TRPV4 causes bronchoconstriction: A possible role in respiratory disease?

Ms. Sara J. 8109 Bonvini sara.bonvini10@imperial.ac.uk [1], Dr. John J. 8110 Adcock j.adcock@imperial.ac.uk [1], Dr. Megan S. 8624 Grace m.grace@imperial.ac.uk [1], Ms. Katie E. 8625 Baker katie.baker10@imperial.ac.uk [1], Dr. Mark A. 8626 Birrell m.birrell@imperial.ac.uk [1] and Prof. Maria G. 8642 Belvisi m.belvisi@imperial.ac.uk [1]. [1] Respiratory Pharmacology, Imperial College, London, United Kingdom, SW72AZ .

Body: TRPV4 is a calcium permeable member of the Transient Receptor Potential family of ion channels. It is expressed in human airway smooth muscle cells where it is thought to play a role in sensing osmolarity and pH changes within the lung (Jia,Y.et al, AJPLCMP 2004,287:272-278). During studies exploring the role of TRPV4 in the activation of airway sensory nerves, we observed that the selective agonist caused a substantial, sustained bronchoconstriction in the guinea pig (GP). As osmolarity and pH are known to be altered in respiratory diseases and excessive bronchoconstriction is a cardinal feature of the diseases, we hypothesised that TRPV4 activation could play a central role. The aim of this study was to investigate the role of TRPV4 in contraction of the trachea and bronchi in the GP and also in donor human tissue. Using an anaesthetised GP preparation, the TRPV4 agonist, GSK1016790a, was found to cause a substantial, sustained contraction of GP trachea, and also caused a concentration dependant increase of PenH in the conscious GP model. In vitro, isolated tracheal tissue from GPs and bronchial and tracheal strips from human lungs were sutured to force-displacement transducers in 10ml organ baths. GSK1016790a caused marked, concentration dependant contraction of both GP and human tissue, which was inhibited by the selective TRPV4 antagonist, HC-067047. In summary, we have shown that activation of TRPV4 can cause bronchoconstriction in anaesthetised and conscious GPs. Furthermore, similar results were obtained using isolated human and GP airway smooth muscle. These results indicate that TRPV4 may play a central role in the bronchoconstriction observed in respiratory diseases such as asthma.