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Title: Black widow spider toxin, α-latrotoxin, contracts large and small airways in different species

Ms. Chantal 25688 Donovan c.donovan@student.unimelb.edu.au [1], Mr. Alen 25689 Faiz afai4257@uni.sydney.edu.au [2], Dr. Brian G. 25690 Oliver brian.oliver@sydney.edu.au [2], Prof. Judy L. 25691 Black judy.black@sydney.edu.au [2], Dr. Brent E. 25692 McParland brentmcparland@med.usyd.edu.au [3], Dr. Janette K. 25698 Burgess janette.burgess@sydney.edu.au [2,3] and Dr. Jane E. 25701 Bourke jane.bourke@unimelb.edu.au [1]. [1] Pharmacology, University of Melbourne, Parkville, VIC, Australia, 3010 ; [2] Cell Biology, Woolcock Institute of Medical Research, Glebe, NSW, Australia and [3] Discipline of Pharmacology, University of Sydney, Darlington, NSW, Australia .

Body: Introduction: Airway hyperresponsiveness (AHR) in asthma is characterised by airways contracting too easily and too much. We recently identified increased expression of latrophilin 1 (LPHN1) in human primary airway smooth muscle (ASM) cells from asthmatic donors that may influence contractile function. In this study we characterised the responses to the LPHN1 agonist, α-latrotoxin (α-LTX), toxin produced by the black widow spider, in various size airways from different species. Methods: Changes in force were measured in guinea pig trachea, mouse trachea and bronchi under isotonic conditions (n=8). Changes in small airway lumen diameter were visualized in mouse lung slices (150μm thick, n=2) using phase-contrast image analysis. Responses to α-LTX (10nM) were compared in the absence and presence of the muscarinic antagonist, atropine (3μM) and compared to the maximal airway contraction to acetylcholine (ACh 1mM). Results: α-LTX caused biphasic contractions in guinea pig trachea, characterised by a transient oscillating contraction and a secondary increase in tone (~65% of ACh max) that was also not sustained. Single atropine-sensitive contractions were observed for mouse trachea and bronchi, with oscillations evident in bronchi only. In small airways in mouse lung slices, α-LTX induced small oscillations without a significant change in airway lumen area. Conclusion: α-LTX elicited contraction in all airways tested, however the profile of contraction differed between species and airway size. Contractile responses can be attributed to ACh release from nerve terminals innervating ASM. It remains to be determined whether direct activation of LPHN1 on ASM contributes to AHR observed in asthma.