Relationship Between Airway Size and In-Vitro Sensitivity to Cholinomimetics

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Introduction/Aim: Small airways have increased airway sensitivity to acetylcholine (ACh), suggesting that airway size is a strong predictor of airway smooth muscle (ASM) responsiveness. However, ACh is actively degraded within the airway wall, which would occur to a lesser extent in small airways with reduced diffusion distance and may explain the increased sensitivity in those airways. Therefore, we investigated the relationship between airway size and sensitivity to both methacholine (MCh), which is partially degraded, and carbachol (CCh), which is resistant to degradation. Methods: Porcine airway segments with internal diameters (ID; 1.4 - 6.9mm) were obtained. Cumulative concentration curves were generated in response to MCh (n = 23) and CCh (n = 22) selectively applied to the outside surface of airway segments. Sensitivity was calculated as the negative log-concentration of MCh or CCh that caused a half maximal increase (pD_2) in luminal pressure. Airway internal diameter (ID) and adventitial wall thickness (AWT), reflecting airway size and diffusion distance, respectively, were measured from images of stained cross-sections. Results: The range of airway wall thickness, in the MCh group, was 1.50±0.65 – 3.8±0.3mm (n=22) and in the CCh group, was 1.30±0.07 – 2.72±0.24mm (n=23). Increased airway wall thickness correlated with increased airway internal diameter in both sets of airways (MCh; $r=0.78$, $p<0.001$ and CCh; $r=0.82$, $p<0.05$). Increased airway wall thickness correlated with increased sensitivity to MCh (pD_2) ($r=0.77$, $p<0.001$), however, there was no relationship between airway wall thickness and sensitivity to CCh (pD_2) ($r=0.01$, $p>0.6$). Conclusion: The present study illustrates that diffusion distance does not alter CCh sensitivity. In contrast diffusion distance does alter sensitivity to MCh, as has previously been shown with ACh. Therefore, diffusion distance is likely a major determinant of airway responsiveness through its effect on metabolite degradation.

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