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Basic / translational Science

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To understand the alterations in airway smooth muscle cell (ASMC) physiology that results in excessive airway contraction and airway hyperresponsiveness associated with asthma by using a precision cut lung slices preparation to characterize the mechanisms of Ca\(^{2+}\) signalling and Ca\(^{2+}\) sensitivity that control the contraction and relaxation of ASMC in airways.

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Jun Chen, PhD
Postdoctoral Research Associate
University of Mass. Medical School
More info on Jun’s research

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Calcium signaling and airway hyper-responsiveness

**Background:** Airway hyper-responsiveness in asthma is driven by excessive contraction of airway smooth muscle cells (ASMCs). Agonist-induced Ca$^{2+}$ oscillations underlie this contraction of ASMCs and the magnitude of this contraction is proportional to the Ca$^{2+}$ oscillation frequency. Sustained contraction and Ca$^{2+}$ oscillations require an influx of extracellular Ca$^{2+}$ but the mechanisms and pathway mediating this Ca$^{2+}$ influx during agonist-induced ASMC contraction are not well defined.

**Hypothesis:** Store-operated calcium entry (SOCE) is the major pathway for the Ca$^{2+}$ influx in agonist-induced airway contraction and Ca$^{2+}$ oscillations within ASMCs.

**Results:** SOCE inhibitors, GSK7975A and GSK5498A, were able to fully relax methacholine (MCh)-induced airway contraction (Figure 1) by abolishing the Ca$^{2+}$ oscillations, in a manner similar to that observed in zero extracellular Ca$^{2+}$ ([Ca$^{2+}$]$_e$). In addition, GSK7975A and GSK5498A inhibited increases in intracellular Ca$^{2+}$ ([Ca$^{2+}$]$_i$) in ASMCs with depleted Ca$^{2+}$-stores in response to increased [Ca$^{2+}$]$_e$, a response consistent with an inhibition of SOCE. By contrast, L-type voltage-gated Ca$^{2+}$ channel (VGCC) inhibitors, nifedipine and nimodipine, only partially reduced airway contraction, Ca$^{2+}$ oscillation frequency and SOCE-mediated Ca$^{2+}$ influx.

**Conclusion:** These data implicate that SOCE is the major Ca$^{2+}$ influx pathway for ASMCs to sustain agonist-induced airway contraction and the underlying Ca$^{2+}$ oscillations. The mechanisms of SOCE may therefore form novel targets for new bronchodilators.

*Figure 1. Methacholine-induced airway contraction is relaxed by calcium channel inhibitors*