Indomethacin (Indo) significantly reduced compound 48/80 induced contractions as induced contractions. (N=7 presented as a percentage of initial contraction to 60 mM muscle strips from C57BL/6 (mast cell sufficient) and Cγ Kit(w-sh) mice. Thus, we hypothesized that phasic contractions caused by the mast cell activator compound 48/80 were due to mast cell degranulation and the subsequent release of prostaglandin E2 from the urothelium.

METHODS

• All procedures followed institutional guidelines and were approved by the Institutional Animal Care and Use Committees of MSU.
• Isometric contractility was performed in urinary bladder strips, with or without the urothelium.

RESULTS

Figure 1. Isometric Contractility

Figure 2. Representative traces of compound 48/80 induced contractions. Isolated bladder smooth muscle strips (A) urothelium-denuded (B).

Figure 3. The effects of compound 48/80 on isolated urinary bladder smooth muscle strips urothelium-intact (A) urothelium-denuded (B). Compound 48/80 (10 µg/mL) significantly increases tone of urothelium and the subsequent release of histamine, prostaglandins, and other inflammatory mediators that can contribute to normal bladder function and lead to profound bladder pathologies.3

Figure 4. The effects of cyclooxygenase (COX) inhibition on compound 48/80-induced contractions. Representative trace of urothelium-intact urothelium-deficient (A). Indomethacin (Indo) significantly reduced compound 48/80-induced contractions as compared to vehicle (DIOH) (B). P<0.05, Student’s t-test (N=7-8).

Figure 5. The effects of the prostaglandin EP1 receptor antagonist on compound 48/80-induced contractions. SC 51099 (10 µM) had no effect on compound 48/80-induced contractions as compared to compound 48/80 alone (A,B). Results are presented as a percentage of initial contraction to 60 mM KCl. P>0.05, Student’s t-test (N=4-8).

Figure 6. The effects of the Gq/11 inhibitor on compound 48/80-induced contractions. YM-254890 (YM) significantly decreased tone as compared to compound 48/80 alone (A,B). Results are presented as a percentage of initial contraction to 60 mM KCl. P<0.05, Student’s t-test for tone (N=7-8).

Figure 7. The effects of purinergic P2 receptor antagonist on compound 48/80-induced contractions. PPADS significantly decreases tone as compared to compound 48/80 alone (A,B). Results are presented as a percentage of initial contraction to 60 mM KCl. P<0.05, Student’s t-test (N=7-8).

SUMMARY & FUTURE DIRECTIONS

• Urothelium-derived prostanoids cause compound 48/80-induced urinary bladder smooth muscle contractions that are of independent of mast cells.
• Compound 48/80-induced contractions are not mediated by EP1 receptors; however, GPCR signaling is involved.
• Future studies will determine which prostanoids are released from the urothelium and identify the pathway responsible for mediating the effects of Compound 48/80 in the urinary bladder.

REFERENCES


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