The Basic Secretagogue Compound 48/80 causes Urothelium Dependent Phasic Urinary Bladder Smooth Muscle Contractions Independent of Mast Cell Activation

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Introduction

- **Mast cell degranulation** and the **release of histamine** contribute to symptoms associated with **painful bladder syndrome**, **urinary tract infections**, **interstitial cystitis** and other **bladder diseases**.[1,2]
- Little is known about the role of **mast cells** and **mediators released from mast cells** that can **alter urinary bladder contractility.**
- **Phasic contractions** in the presence of **inflammatory mediators** are viewed as **initial disruptors** of normal bladder function and can lead to profound **bladder pathologies**.[3]
- 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.

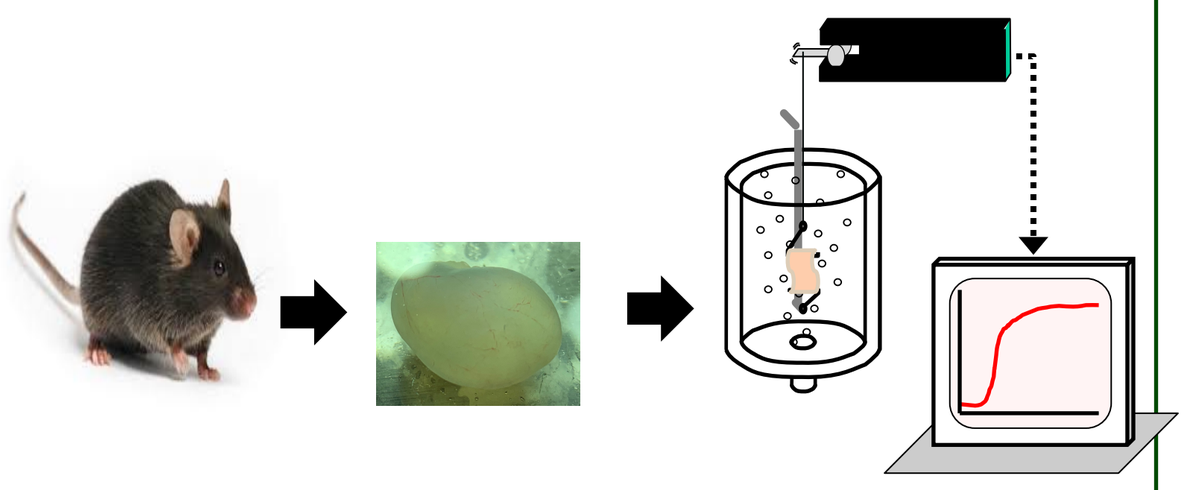

Figure 1. Isometric Contractility

RESULTS

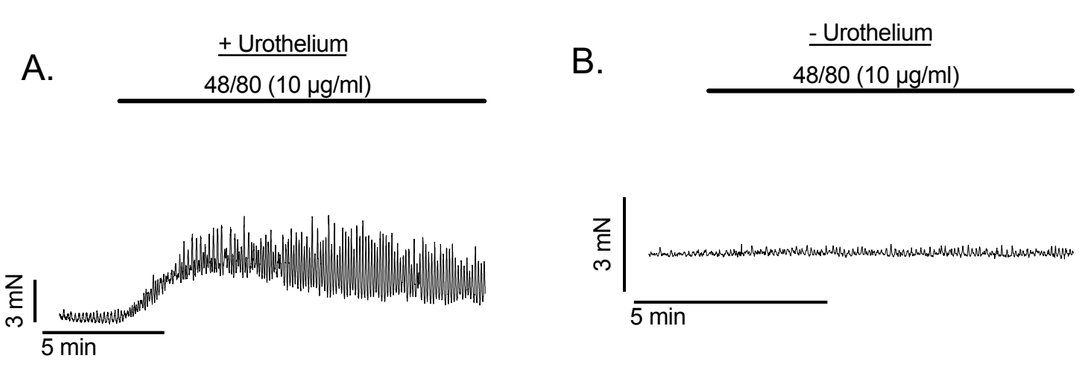

Figure 2. Representative traces of compound 48/80 induced contractions. Isolated bladder smooth muscle strips urothelium-intact (A) urothelium-denuded (B).

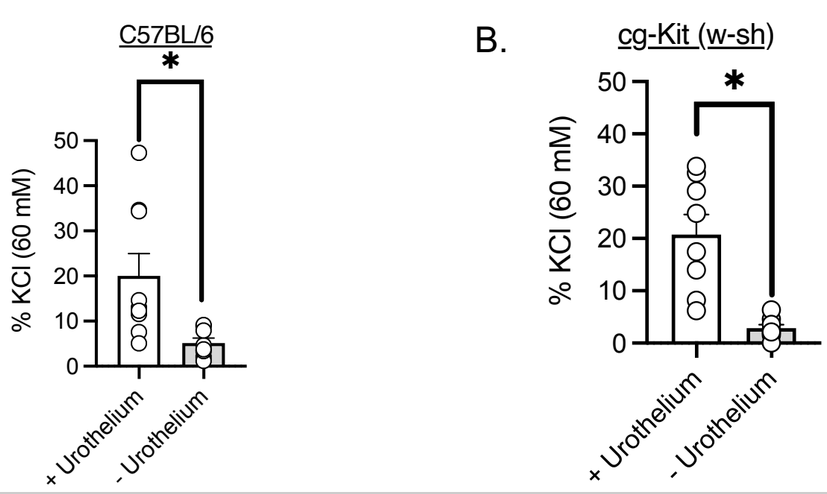

Figure 3. The effects of compound 48/80 on isolated urinary bladder smooth muscle strips from C57BL/6 (mast cell sufficient) and Cg-Kit(w-sh) (mast cell deficient) mice. Compound 48/80 (10 µg/mL) significantly increases tone of urothelium-intact (+) as compared to urothelium-denuded (-) in both species (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).

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

RESULTS

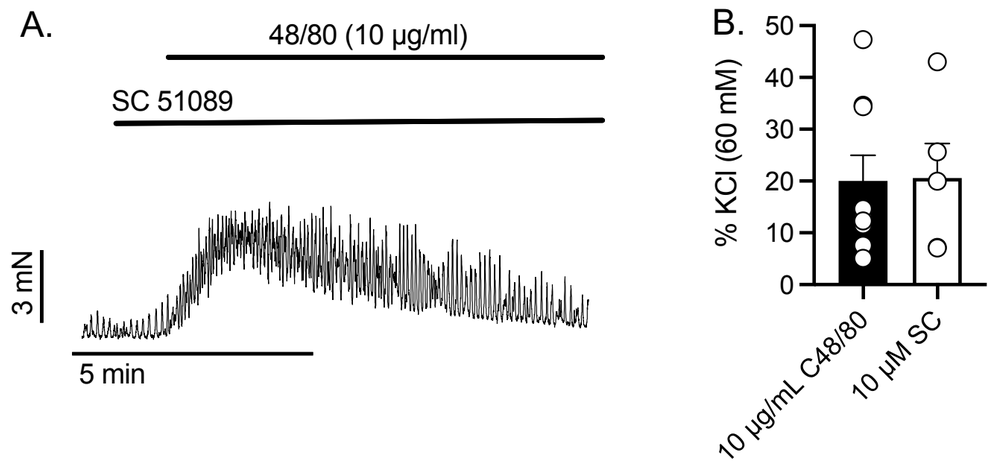

Figure 5. The effects of the prostanoid EP1 receptor antagonist on compound 48/80-induced contractions. SC 51089 (10 µM) had no effect on compound 48/80-induced contractions as compared to compound 48/80 alone (A,B). Results are presented as a percentage of initial contraction to 60 mM KCl. P>0.05, Student's t-test (N=4-8).

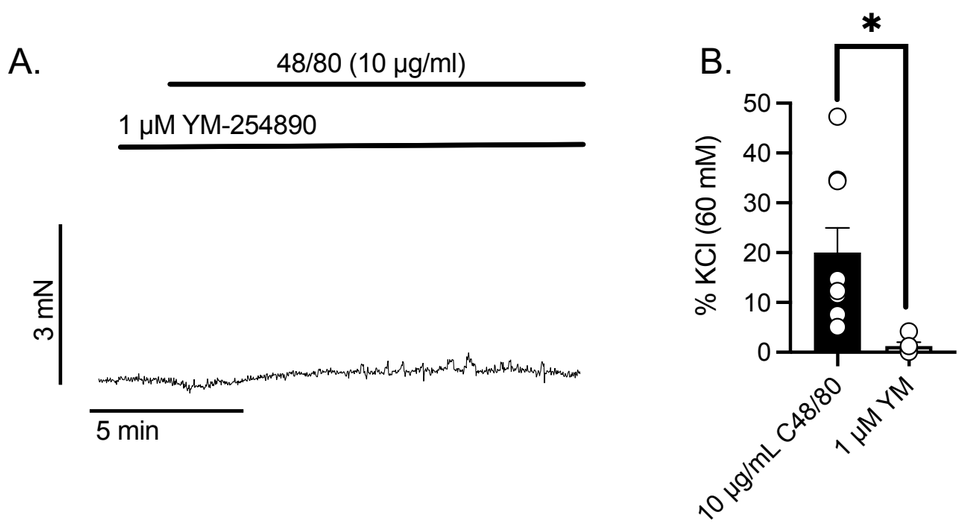

Figure 6. The effects of the G_q/G_s inhibitor on compound 48/80-induced contractions. YM-254890(YM) significantly decreased tone as compared to compound 48/80 alone (A,B). Results are presented as a percentage of initial contraction to 60 mM KCl. P>0.05, Student- t-test for tone (N=7-8).

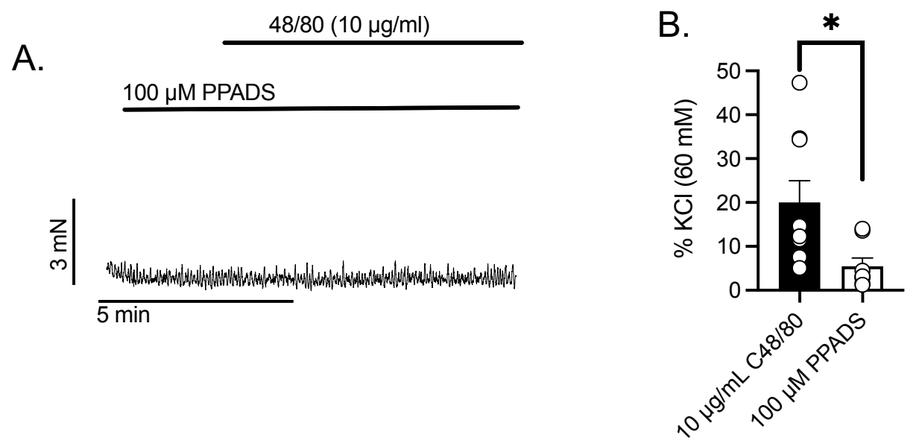

Figure 7. The effects of purinergic P2 receptor antagonist on compound 48/80-induced contractions. PPADS significantly decreases tone as compared to compound 48/80 alone (A,B) Results are presented as a percentage of initial contraction to 60 mM KCl. P>0.05, Student's t-test (N=7-8).

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.

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The Tykocki Lab
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