

SUPPRESSION OF THE STRETCH-EVOKED ATP AND PGE₂ RELEASE FROM THE BLADDER UROTHELIUM BY CYCLOOXYGENASE INHIBITORS

Hypothesis / aims of study

Several clinical trials have demonstrated that cyclooxygenase (COX) inhibitors show some efficacy in patients with lower urinary tract symptoms [1], but their underlying mechanism has been unknown. The bladder epithelium has been shown to play an important role in mechanosensory transduction. ATP and PGE₂ are included in the transmitters released from bladder epithelial cells in response to distension. It has been reported that ATP release from the bladder epithelium is suppressed by anticholinergic agents (e.g. tolterodine) or epithelial-sodium channel antagonists (e.g. amiloride) [2, 3]. In the present study, we evaluated the effects and active mechanisms of COX inhibitors on stretch-evoked ATP and PGE₂ releases from the bladder epithelium.

Study design, materials and methods

Normal rats were deeply anesthetized with halothane and then bled to death. The whole urinary bladder with the urethra was removed, and the weight was measured. A catheter infusing krebs or drug solution was inserted through the urethra and fixed with surgical sutures. The bladder was fixed vertically in an organ bath with krebs solution equilibrated with 5% carbon dioxide and 95% oxygen. Administration of 0.3 mL krebs solution (baseline), followed by 1.5 mL vehicle (control) or drug solutions, was carried out and maintained for 10 minutes. After the solutions were collected by spontaneous dripping, the ATP and PGE₂ amounts were measured with the luciferin-luciferase assay and ELISA assay, respectively.

Results

The ATP and PGE₂ release (control: CON) elicited by extension increased significantly, reaching 80 and 18 times as much as those of the baseline. Nonselective COX inhibitors, FYO-750 (FYO: 100 μM), ketoprofen (KET: 100 μM), indomethacin (IND: 100 μM), amiloride (AMI: 1 mM), and tolterodine (TOL: 100 μM) suppressed 79.5±7.6%, 70.6±14.7%, 82.5±13.7%, 86.5±6.1%, and 91.4±2.9% of the ATP release elicited by the extension, respectively. FYO, KET, IND, and AMI suppressed 88.1±1.8%, 98.8±2.4%, 89.7±1.9%, and 70.8±3.7% of the PGE₂ release elicited by the extension, respectively. However, TOL did not suppress PGE₂ release. The percentage inhibitions of ATP and PGE₂ release by FYO or IND (1 μM) were reduced 53.5±18.2% and 57.1±7.6% or 43.6±27.4% and 54.3±8.9%, respectively. The inhibitions of ATP release by FYO and IND (100 μM) were antagonized by coadministration of PGE₂ (10 ng/mL). Furthermore, 10 nM and 1 μM of ONO-8711 (selective EP1 receptor antagonist) or ONO-AE5-599 (selective EP3 receptor antagonist) suppressed 52.8±16.6% and 80.2±6.6% or 20.7±24.9% and 78.2±11.8% of the ATP release elicited by the extension, respectively.

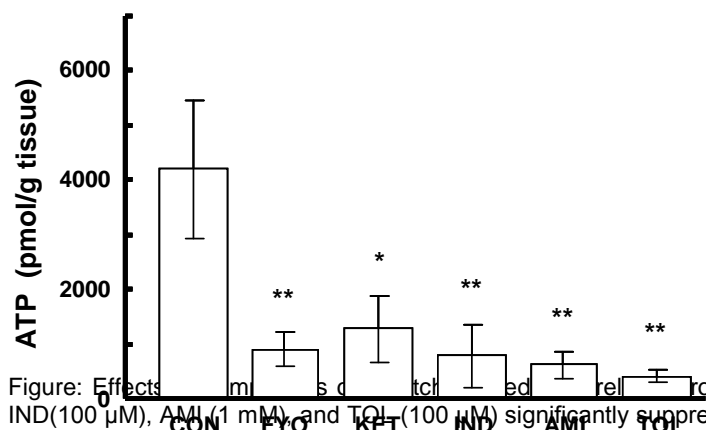


Figure: Effects of indomethacin (IND), ketoprofen (KET), amiloride (AMI), tolterodine (TOL), and FYO-750 (FYO) on ATP release from whole bladder of normal rats. FYO (100 μM), KET (100 μM), IND (100 μM), AMI (1 mM), and TOL (100 μM) significantly suppressed the ATP release elicited by extension. Values are shown as mean ± SE in 6 bladders. * p<0.05 or ** p<0.01: significant difference from control (Dunnett test).

Interpretation of results

These results suggest that COX inhibitors suppress ATP release from the epithelium via a decrease in PGE₂ product. EP1 and EP3 receptors are believed to participate in this mechanism.

Concluding message

Cyclooxygenase inhibitors may suppress the stretch-evoked ATP and PGE₂ release from the bladder urothelium.

References

1. Drug Discov Today Ther Strat 2: 7, 2005
2. Urology 69: 590, 2007
3. Neurosci Lett 429: 142, 2007

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Is this a clinical trial?	No
What were the subjects in the study?	ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	Yes
Name of ethics committee	The Institutional Animal Care and Use Committee of the University of Fukui

