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EFFECTS OF LOCAL ANESTHETICS ON THE CONTRACTILITY OF HUMAN URINARY BLADDER

Aims of Study
The use of local anaesthetic (LA) drugs against overactive bladder diseases, interstitial cystitis, and even in female urge incontinence have been reported. Intravesical administration of lidocaine increases the bladder capacity of patients with spinal cord injury and cerebrovascular disease [1]. However, a report has also been published that denies the relaxation effect of LA agents on bladder function [2], which suggest that the action mechanisms of LA agents are complex. Our previous study revealed that the primary action of the LA agents on the rat bladder was inhibitory [3]. We investigated the effects of LA drugs on the human bladder tissue.

Methods
Human bladder preparation was obtained from 20 patients undergoing radical cystectomy for bladder malignancy. In vitro isometric contraction of detrusor strips was measured. The effects of tetracaine, bupivacaine and lidocaine, and ropivacaine on the basal spontaneous contractions and contractions induced by various stimuli: KCl (60mM), carbachol (CCh), and electrical field stimulation (EFS, 0.8 msec pulse duration for nerve-mediated detrusor contraction or 100 msec for direct muscle stimulation) were investigated. The effect of LA agents on the Ca\(^{2+}\)-independent sustained tonic contraction (SuTC) of the detrusor [4], a unique component of contractile response to the repetitive application of CCh were also explored. The pH of the bath solution was adjusted and controlled. Concentrations of LA agents causing half the maximal inhibitory response (IC\(_{50}\)) were estimated by nonlinear modelling of concentration-response relationships.

Results
No spontaneous contraction was observed in 181 of the human bladder strips (96.8%). LA agents inhibited nerve-mediated detrusor contraction (EFS, 0.8 msec pulse duration) in a concentration-dependent manner, and also inhibited non-nerve mediated detrusor contractions induced by KCl, CCh, or EFS (100 msec pulse duration). The rank order of inhibitory potency on maximal nerve-mediated contraction was ropivacaine, tetracaine, bupivacaine, and lidocaine, while that on KCl- or CCh-induced contraction was ropivacaine, tetracaine, lidocaine, and bupivacaine in order (Table & Figure). Higher concentrations of LA agents were needed to inhibit non-nerve-mediated bladder contraction than nerve-mediated contraction.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine (µM)</th>
<th>Bupivacaine (µM)</th>
<th>Tetracaine (µM)</th>
<th>Ropivacaine (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (n=10)</td>
<td>168.1</td>
<td>68.6</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>KCl (n=8)</td>
<td>905.6</td>
<td>1775.1</td>
<td>189.6</td>
<td>17.6</td>
</tr>
<tr>
<td>CCh (n=8)</td>
<td>1680.7</td>
<td>3334.4</td>
<td>104.3</td>
<td>90.8</td>
</tr>
</tbody>
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Table 1.
Mean IC\(_{50}\) of local anesthetic agents on the nerve-mediated, KCl-, and carbachol-induced bladder contractions

Figure 1.
CCh induced a SuTC even after the depletion of both internal and external Ca\(^{2+}\) sources. The amplitude of SuTC remained as the mean 6.5(±2.8, S.D.)% of the contractile amplitude elicited in the Tyrode solution contained 1.5mM of CaCl\(_2\). This Ca\(^{2+}\)-independent SuTC was partially suppressed by LA agents.
Conclusions
Our study demonstrates that LA agents have a wide spectrum of inhibitory effects on the contraction of human bladder induced by various stimulants at different contractions. Their effects and different potencies on both intrinsic nerves and the smooth muscle of the urinary bladder, suggests that they might be considered to be potentially useful diagnostic and therapeutic agents for bladder dysfunction. A deeper understanding of the action mechanisms of LA agents would widen our therapeutic options and provide indications for voiding disorders.

References
2. Br J Urol, 1987; 60: 516
4. BJU Int, 1999; 84: 343