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EFFECT OF THE RHO KINASE INHIBITOR, FASUDIL, ON BLADDER OVERACTIVITY IN AN EXPERIMENTAL CYSTITIS RAT MODEL

Hypothesis / aims of study

Overactive bladder frequently arises in the general population but the effectiveness and tolerability of current treatments are limited. Rho kinases (ROCK) play a central role in the regulation of smooth muscle contraction, including that of the urinary bladder. Recent experimental evidence indicates that this role could be deregulated and exacerbated under local and systemic pathological conditions that affect the bladder. Studies *in vitro* with prototypical ROCK inhibitors such as hydroxyfasudil indicate that these drugs have potential as future treatments for detrusor overactivity. The effect of hydroxyfasudil on detrusor overactivity *in vivo* has not been reported as far as we understand. Thus, the present study investigates the effects of the Rho-kinase inhibitor, hydroxyfasudil, on detrusor overactivity in a rat model of cystitis.

Study design, materials and methods

Female Sprague-Dawley rats received a single intraperitoneal injection of cyclophosphamide (CYP; 200 mg/kg). Four days later, bladder function was evaluated (i) by monitoring micturition behavior in metabolic cages between hydroxyfasudil- or vehicle-treated animals, (ii) by measuring changes in continuous cystometrograms in response to intravenous hydroxyfasudil under urethane anesthesia, and (iii) by examining the effect of hydroxyfasudil on concentration-response curves (CRC) to carbachol in bladder tissue strips in a functional study.

Results

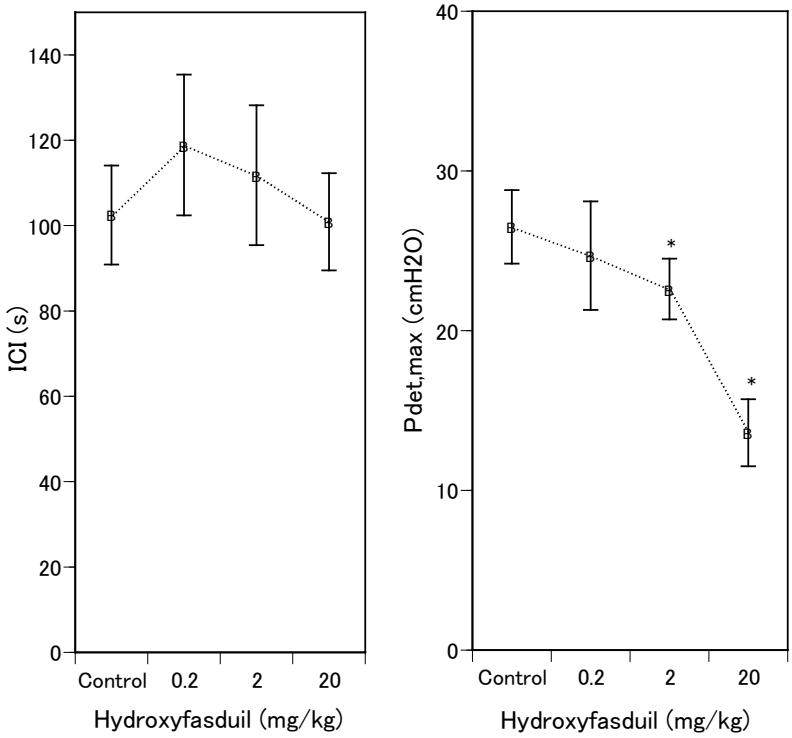
The intraperitoneal injection of hydroxyfasudil (10 mg/kg) significantly increased both average and maximal voided volumes (Table 1). The urodynamic results in the figure 1 show that hydroxyfasudil significantly decreased maximal detrusor pressure, whereas the intercontraction interval was not significantly affected (n = 6). The results of the function study showed that the maximal contraction of CRC to carbachol was significantly reduced after the administration of 0.1, 0.3 and 1 μM hydroxyfasudil (to 74.5 ± 4.2%, 55.2 ± 5.6% and 29.4 ± 5.6%, respectively, of the control value; n = 8).

Table 1. Comparison of micturition behaviour in the experimental rats

	Control	*Hydroxyfasduil*
Urine production (ml/day)	14.0 ± 3.4	19.9 ± 4.0
Micturition frequency (/ day)	21.9 ± 2.4	18.1 ± 1.8
Average voided volume (ml)	0.6 ± 0.1	1.1 ± 0.1*
Maximal voided volume (ml)	1.0 ± 0.1	2.1 ± 0.2*

Values are shown as means ± SEM. *: $p < 0.05$ compared with Control. (n = 7 rats per group)

Figure 1. Effect of hydroxyfasudil on the cystometrograms.



Values represent means ± SEM. ICI, Intercontraction interval; Pdet max, Maximal detrusor pressure. *: $p < 0.05$ compared with Control.

Interpretation of results

Void volumes of rats with CYP-induced cystitis administered with intraperitoneal hydroxyfasudil *in vivo* were increased. While intravenous hydroxyfasudil did not apparently increase cystometric capacity, it significantly inhibited bladder contraction during cystometrogram. Furthermore, our functional findings *in vitro* suggested that hydroxyfasudil inhibits carbachol-induced contraction in the bladders of rats with CYP-induced cystitis as previously indicated in studies of normal animals.

Concluding message

The present findings indicate that hydroxyfasudil could treat detrusor overactivity associated with inflammation.

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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 University of Tottori institutional Animal Care and Use Committee**