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MUSCARINIC AND PURINERGIC RECEPTORS ARE ALTERED IN THE BLADDER OF RAT MODELS WITH INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Interstitial cystitis is a chronic, abacterial inflammatory disease of the urinary bladder characterized by urinary frequency, urgency and suprapubic pain associated with bladder filling and relieved by voiding, but its exact etiology and pathogenesis remain unclear. Currently, there are increasing evidences to suggest the idea that the abnormality of muscarinic and purinergic signaling transduction in the bladder is implicated in the development of interstitial cystitis. In this regard, it is of interest to note that expression of $P2X_2$ and $P2X_3$ receptors was significantly altered in the bladder urothelium of patients with interstitial cystitis [1]. The intravesical instillation of HCl and repeated treatment with cyclophosphamide (CYP) in rats are reported to induce animal models of interstitial cystitis. Therefore, to investigate whether the alteration of muscarinic and purinergic signalings is implicated in the pathophysiology of interstitial cystitis, we have characterized muscarinic and purinergic (ATP) receptors in the bladder of rats pretreated with HCl and CYP by using specific radioligands, [N-methyl-^{3}H]scopolamine ([^{3}H]NMS) and [^{3}H] -methylene ATP ([^{3}H] -MeATP), respectively.

Study design, materials and methods

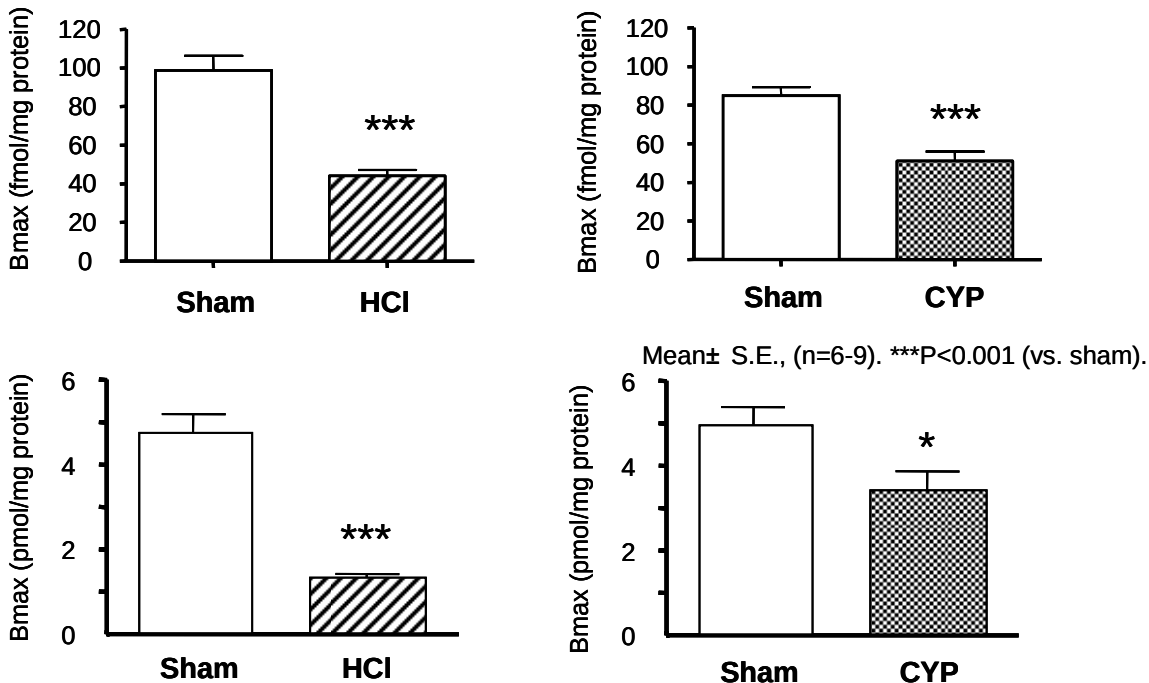
The rat models with interstitial cystitis were induced by the intravesical instillation of 0.4 N HCl (0.2 ml) and by the intraperitoneal injection of CYP (75 mg/kg) every third day for a total of four injections. The mechanical responses of bladder in these rats were monitored by the cystometric method under an anaesthesia. Then, rats were sacrificed by the exsanguination from descending aorta, and the bladder was excised. Muscarinic and ATP receptors in the rat bladder homogenates were measured by measuring specific binding of [^{3}H]NMS and [^{3}H] -MeATP, and binding parameters of apparent dissociation constant (Kd) and maximal number of binding sites (Bmax) for [^{3}H]NMS were estimated by Scatchard analysis.

Results

Compared with that of control rats, the body weight of HCl-pretreated rats was similar and that of CYP-pretreated rats was significantly decreased. In addition, the bladder weights of both HCl- and CYP-pretreated rats were significantly increased. In the cystometry of HCl-pretreated rats, there were significant decreases of micturition intervals and micturition volumes and also marked increase in the frequency of micturition. Similarly, the cystometry of CYP-pretreated rats showed significant decreases of micturition intervals and micturition volumes with a marked increase in the frequency of micturition. The Bmax values for specific [^{3}H]NMS binding were significantly (55% and 43%, respectively) decreased in the bladder of both HCl- and CYP-pretreated rats compared with control rats (Fig. 1). Similarly, there were significant decreases (72% and 31%, respectively) of Bmax for specific [^{3}H] -MeATP binding in the bladder of both HCl- and CYP-pretreated rats compared with control rats. On the other hand, Kd values for specific binding of [^{3}H]NMS and [^{3}H] -MeATP in the bladder were not significantly altered by the treatment with HCl and CYP (Fig. 1). Furthermore, The identification of subtypes of muscarinic and ATP receptors and measurement of ATP release in the bladder of these control and cystitis-induced rats are under way.

Interpretation of results

These data suggest that pretreatment with HCl and CYP in rats causes significant increase in the bladder weight and significant decrease in the density of ligand binding sites of not only muscarinic receptors but also ATP receptors in this tissue, accompanied by the decreases of micturition intervals and micturition volumes and by the increase in the frequency of micturition.



Mean± S.E., (n=6-9). ***P<0.001 (vs. sham).

Fig. 1. Muscarinic (upper panel) and ATP (lower panel) receptor densities (Bmax) in the bladder of sham rats and HCl- or CYP-induced cystitis rats.

Concluding message

The present study has provided the first evidence to suggest that muscarinic and ATP receptors in the bladder may be at least partly involved in the pathophysiology of interstitial cystitis.

References:

[1] BJU International 93: 1344-1348, 2004.
[2] J Urol 157: 1937-1940, 1997.
[3] J Comp Neurol 469: 262-274, 2004.

FUNDING: NONE
DISCLOSURES: NONE
ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Shizuoka