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Asthma-associated prostate enlargement and bladder smooth muscle hypercontractility: unveiling a potential link to LUTS

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Abstract

Background In male patients, benign prostate hyperplasia (BPH) and overactive bladder (OAB) secondary to BPH are the primary causes of Lower Urinary Tract Symptoms (LUTS). Recent clinical studies have reported an increased risk of LUTS, particularly severe LUTS conditions, in male asthmatic patients. However, the potential link and mechanism remain unclear. In this study, we investigated the structural and molecular characteristics of the prostate, and the structural and functional characteristics of the bladder in an asthma rat model.

Methods An asthma model was induced in rats through the intraperitoneal injection of ovalbumin. Prostate and bladder tissue structure was examined with Hematoxylin and Eosin (H&E) and Masson's trichrome (MT) staining, respectively. Prostatic smooth muscle contraction-related and synthesis-related protein levels were assessed using western blotting. Detrusor contractions were examined in an organ bath.

Results Prostate epithelial thickness was significantly increased in asthmatic rats, accompanied by changes in molecular markers, including increased expression of desmin and tropomyosin and decreased expression of vimentin in the prostate tissue. The bladder wall structure and bladder weight were similar in both the asthma and control groups. Acetylcholine induced concentration-dependent bladder smooth muscle contractions, which were significantly enhanced in strips from asthmatic rats, however, acetyl-β-methylcholine and carbachol induced concentration-dependent bladder smooth muscle contractions were similar in both groups.

Conclusions Our findings suggest a potential association between asthma and LUTS, with asthma possibly contributing to organ-specific changes, including prostate enlargement and increased smooth muscle contraction in the prostate and bladder. These results provide evidence for a biological connection between asthma and LUTS, laying a promising foundation for exploring new therapeutic strategies to manage LUTS in patients with asthma.

Keywords Asthma, Lower urinary tract symptoms, Benign prostate hyperplasia, Overactive bladder, Smooth muscle contraction

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Background

Lower urinary tract symptoms (LUTS) encompass a spectrum of bothersome clinical manifestations related to the lower urinary system, ranging from storage to voiding dysfunctions [1]. The prevalence of LUTS increases with age, therefore, it is common in geriatric males [2]. It has been widely accepted that benign prostate hyperplasia (BPH) and overactive bladder (OAB) are the most common causes of LUTS. The pathophysiology of BPH consists of two main components: a static component, stemming from prostate enlargement that physically compresses the urethra, and a dynamic component, involving increased smooth muscle tone in the prostate and bladder. These changes result in urinary tract obstruction, reduced bladder emptying efficiency [3]. However, increasing evidence indicates that other risk factors, such as cigarette smoking, alcohol consumption, insufficient physical activity, elevated body mass index (BMI), metabolic syndrome, depression, diabetes, neurological diseases, and heart diseases, may also contribute to LUTS [4–6].

A survey of 100,000 patients indicated that asthma was significantly associated with bothersome OAB in men, but not in woman [7]. Another recent clinical study reported that asthma patients not only have more severe LUTS (storage and voiding symptoms), but also account for higher proportions of both moderate LUTS (International Prostate Symptom Score [IPSS] score 8–19) and severe LUTS (IPSS score 20–35) than those patients without asthma [8]. Although the urinary and respiratory systems may seem anatomically distant, recent studies have explored commonalities in their pathophysiological processes, including inflammation, neural regulation, and smooth muscle dysfunction [9, 10]. In fact, some pharmacological therapeutic targets have been demonstrated to be effective both in lower urinary tract and airway. Previous studies have identified key proteins, such as LIMK and RhoA/ROCK2, that play crucial roles in both systems [11–15].

Asthma is a chronic respiratory disease characterized by reversible airway obstruction, chronic airway inflammation, hyperresponsiveness and bronchial reconstruction [16]. Corticosteroids or biologics targeting inflammation, cytokines, or their receptors can alleviate asthma symptoms, but these approaches do not address the underlying contribution of airway smooth muscle (ASM) to hyperresponsiveness and particularly remodeling. The primary treatment approach to target abnormal contractility mechanisms in ASM and/or ASM's role in remodeling is to relax the airways smooth muscle contraction [16]. β-receptor agonists are widely used for the treatment of asthma by relaxing the airway smooth muscle [16], however, they may also affect contraction in urinary smooth muscle [17, 18]. Although previous studies have drawn a possible conclusion that asthma might be a risk factor for LUTS, the direct link between asthma and LUTS remains undetermined because LUTS observed in asthma patients could be caused by the side-effects of β-receptor agonists or other alternative treatment. Therefore, in the present study, we evaluated functions of prostate and bladder in asthmatic rats to explore the possible mechanism of asthma- associated LUTS.

Materials and methods

Animal and asthma model

Twelve eight-week-old male Sprague-Dawley rats (weighing 250–280 g) were obtained from the Guangdong Medical Laboratory Animal Center, China. The rats were randomly and evenly divided into control and asthma groups. The establishment of asthma model was performed according to previous reports [19, 20]. Briefly, the asthma group was induced with allergy by intraperitoneal injection of a mixture containing 10 mg of ovalbumin (OVA, Sigma Aldrich, St. Louis, MO, USA) and 10% aluminum hydroxide on days 1 and 8. From the 15th day, the rats in the asthma group received nebulized inhalation of 1% OVA aerosol for 30 min every other day, lasting for a total of 7 days. Rats in the control group received saline by intraperitoneal injection and nebulized inhalation. Throughout the experiment, all rats were allowed to eat regular food ad libitum and were kept under a light/dark cycle at 25 °C. The following Asthma Attack Scale was used to score the asthmatic rats' behavior which include symptoms of coughing, shortness of breath, abdominal muscle twitching, and cyanosis of the lips and mouth within 6 hours [21]. The Asthma Attack Scale: 0 points for normal breathing; 1 point for trembling or nodding; 2 points for coughing, obvious shortness of breath, irritability, and cyanosis; 3 points for rhythmic retracted wheezing or abdominal twitching; 6 points for extreme respiratory distress with prostration or fall. Following the assessment of asthmatic rat behavior, the rats were anesthetized with an intraperitoneal injection of 3% pentobarbital sodium (30 mg/kg). Prostate, bladder, lung, and airway tissues were then collected for subsequent experiments. All procedures were performed in accordance with the Regulations of the Ministry of Health of the People's Republic of China on Animal Management and approved by the Animal Health Professional Committee of the First Affiliated Hospital of Guangzhou Medical University.

Tissue processing and histological evaluation

Prostates and bladders from both groups of rats were collected and weighed. The prostate, bladder, lung, and airway tissues were fixed overnight in 4% paraformaldehyde, and embedded in paraffin blocks. For histopathologic evaluation, prostate tissues from ventral lobes, lung, and

airway tissues were stained with Hematoxylin and Eosin (H&E), while bladder tissues were stained with Masson's trichrome (MT). Quantitative digital image analysis was performed with ImageJ software. Histological sections were scored by an evaluator blinded to group assignment. The remaining prostate tissue was used to extract proteins for Western blot analysis, and the remaining bladder tissue was used for Tension measurements.

Tension measurements

Detrusor strips (6 mm × 3 mm × 3 mm) were isolated from the bladders of asthmatic and normal control rats, and contractions were assessed using the previously described method [12]. Cumulative concentration-response curves of acetylcholine, carbachol, and acetyl-β-methylcholine (Sigma-Aldrich, St. Louis, MO, USA) were generated to evaluate detrusor contraction. For the calculation of agonist-induced contractions, percentage of KCl-induced contractions were used to express the tensions, as this corrects for different smooth muscle content in each strip.

Western blot analysis

Proteins in prostate tissues were extracted according to a previously described method [22]. Primary antibodies for western blot analyses included rabbit anti-vimentin (ab92547), rabbit anti-desmin (ab32362), rabbit anti-GAPDH (ab128915) (Abcam, Cambridge, UK), mouse anti-tropomyosin (sc-74480) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and rabbit anti-β-actin (GB11001) (Servicebio, Wuhan, China). Detection was continued using secondary antibodies IRDye 800CW goat anti-mouse (or rabbit) IgG.Bands were detected using the Odyssey Clx Imaging Systems and quantified with respect to GAPDH using ImageJ software.

Statistical analysis

Data are presented as mean ± standard error of mean (SEM) with the indicated number (n) of independent experiments. Multivariate analysis of variance was used for comparison of whole concentration/frequence response curves, and two-way ANOVA was used for comparison of contractions at single concentrations. The remaining data were analyzed using Student's t test to assess statistical differences and the analyses were performed with SPSS version 23.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA). In all tests, P values < 0.05 were considered statistically significant.

Results

Evaluation of the asthmatic rat model

Asthmatic rats exhibited symptoms of shortness of breath, coughing and wheezing, which resulted in behavior score significantly increased by $1.833 \pm 0.25 (p < 0.001)$ (Fig. 1A). H&E staining of lung and tracheal tissues from asthmatic rats revealed remarkable increases in inflammatory cell infiltration in the peribronchial and perivascular zones in the lung (Fig. 1B), and increased goblet cells in the trachea (Fig. 1C) compared to normal control rats.

Evaluation of prostate and bladder in asthmatic rats

As shown in Fig. 2A, the difference in body weight between control group and asthma group was not significant. Following behavioral observation, both prostates and bladders were excised and weighed. The calibrated weight of both the prostate and bladder was calculated as permillages of body weight and identified as prostate index (PI) and bladder index (BI), respectively. The PI of asthmatic rats showed an increase of 0.724 ± 0.14 (mg/g) compared to control, however, the difference was not statistically significant ($P = 0.09$) (Fig. 2B). H&E staining in prostate tissues indicated that the epithelial thickness in asthmatic rats was significantly increased by 15.941 ± 0.003 (μm) compared to control ($P<0.01$) (Fig. 2D). The BI of asthmatic rats showed a decrease of 0.056 ± 0.01(mg/g) compared to control ($P = 0.29$) (Fig. 2C), and MT staining in bladder smooth muscle revealed a similar bladder structure in both groups (Fig. 2E).

Contraction-related proteins in the prostate are elevated in asthmatic rats

To assess the contraction of prostate smooth muscle in asthmatic rats, expression levels of smooth muscle contraction-related proteins, desmin, α-b-tropomyosin (TPM), and synthesis-related protein vimentin were detected by western blot analysis. The desmin content in the prostate tissue from asthmatic rats was significantly increased by 0.287 ± 0.07 ($p < 0.001$), and the TPM content was significantly increased by 0.305 ± 0.01 ($p < 0.05$) when compared with the control group, respectively. In contrast, the content of vimentin protein in asthmatic rats was significantly reduced by 0.360 ± 0.11 ($p < 0.01$) when compared with controls (Fig. 3).

Detrusor contraction is enhanced in asthmatic rats

Acetylcholine (0.1–1000 μmol/mL) induced concentration-dependent bladder smooth muscle contractions, which were significantly enhanced in strips from asthmatic rats compared with the control group. The enhancement was significant after multivariate analysis at 100, 300 and 1000 μmol/mL acetylcholine (Fig. 4A). However, acetyl-β-methylcholine (0.1–1000 μmol/mL) and carbachol (0.1–1000 μmol/mL) induced concentration-dependent bladder smooth muscle contractions were similar in both groups (Fig. 4B and C).

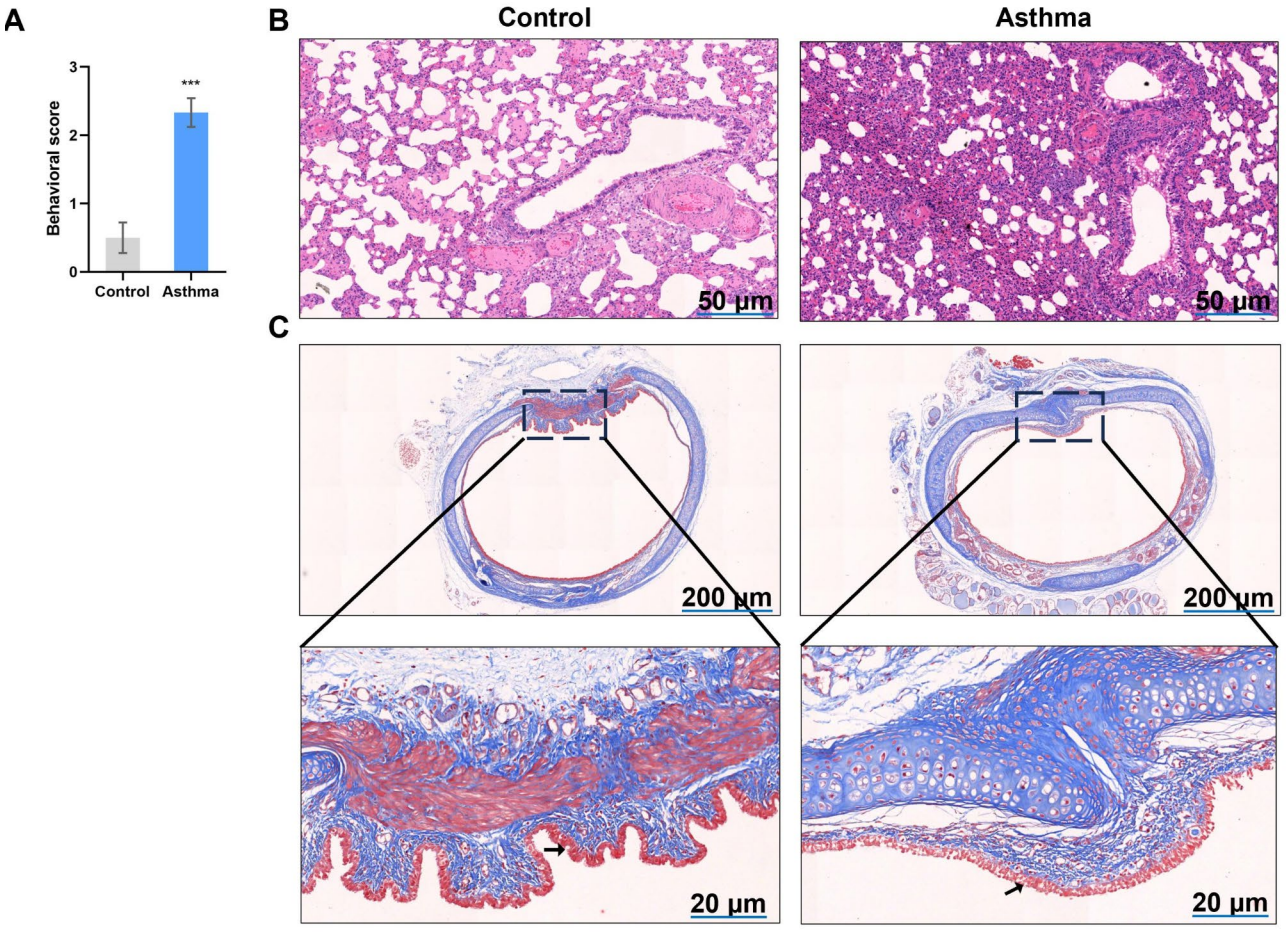

Fig. 1 Evaluation of lung and tracheal in asthmatic rats. Behavioral score of rats (**A**). Lung and tracheal tissues (**B, C**) were subjected to hematoxylin and eosin (H&E) staining to observe infiltration of eosinophils, monocytes, and lymphocytes. Arrows point to goblet cells in Figure **C** (scale bar 20 μm). Data are mean ± SEM from a series of tissues ($n = 6$) from the asthma group and control group. ***$P < 0.001$ for control vs. asthma

Discussion and conclusions

In the present study, we established an asthma rat model to explore potential structural and molecular changes in the prostate and bladder associated with LUTS. Our findings revealed significant epithelial thickening in the prostates of asthmatic rats, suggesting hyperplasia, accompanied by molecular changes indicative of a shift toward a more contractile smooth muscle phenotype. For the bladder, although its overall weight and structure remained similar between groups, detrusor contractions induced by acetylcholine were significantly enhanced in asthmatic rats, pointing to increased sensitivity rather than structural remodeling. These results indicate that asthma may contribute to LUTS by inducing both structural alterations in the prostate and functional changes in bladder smooth muscle.

In male patients, LUTS could be caused by disorders in the prostate or bladder, or both [23]. BPH is one of the most common etiologies for male LUTS, as the enlarged prostate and the increased prostate smooth muscle tone may impair bladder emptying and cause LUTS [24]. OAB, caused by spontaneous and exaggerated contractions in bladder smooth muscle, is the most bothersome symptoms in LUTS [25]. In men with BPH, the bladder is usually an innocent organ of BPH, therefore, LUTS could be caused by both BPH and secondary OAB [26]. A clinical study on a Korean population indicated a significantly higher prevalence of BPH in asthmatic patients (17.1%) than in individuals without asthma (8.7%) [27]. The underlying pathophysiologic mechanisms of the association between BPH and asthma have not yet been determined. However, previous studies have reported significant elevated levels of several cytokines such as IL-2, IL-4, and IL-17 both in BPH specimen [28, 29] and bronchoalveolar lavage fluid of symptomatic asthma patients [30, 31]. These findings may indicate a possible immune-mediated inflammatory mechanism linking BPH and asthma. Another study on a Taiwan population indicated that the risk of BPH, and the need of receiving transurethral resection of the prostate (TURP) in the asthma

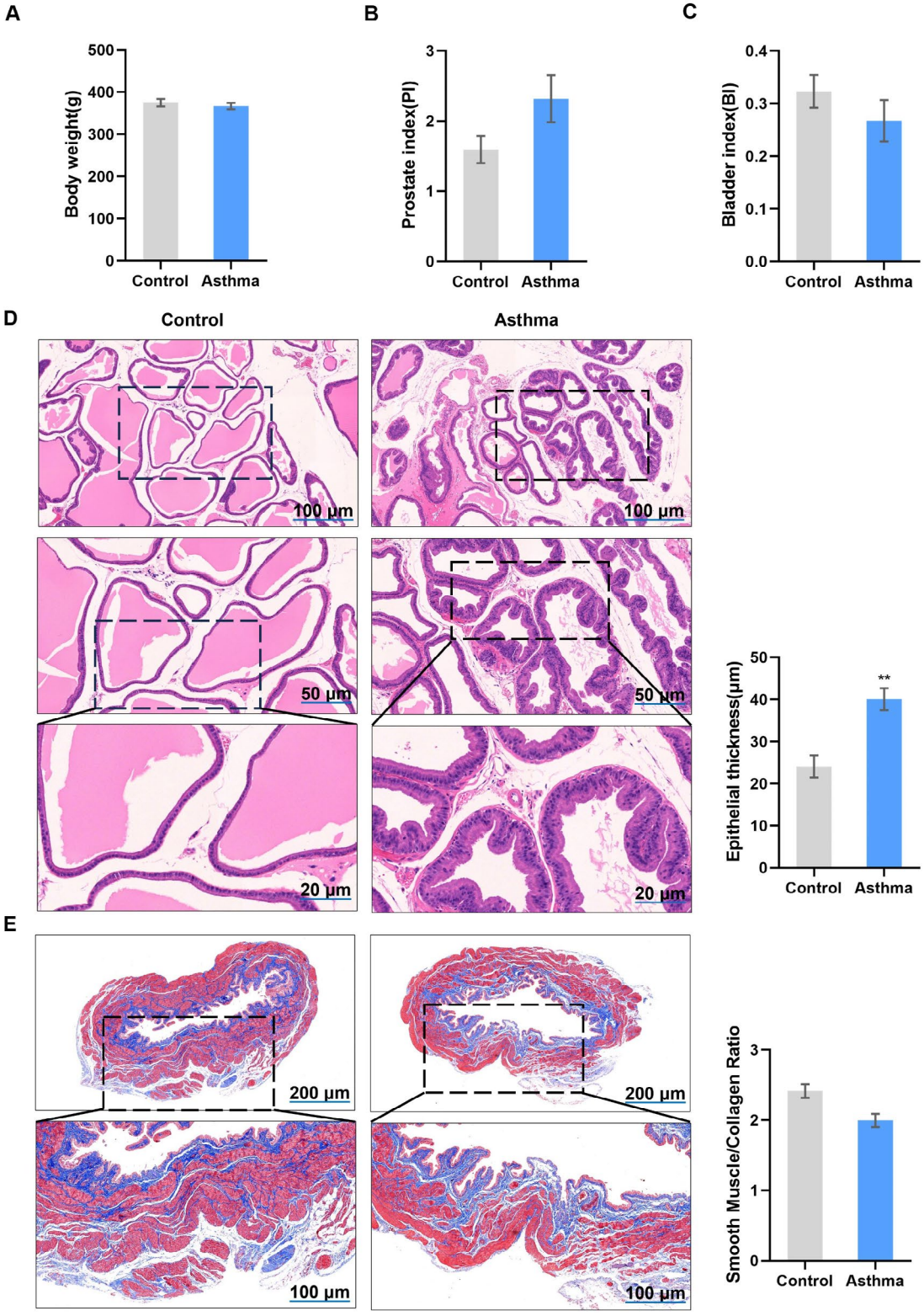

Fig. 2 Evaluation of prostate and bladder in asthmatic rats. The bodies, prostates and bladders from the experimental rats were weighed and calculated PI and BI (**A**, **B**, **C**). Subsequently, prostate tissues (**D**) were subjected to hematoxylin and eosin (H&E) staining to observe the structure of the tissue and detrusor tissues (**E**) were subjected to Masson trichrome staining to visualize the bladder smooth muscle (stained red) and collagenous fiber (stained blue). Data are mean ± SEM from a series of tissues ($n = 6$) from the asthma group and control group. The data in Figures **A**, **B**, **C**, and **E** were included in the statistical analysis, with all $P > 0.05$. In Figure D, $^{**}P<0.01$ for control vs. asthma

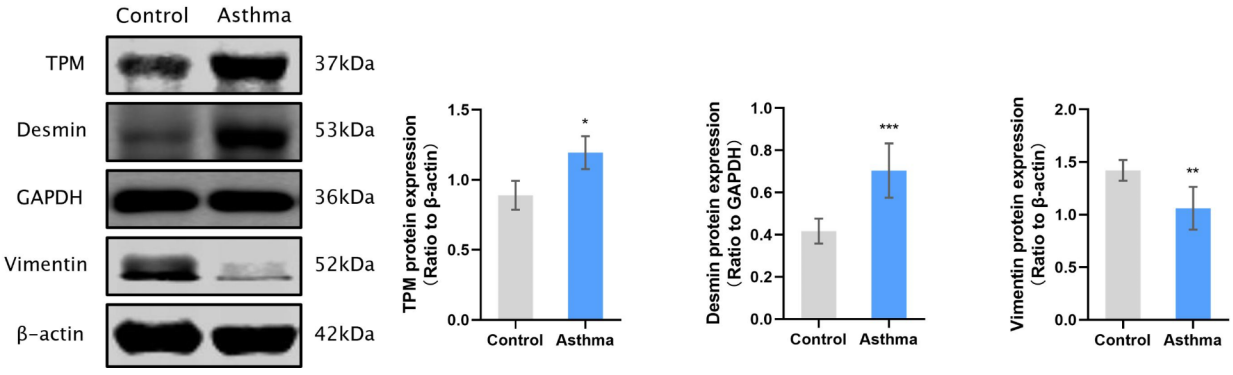

Fig. 3 Expressions of contraction-related proteins and synthesis-related proteins in prostate tissue of asthmatic rats. Expressions of Vimentin, Desmin and TPM were measured by Western blot analysis. Values for each sample were calculated as fold of the content of GAPDH or β-actin and normalized to the mean of the corresponding control group. Data are mean ± SEM from a series of tissues ($n = 6$) from the asthma group and control group. *$P < 0.05$ for control vs. asthma

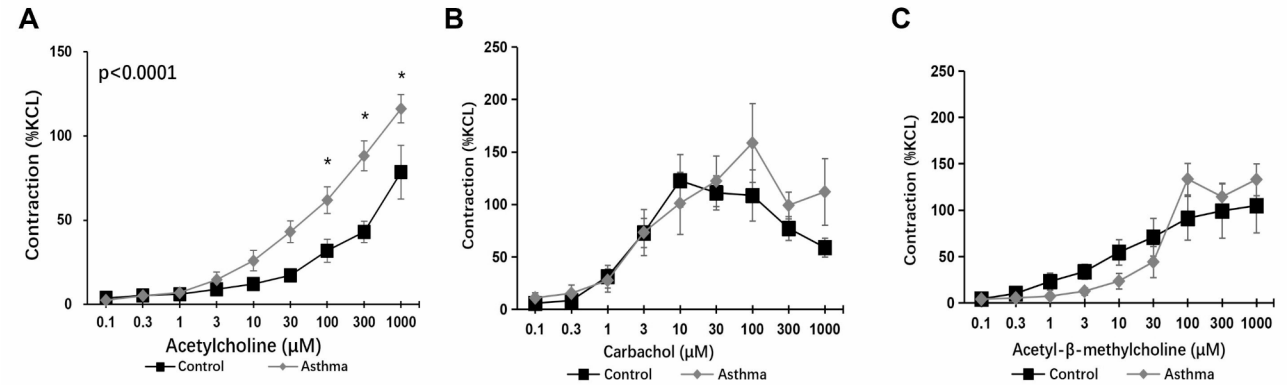

Fig. 4 Evaluation of bladder detrusor contraction in asthmatic rats. The contraction of detrusor strips in asthmatic and normal rats was compared under the induction of agonist and KCl. To eliminate heterogeneities due to individual variations or different smooth muscle content in each strip, tensions were expressed as percentage of contraction (%) induced by high molar KCl. The contraction of the detrusor muscle was compared between the asthma group and the control group induced by a gradient of concentrations of three agonists (acetylcholine (**A**), carbachol (**B**) and acetyl-β-methylcholine (**C**)). KCl-induced contractions of detrusor strips in an organ bath were first assessed, followed by gradient concentration agonist-induced contraction of the detrusor muscle. Data are mean ± SEM from a series of tissues from rats ($n = 6$) for the asthma group and control group. *$P < 0.05$ for control vs. asthma

group were 1.40 and 1.30 folds higher than non-asthma group, respectively [32]. However, a direct link between asthma and the risk of BPH and TURP is still undetermined, as inhaled anticholinergic drugs could cause acute urinary retention and therefore increase the risk of BPH and the need for surgery [33, 34]. In our present study, we observed that the PI of asthmatic rats showed a trend toward an increase (0.724 ± 0.14 mg/g) compared with rats in the control group; however, this difference was not statistically significant ($P = 0.09$). Despite the lack of significant weight change, H&E staining revealed a notable thickening of the prostate epithelium in the asthma group. These findings suggest that while asthma may not significantly alter prostate weight, it could induce structural changes in the prostate, potentially indicative of early proliferative alterations. Further investigation with larger sample sizes is needed to clarify the extent and clinical implications of these changes within the context of prostatic pathology. Additionally, western blot analysis revealed that the expression of smooth muscle contraction-related proteins desmin and TPM were significantly increased, while synthesis-related protein vimentin was significantly decreased, which indicated that smooth muscle cells in the prostate of asthmatic rats may undergo a phenotypic shift towards a more contractile phenotype, leading to enhanced contraction ability [35]. Chronic inflammation and hypoxia, both hallmarks of asthma, may drive the observed phenotypic shift in the prostate towards a more contractile state. Elevated levels of Th2 cytokines, such as IL-4 and IL-13, can promote the expression of contraction-related proteins and suppress synthetic markers through calcium signaling pathways and receptor upregulation [36]. Hypoxia exacerbates this process by activating the RhoA-ROCK signaling pathway, which increases myosin light chain (MLC) phosphorylation and inhibits myosin phosphatase, leading to sustained and amplified contraction in smooth muscle cells [37]. These combined factors may contribute to the

enhanced contractile phenotype observed in the prostate of asthmatic rats. While our findings suggest a potential link between asthma-induced systemic changes, such as chronic inflammation and hypoxia, and alterations in prostate smooth muscle contraction and proliferation, this remains a hypothesis that requires further validation. Further studies are needed to confirm these mechanisms and their role in prostate pathophysiology.

We observed that the muscarinic agonist acetylcholine induced concentration-dependent bladder smooth muscle contractions, which were significantly enhanced in strips from asthmatic rats. This may indicate a role of asthma in the storage symptoms of LUTS, as enhanced contraction in detrusor might cause frequency, urgency and OAB [12]. However, we observed that other muscarinic agonists, carbachol and acetyl-β-methylcholine induced concentration- dependent bladder smooth muscle contractions, which were not significantly enhanced in stripes from asthmatic rats. Muscarinic receptors (M1–M5) are widely distributed in the human body and mediate various physiological functions [38]. Acetylcholine is the predominant endogenous neurotransmitter that activates all muscarinic receptor subtypes, while synthetic agonists like carbachol or acetyl-β-methylcholine have varying affinities for these receptors. Studies suggest that acetylcholine exhibits a higher efficacy for activating certain muscarinic receptor subtypes (e.g., M2 and M3) compared to synthetic agonists, which may explain its stronger contractile response in the bladder [39, 40]. In asthma, elevated parasympathetic activity increases acetylcholine release, leading to exaggerated smooth muscle responses [41]. We hypothesize that this enhanced acetylcholine signaling may extend beyond the airways, affecting the bladder by upregulating or sensitizing specific muscarinic receptor subtypes. Unlike acetylcholine, carbachol and acetyl-β-methylcholine may not fully replicate this enhanced signaling due to differences in receptor subtype activation or downstream signaling pathways [42]. Further studies are needed to investigate muscarinic receptor subtype expression and function in the bladder of asthmatic models to confirm these mechanisms.

Although detrusor contraction in asthmatic rats was enhanced compared to normal control rats, the BI was similar in both groups. MT staining in bladder tissues revealed that the ratio of smooth muscle to collagen fibers was similar in both groups. These results may indicate that the enhanced contraction in detrusor might be caused by increased sensitivity to acetylcholine, rather than by bladder remodeling. However, the possibility of asthma affecting bladder remodeling could not be fully excluded, as the duration of rat model establishment is relatively short, therefore, a longer observation duration would be helpful for a comprehensive evaluation. Additionally, unlike humans, rats lack a prostatic capsule, so prostate enlargement and subsequent BOO, which are common in human BPH, are unlikely to contribute to the enhanced detrusor contraction in our model. This further supports the idea that the observed changes in bladder function are more likely related to asthma-induced alterations in muscarinic receptor sensitivity or other mechanisms.

In conclusion, our findings suggest a potential association between asthma and LUTS, with asthma possibly contributing to organ-specific changes, including prostate enlargement and increased smooth muscle contractions in both the prostate and bladder. These results provide evidence for a biological link between asthma and LUTS, highlighting the potential impact of asthma-associated systemic and local changes on LUTS. Furthermore, this study offers a promising foundation for exploring new therapeutic strategies to manage LUTS in patients with asthma.

Abbreviations

BPH	Benign prostate hyperplasia
OAB	Overactive bladder
LUTS	Lower urinary tract symptoms
OVA	Ovalbumin
TPM	Tropomyosin
TURP	Transurethral resection of the prostate
IPSS	International prostate symptom score
ASM	Airway smooth muscle

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12894-024-01686-3.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

QY was involved in the conception and design of the study. PC, MC, and XQ conducted the experiments. HL and XZ performed the data analysis and interpretation. PC and QY contributed to drafting the manuscript. WG, ML and GZ critically revised the manuscript for important intellectual content. PC and QY are the guarantors of the article, fully responsible for the research work and conduct, have access to the data, and supervise the decision to publish. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

All animal experiments were carried out in accordance with national standards and protocols approved by the Animal Ethical and Welfare Committee (AEWC) of Guangzhou Miles Biosciences Co. Ltd (No. IACUC-MIS20230043).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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