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AN INFLAMMATORY CYTOKINE IL-1B IS INVOLVED IN BLADDER REMODELLING AFTER PARTIAL BLADDER OUTLET OBSTRUCTION IN MICE

Hypothesis / aims of study

In partial bladder outlet obstruction (PBOO), such as benign prostatic hyperplasia and neurogenic bladder, hypoxia/ischemia and mechanical stress in the urinary bladder induce morphological and functional changes of the urinary bladder, which usually cause lower urinary tract (LUT) symptoms and LUT dysfunction. Recently, several growth factors or cytokines have been pointed out to be involved in inflammation of the urinary bladder and resulted in the bladder remodeling after PBOO[(1)]. In the present study, we focused on IL-1β, inflammatory cytokine, after PBOO, and hypothesized that IL-1β could be associated with morphological and functional changes in the urinary bladder after PBOO.

Study design, materials and methods

Wild-type 8-week-old female C57/BL6 mice (WT) and female IL-1β-/- mice (KO), which were obtained from Dr. Iwakura in University of Tokyo, were used. We underwent PBOO surgery on animals and then sham surgery was performed as control mice. Experimental animals were sacrificed at week-1, week-3 and week-12 after the surgery and the bladders were carefully harvested. Bladder weight was measured and RT-PCR was underwent to determine the expression of cytokines quantitatively (IL-1β, IGF-1 and TGF-β). The bladders were used for histological analysis with hematoxylin and eosin (HE) staining to evaluate morphological changes. Regarding functional study, mice were anesthetized and a polyethylene catheter was implanted into the bladder under anesthesia at week-3. After complete recovery of animals from anesthesia, cystometric study was performed on consciousness. LUT function was evaluated using the following urodynamic parameters: 1) bladder capacity (BC), 2) the maximal pressure at micturition (MP), 3) the frequency of non-voiding contraction (NVC) and 4) residual urine volume (RUV). Furthermore, IGF-1 (50μg/kg/day) was administered intraperitoneally in KO mice, and then bladder weight and histological changes were investigated. Data were expressed as means ± standard error. Statistical analysis was performed using the non-parametric Mann-Whitney U-test to compare data in different groups. P-value <0.05 was considered to indicate a statistically significant difference.

Results

The bladder weight in WT mice was significantly increased in PBOO compared to sham. In WT mice, although the maximal bladder weight in PBOO was observed at week-1 and gradually decreased thereafter, the bladder weight was still heavier in PBOO than in sham at week-12 (Fig. 1). HE staining in WT mice revealed that edema at the interstitium occurred at week-1 and muscle hypertrophy was observed after week-3 in PBOO. In KO animals, the increase of bladder weight in PBOO, which was seen in WT-PBOO, was significantly suppressed (Fig. 1) and muscle hypertrophy was slight-to-moderate compared to WT-PBOO. Meanwhile, KO mice with IGF-1 administration have similar bladder weight change (Fig. 1) and morphological changes in WT mice after PBOO. Regarding the expression of cytokines in WT animals, IL-1β was significantly increased from week-1 to week-12 in PBOO compared to sham (Fig. 2), while IL-1β was not detected in KO animals. Also, IGF-1 was significantly increased from week-1 to week-12 in PBOO and TGF-β was significantly increased in week-1 and week-3 in PBOO. In KO animals, IGF-1 or TGF-β was not increased significantly in PBOO compared to WT-sham (Fig. 3). In urodynamic parameters, although MP and BC in WT mice were significantly increased in PBOO compared to sham, these changes were not seen in KO animals. There was no significant difference in NVC and RUV among groups (Table).

Figure 1 Bladder weight

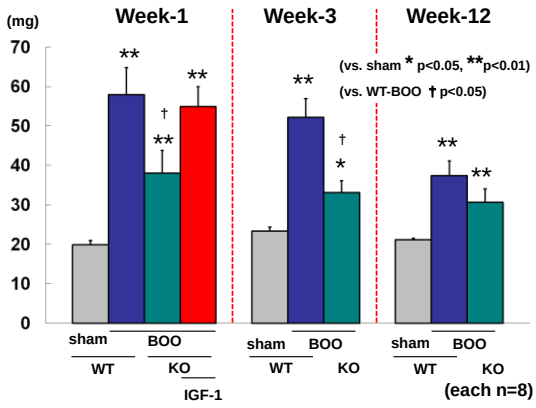


Figure 2 Expression of IL-1β

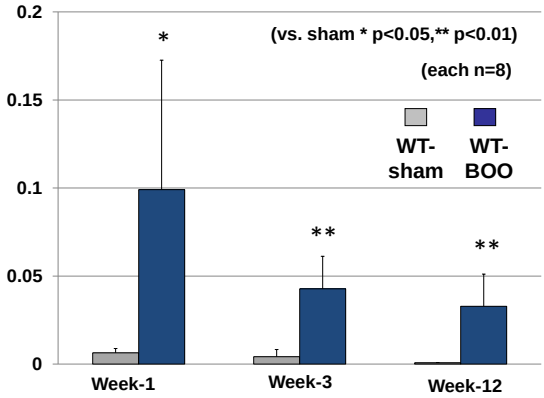
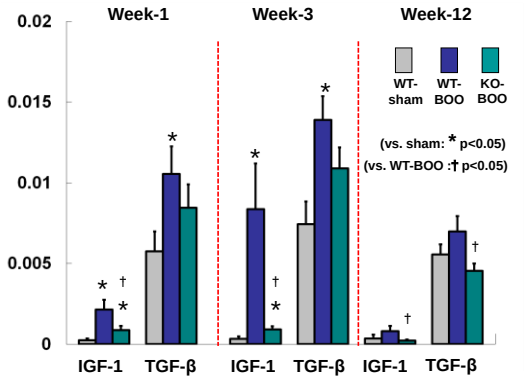


Figure 3 Expression of cytokines

Table Urodynamic parameters



	WT-sham	WT-BOO	KO-BOO
Bladder capacity (μl)	51 (±12)	199* (55)	77† (±22)
Micturition pressure (mmH_2O)	40.6 (±6.3)	54.8* (±7.0)	47.8† (±4.8)
Non-voiding contraction (times/micturition)	1.3 (±1.3)	7.2 (±4.3)	4.2 (±1.5)
Residual urine (μl)	0 (±0)	75 (±48)	50 (±29)

(*: p<0.05 vs. WT-sham)

(†: p<0.05 vs. WT-BOO)

Interpretation of results

IL-1β was increased from week-1 and stimulated IGF-1 and TGF-β expression in PBOO. In KO animals, the morphological and functional changes as well as the increase of IGF-1 in PBOO were suppressed compared to WT mice. However, IGF-1 administration induced the increase of bladder weight and muscle hypertrophy in KO-PBOO similar to WT-PBOO. Thus, IL-1β have the potential of influencing bladder remodeling in PBOO, especially muscle hypertrophy could occur via IGF-1 stimulation induced by IL-1β. TGF-β, which has been involved in fibrosis of tissue and was increased at week-1 and week-3 after PBOO in the present study, could be implicated in bladder fibrosis.

Concluding message

IL-1β as an inflammatory cytokine has the potential to induce bladder remodeling and deteriorate urodynamic parameters in PBOO. Especially, muscle hypertrophy in the urinary bladder could occur via IGF-1 stimulation induced by IL-1β.

References

1. Sano, et al. LUTS 4:154-160 (2012)

Disclosures

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