

EXPRESSION OF CANNABINOID 1 (CB1) AND CANNABINOID 2 (CB2) RECEPTOR AND EFFECTS OF CB1 / CB2 RECEPTOR AGONISTS ON DETRUSOR OVERACTIVITY ASSOCIATED WITH BLADDER OUTLET OBSTRUCTION IN RATS

Hypothesis / aims of study

Detrusor overactivity (DO) is one of functional changes which can be induced by bladder outlet obstruction (BOO). Various receptors in the urinary bladder mediate pathophysiology of DO. Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) receptor are known to be expressed in the urinary bladder detrusor and urothelium. These receptors activation could modulate the bladder afferent activity and the micturition reflex. An immunohistochemical study has shown increased CB1 immunoreactive suburothelial nerve fibers in patients with idiopathic DO, and their correlation with clinical symptoms.(1) Other study showed higher expression of CB2 than CB1 in the urothelium, and CB2 mediated modulatory effect on cholinergic nerve activity.(2) Therefore, CB1 and CB2 receptor may have a role as one of receptors in the urinary bladder which control the bladder function. However, the definite role of CB1 and CB2 receptor on bladder function is still incompletely known. In this study, we investigated the change of expression of CB1 and CB2 receptor and effects of CB1 and CB2 agonists on DO associated with BOO in rats.

Study design, materials and methods

Male Sprague Dawley rats were randomly assigned to four groups. The control group (n = 10) included sham-operated rats. The animals in the BOO (n = 10), CB1 agonist group (n = 10) and CB2 agonist group (n = 10) underwent partial BOO surgery. Three weeks postoperatively, cystometry (CMG) was performed in all rats. After confirming DO in CB1/CB2 agonists groups, CB1 receptor agonist (WIN 55,212-2) and CB2 receptor agonist (CB65) were instilled intravesically, and then we performed CMG again. CMG parameters were investigated, including contraction interval (CI) and contraction pressure (CP).

Bladders of control and BOO groups were excised following CMG. The bladder body was cut vertically and dissected under a microscope into the urothelium and detrusor muscle. Immunofluorescence staining was performed to localize the expression of CB1/CB2 in the urothelium and detrusor muscle. The immunofluorescence signals were assessed using a computerized image analysis system. In addition, the expression levels of CB1/CB2 in the urothelium and detrusor muscle were quantified by western blotting.

Results

The BOO group had significantly shorter CI (4.42 ± 0.76 min, vs 10.52 ± 1.07 min, $P < 0.05$) and significantly higher CP (28.03 ± 3.94 cmH₂O, vs 23.03 ± 3.07 cmH₂O, $P < 0.05$) compared to the control group. In the CB1 agonist group, CI (8.61 ± 0.61 min, vs 4.42 ± 0.76 min, $P < 0.05$) was significantly longer, and CP (19.88 ± 3.14 cmH₂O, vs 28.03 ± 3.94 cmH₂O, $P < 0.05$) was significantly lower compared to the BOO group. In the CB2 agonist group, CI (9.51 ± 0.55 min, vs 4.42 ± 0.76 min, $P < 0.05$) was significantly longer, and CP (23.76 ± 4.78 cmH₂O, vs 28.03 ± 3.94 cmH₂O, $P < 0.05$) was significantly lower compared to the BOO group too. CB1 receptor immunofluorescence signals were significantly increased in the urothelium and detrusor muscle in BOO group, compared with the control. CB2 receptor immunofluorescence signals were increased in BOO groups, although this was not significant. In western blotting, immunoreactive bands indicating expression of CB1 were significantly increased in the BOO group compared with the control in the urothelium and detrusor muscle ($P < 0.05$). The immunoreactive bands of CB2 were increased in the BOO group, although this was not significant ($P > 0.05$).

Interpretation of results

CMG parameters in BOO group were significantly improved by inhibitory effect of CB1 and CB2 receptor agonists on DO associated with BOO. The expression of CB1 was significantly increased in the urothelium and detrusor muscle in DO associated with BOO, but no significant change of CB2 expression was observed. These findings suggest a role of CB1 and CB2 receptor, especially CB1, in regulation of bladder function in rats with DO associated with BOO.

Concluding message

CB1 and CB2 receptors, especially CB1, have a role in pathophysiology of DO associated with BOO, and can serve as therapeutic targets of DO associated with BOO.

References

1. Mukerji G, Yiangou Y, Agarwal SK, et al. Increased cannabinoid receptor 1-immunoreactive nerve fibers in overactive and painful bladder disorders and their correlation with symptoms. *Urology*. 2010;75:1514.e15-20.
2. Tyagi V, Philips BJ, Su R, Smaldone MC, et al. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. *J Urol*. 2009;181:1932-8.

Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The institutional Animal Care and Use Committee of the Catholic University of Korea