520

Chuang Y[1], Tyagi P[2], Huang C[3], Yoshimura N[4], Chancellor M[5]

1. *Chang Gung Memorial Hospital, Kaohsiung, Taiwan,* ***2.*** *Department of Urology, William Beaumont Hospital, Royal Oak, Michigan,* ***3.*** *Pathology3, Chang Gung Memorial Hospital, Kaohsiung Medical Center,* ***4.*** *Department of Urology, University of Pittsburgh School of Medicine,* ***5.*** *Department of Urology, William Beaumont Hospital*

MECHANISMS AND URODYNAMIC EFFECTS OF A POTENT AND SELECTIVE EP4 RECEPTOR ANTAGONIST (MF191) ON CYCLOPHOSPHAMIDE AND PROSGLANDIN E2 INDUCED BLADDER OVERACTIVITY IN RATS

Hypothesis / aims of study

Upregulation of the prostaglandin E_2 (PGE_2) receptor subtype 4 (EP4) in the bladder has been suggested to involve in bladder overactivity. We investigated the mechanism and urodynamic effects of a potent and selective EP4 receptor antagonist (MF191) on cyclophosphamide (CYP) or PGE_2 induced bladder overactivity in rats.

Study design, materials and methods

Experimental and control rats were injected with CYP (200 mg/kg intraperitoneally) or saline on day 1. Continuous cystometrogram (CMGs) were performed on day 3. In group 1, MF191 (vehicle, 0.1 and 1 mg/kg) was given intravenously. The bladder was then harvested for histology. Some bladders were harvested for analysis of EP4 expression by western Blotting. In group 2, MF191 (vehicle, 10 nM, and 100 nM) was continuously infused into bladder. In group 3, bladder overactivity was produced by intravesical instillation of PGE_2 (200 uM) and vehicle or MF191 (1 mg/kg) was given intravenously.

Results

CYP induced bladder inflammation, EP4 upregulation, and overactivity. The CYP effects were suppressed by MF191 (1mg/kg) intravenous injection (intercontraction interval, ICI- 39.4% increase, inflammatory cells infiltration score- 26.1% decrease, and EP4 expression- 89.9% decrease). Intravesical instillation MF191 (100 nM) suppressed CYP induced bladder overactivity (ICI- 71.8% increase). PGE_2 induced bladder overactivity was suppressed by MF191 (ICI- 43.2% increase). MF191 had no significant effects on other CMG parameters and on control rats.

Interpretation of results

EP4 receptor antagonist MF 191 may have effects on the bladder urothelium and inflammatory cells infiltration and suppressed CYP or PGE_2 induced bladder overactivity.

Concluding message

Systemic or intravesical MF 191 administration may be promising for treatment of overactive bladder in humans.

References

1. Chuang YC, Yoshimura N, Wu M, Huang CC, Chiang PH, and Chancellor MB Intravesical Botulinum Toxin A Administration Inhibits COX-2 and EP4 Expression and Suppresses Bladder Hyperactivity in Cyclophosphamide Induced Cystitis In Rats. Eur Urol2009; 56: 159-167.
2. Jiang, Y., Araki, I., Kobayashi, H. et al. The expression of prostaglandin E2 receptors (EP1, 2, 3 and 4) in the human urinary bladder epithelium of normal and bladder outlet obstruction- a novel mechanism in the afferent hyperactivity of bladder. 2008 AUA Meeting (Abstract 1318), J. Urology2008; 179: 472.
3. Blouin M., Han Y., Burch J. et al. The Discovery of 4-{1-({2,5-Dimethyl-4-4-(trifluoromethyl)benzyl-3-

Specify source of funding or grant	**National Science Council Taiwan; Chang Gung Memorial Hospital**
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	**laboratory animal committee Chang Gung Memorial Hospital Kaohsiung**