464

Lee S J[1], Lee D[2]
1. *Kyunghee University Hospital,* ***2.*** *Kyunghee University Gangdong Hospital*

EFFECT OF T-TYPE CALCIUM CHANNEL BLOCKER MIBEFRADIL ON CYCLOPHOSPHAMIDE-INDUCED CYSTITIS IN MOUSE

Hypothesis / aims of study

In nociceptive pathway, T-type calcium channel promotes pain signal at pain receptor of peripheral nerve and spinal cord. To date, three molecular subtypes are known for the α_1 subunit of low voltage-activated T-type Ca^{2+} channel, namely $alpha_{1G}$ ($Ca_v3.1$), $alpha_{1H}$ ($Ca_v3.2$) and $alpha_{1I}$ ($Ca_v3.3$). Blockage of calcium channels in vascular smooth muscle results in relaxation (1). Detrusor myocytes from overactive human bladder have a higher T-type Ca^{2+} channel current density (2). Mibefradil is an antagonist to T-type Ca^{2+} channel ($alpha_{1G}$). We investigated that to determine whether mibefradil has an effect or not on cyclophosphamide-induced cystitis in mouse.

Study design, materials and methods

To evaluate the role of T-type calcium channel for voiding, capsaicin was injected intravesically to alpha1H T-type calcium channel ($Ca_v3.2$) lacking mice and $Ca_v3.2$ null mutation mice. Cystometry (CMG) was performed. Inter-contraction interval (ICI), pressure threshold (PT) and maximum voiding pressure (MVP) were measured. On the other hands, to evaluate the effect mibefradil, cyclophosphamide-induced cystitis mice were generated. After then, dose-response curves were constructed by administering increasing dose of mibefradil (0.1, 0.5, and 1mg/kg intraperitoneally).

Results

In $Ca_v3.2$ lacking mice, ICIs were not changed (control vs capsaicin 20μM/ml vs capsaicin 50μM/ml, 245.8±24.6 vs 250.2±21.3 vs 243.3±22.5 sec) ($p>0.05$). But in $Ca_v3.2$ null mutation mice, ICIs were significantly decreased (control vs capsaicin 20μM/ml vs capsaicin 50μM/ml; 342.1±29.02 vs 284.5±19.58 vs 241.9±16.96 sec) ($p<0.05$). In cyclophosphamide-induced cystitis model, voiding parameters were not changed after intraperitoneally injection of saline as control (71.13±15.31 sec) ($p>0.05$). Low doses of mibefradil (0.1mg/kg) did not alter any CMG parameter, whereas 0.5mg/kg and 1mg/kg dosages of mibefradil significantly increased the ICI (control vs mibefradil 0.5mg/kg 71.1±15.3 vs 124.6±24.7 and control vs mibefadil 1mg/kg 71.1±15.3 vs 175.5±30.9 sec) ($p<0.01$). But MVP and PT were not changed.

Interpretation of results

In $Ca_v3.2$ lacking mice, capsaicin had no effect on voiding. It was considered that pain signal from dorsal root ganglion was blocked in $Ca_v3.2$ lacking mice. Mibefradil (0.5mg/kg and 1mg/kg) has significantly induced increase of the ICI on cyclophosphamide-induced cystitis in mouse.

Concluding message

These results suggest that T-type calcium channel blocker might become a possible drug as treatment agent of overactive bladder.

References

1. Wang GJ, Shum AY, Chen CF (2001) Calcium Channel Blockade in Vascular Smooth Muscle Cells: Major hypotensive mechanism of S-Petasin, a Hypotensive Sesquitepene from Petasites formosanus JPET 297: 240-246
2. Sui GP, Wu C, Fry CH (2007) The association between T-type Ca2+ current and outward current in isolated human detrusor cells from stable and overactive bladders. BJU Int 99:436-441

Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Mouse **Ethics Committee:** Kyung Hee Medical Center IACUC