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 α1 subunit of low voltage-activated T-type Ca\(^{2+}\) channel, namely α1G (Ca\(^{3.1}\)), α1H (Ca\(^{3.2}\)) and α1I (Ca\(^{3.3}\)). 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 (α1G). We investigated 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 α1H T-type calcium channel (Ca\(^{3.2}\)) lacking mice and Ca\(^{3.2}\) 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 administring increasing dose of mibefradil (0.1, 0.5, and 1mg/kg intraperitoneally).

Results
In Ca\(^{3.2}\) 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\(^{3.2}\) 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 mibefradil 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\(^{3.2}\) lacking mice, capsaicin had no effect on voiding. It was considered that pain signal from dorsal root ganglion was blocked in Ca\(^{3.2}\) 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