Possible involvement of TRPM4 channels in the cholinergic contractile responses in mouse detrusor and ileal smooth muscles

Firoj Alom¹, Hayato Matsuyama², Hiroshi Nagano¹, Yasuyuki Tanahashi³, Toshihiro Unno²

¹Department of Pathogenetic Veterinary Science, United Graduate School of Veterinary Science, Gifu University, Japan, ²Laboratory of Veterinary Pharmacology, Department of Veterinary Medicine, Faculty of Applied Biological Science, Gifu University, Japan, ³Department of Animal Medical Sciences, Faculty of Life Sciences, Kyoto Sangyo University, Japan

Background: In visceral smooth muscle cells, opening of several types of cationic channels are involved in contractile responses induced by receptor activation. Recently, transient receptor potential melastatin 4 (TRPM4) channels have been suggested to mediate contractions of a certain type of smooth muscle. In the present study, we investigated effects of 9-phenanthrol, a novel, specific inhibitor of TRPM4 channels, on contractile responses induced by an electrical field stimulation (EFS) or a muscarinic agonist to explore the involvement of TRPM4 channels in cholinergic contractile responses in mouse detrusor and ileal smooth muscles.

Methods: Urinary bladder and ileal part of intestine were isolated from mice of either sex (2-11 months old), and detrusor and ileal longitudinal muscle strips were prepared for isometric tension recordings. Cholinergic contractions were recorded by application of carbachol or EFS (pulse width: 0.5 ms, strength: 50 V, frequency: 1-100 Hz) for 5 s. Alpha, beta-methylene ATP (50 micromole) was applied to bath solution (Tyrode solution) to inhibit purinergic component for the recording of detrusor contraction, and guanethidine (1 micromole) and L-NAME (100 micromole) were treated to inhibit adrenergic and nitrenergic components for the recording of ileal contraction. In some experiments, intracellularly released calcium-mediated contractions induced by carbachol (10 micromole) were recorded in the presence of calcium-free, 140 mM KCl Tyrode solution.

Results: EFS elicited a transient detrusor contraction in frequency-dependent manner, and application of atropine or tetrodotoxin abolished the transient contraction. 9-phenanthrol (3-30 micromole) significantly inhibited EFS-induced or carbachol-induced cholinergic detrusor contractions. However, 9-phenanthrol (10 micromole) had no significant inhibitory effect on the intracellularly released calcium-mediated and 70 mM KCl-induced detrusor contractions. In ileal longitudinal muscle preparations, EFS elicited a transient, atropine-sensitive contraction in frequency-dependent manner, and 9-phenanthrol (30 micromole) also significantly inhibited EFS-induced or carbachol-induced cholinergic ileal contractions without affecting 70 mM KCl-induced contraction.

Conclusion: These results suggest that muscarinic receptor activation stimulates the opening of TRPM4 channels to produce membrane depolarization and then induces muscle contraction in mouse detrusor and ileal longitudinal smooth muscles.