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EFFECT OF RASPBERRY KETONE ON DETRUSOR SMOOTH MUSCLE CONTRACTION IN RATS

Hypothesis / aims of study
Raspberry ketone (4-(4-hydroxyphenyl) butan-2-one) is a major aromatic compound of red raspberry (Rudus idaeus). The structure of raspberry ketone is similar to that of capsaicin (1). Transient receptor potential vanilloid subfamily 1 (TRPV1), which is activated by capsaicin, has an important role in afferent micturition pathway especially in pathological condition. TRPV1 desensitization by intravesical capsaicin or resiniferatoxin administration has been used for the treatment of neurogenic detrusor overactivity. Like capsaicin, raspberry ketone increased CGRP release from dorsal root ganglion neurons via TRPV1 stimulation and increased dermal insulin-like growth factor-1 production through sensory neuron activation, thereby promoting hair growth and increasing skin elasticity (2). This result suggest that raspberry ketone might influence on the function of urinary bladder via TRPV1 stimulation. The aims of this study was to investigate the effect of raspberry ketone on detrusor smooth muscle contraction in rats.
Study design, materials and methods
Female Sprague-Dawley rats weighing 230 to 290 g were used. Animals were killed by decapitation and the bladder was immediately excised. Longitudinal strips of detrusor (10mm × 2mm) were cut and placed in 10-ml organ baths containing Krebs-Ringer solution, which was gassed with 95% O_2 and 5% CO_2, and maintained at 37°C. Tissues were allowed to equilibrate for 1 hour under a resting tension of 1 g. Mechanical responses were recorded using an isometric transducer. After equilibration, strips were precontracted with 40 mM KCl. After 26 min, when the KCl-exposed strips had reached a stable tension, 3 μM - 3 mM raspberry ketone or its vehicle added cumulatively. Some strips were pretreated with adenylyl cyclase inhibitor SQ22,536 (300 μM), BK_{Ca} channel inhibitor charybdotoxin (1 μM) or TRPV1 antagonist BCTC (1 μM) before addition of raspberry ketone. In another set of experiment, strips were exposed to 10 μM carbachol at 25-min intervals. Once contractions induced by carbachol had stabilized, 0.3, 1, or 3 mM raspberry ketone or its vehicle were applied to the strips 10 min before the application of carbachol. Moreover, the effect of raspberry ketone on carbachol-induced contraction in calcium-free Krebs solution with 10 μM EGTA and 10 nM nifedipine (L-type calcium channel blocker) was also examined.
Results
10 μM - 3 mM raspberry ketone relaxed a KCl-precontracted preparation in a concentration-dependent manner with a maximum reduction of 78.5% ($p<0.01$, n=10). SQ22,536, charybdotoxin and BCTC did not cause statistically significant alterations of raspberry ketone-induced relaxation of precontracted bladder strips (n=6). Raspberry ketone at 0.3, 1, and 3 mM inhibited the cabachol-induced contraction by 4.6%, 11.5%, and 48.3%, respectivery ($p<0.01$, n=10). 0.3 and 1 mM raspberry ketone did not inhibit the carbachol-induced contraction in calcium-free Krebs solution with EGTA and nifedipine ($p=0.29$, $p=0.23$, respectively, n=9). But 3 mM raspberry ketone inhibited the carbachol-induced contraction in calcium-free Krebs solution with EGTA and nifedipine by 90.7% ($p<0.01$, n=6).
Interpretation of results
Raspberry ketone relaxed KCl-precontracted preparation. SQ22,536, charybdotoxin and BCTC had no effect on raspberry ketone-induced relaxaxion. These results indicate that detrusor smooth muscle relaxation mediated by raspberry ketone is not through the activation of adenylyl cyclase or BK_{Ca} channel and TRPV1 is not involved in this response. Raspberry ketone inhibited the contraction induced by carbachol. 0.3 and 1 mM raspberry ketone did not inhibit the carbachol-induced contraction in calcium-free Krebs solution with L-type calcium channel blocker, whereas 3 mM raspberry ketone inhibited the carbachol-induced contraction even in calcium-free Krebs solution with L-type calcium channel blocker. These results suggest that the inhibitory effect of raspberry ketone on carbachol-induced contraction is probably through the inhibition of calcium influx and the modulation of intracellular calcium movement or calcium sensitization.
Concluding message
Raspserry ketone inhibits rat detrusor muscle contraction probably through the inhibition of calcium influx and the modulation of intracellular calcium movement or calcium sensitization.

References
1. Life Sciences (2005) 77 : 194-204
2. Growth Hormone & IGF Research (2008) 18 : 335-344

Specify source of funding or grant	**None**
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	**Animal Experimentation Committee of Kagoshima University**