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THE EFFECT OF TRPM8 AGONISTS ON BLADDER AFFERENT FIRING

Hypothesis / aims of study

Patients presenting with disorders of the lower urinary tract demonstrate altered sensitivity to normal bladder filling such as pain or urgency. Understanding the interaction between the bladder urothelium and afferents may provide more information on the origin of bladder sensations in addition to identifying novel targets for therapy. Many receptors have been proposed to play a significant role in bladder mechanosensitivity. One such receptor is the Transient Receptor Potential Melastatin (TRPM) 8 channel. TRPM8 has been suggested to be a cold activated receptor involved in mediating bladder response in the ice water test. However, there is no direct evidence that TRPM8 can be functionally activated on bladder afferents. In the present investigation, we examined the effect of menthol and WS-12 on the bladder afferents of wild type (WT) and TRPM8 knockout (KO) mice. Additionally, we investigated the interaction between TRPM8 and TRPV1 agonists on baseline firing.

Study design, materials and methods

The afferent nerve firing and intravesical pressure was recorded from an isolated mouse bladder tissue. The whole pelvic region was dissected and placed in a recording chamber that was continually perfused with oxygenated (95% O2 and 5% CO2) Krebs-bicarbonate solution at 35 °C. Bladders were catheterised to allow recording of intravesical pressure both at rest and during distension. Afferent nerve fibres innervating the bladder were dissected and inserted into a suction electrode for recording. Multiunit nerve recording were performed both at baseline and during bladder distension. Experiments were performed using intra- and extraluminal application of menthol, WS-12, and capsaicin.

Results

Extraluminal administration of menthol (up to 150μM) resulted in a concentration dependent increase in both mechanosensitivity and spontaneous afferent firing in WT mice ($P<0.01$, N=6). No significant effect was observed in the KO mice Interestingly at higher concentrations of menthol (2mM) this effect was lost and a significant inhibition of afferent firing ($P<0.001$, N=6) was observed (in both the WT and KO) indicating that this was independent of TRPM8. Intraluminal infusion of menthol resulted only in an increase in mechanosensitivity ($P<0.01$, N=6) with no effect on baseline firing. Furthermore, intra- and extraluminal exposure to WS-12 (1μM) resulted in a dose-dependent increase in mechanosensitivity ($P<0.001$, N=6), with no effect on baseline firing. Intraluminal administration of capsaicin (100μM) resulted in an increase in spontaneous afferent ($P<0.01$, N=6) firing in wild-type (WT) mice. Interestingly, the response to intraluminal administration of capsaicin (100μM) in the presence of menthol was significantly attenuated ($P<0.001$, N=6). Intraluminal administration of hydrogen sulphide (300μM) resulted in a significant increase in bladder afferent firing ($P<0.01$, N=6).

Interpretation of results

Menthol causes an increase in mechanosensitivity which is mediated via TRPM8. However, mechanosensitivity is inhibited at higher concentration, through a TRPM8-independent mechanism. WS-12 exhibits a more specific effect at both high and low concentration. The afferent response to capsaicin is attenuated in the presence of menthol, suggesting a possible interaction between TRPM8 and TRPV1.

Concluding message

These data suggest that TRPM8 is expressed on bladder afferents and can be activated in the presence of menthol and WS-12. TRPM8 may also interact with other TRP channel and play a role in sensations from the bladder.

Disclosures

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