## **RESEARCH HIGHLIGHTS**

## URINARY INCONTINENCE TRPM8 INFLUENCES BLADDER FILLING

Dysfunctional afferent signalling can result in hypersensitive bladder disorders such as overactive bladder (OAB) or interstitial cystitis/bladder pain syndrome (IC/BPS). Now, new research shows that the transient receptor potential melanostatin 8 (TRPM8) receptor has an important role in bladder afferent function, and has some potential as a target of small-molecule inhibitors.

Lead author Yasuhiko Igawa explains "Effects of a TRPM8 antagonist on cystometric parameters in conscious rats and on single-unit mechanosensitive bladder afferent activities (SAAs) were recorded using a new *ex vivo* rat bladder model." This model enables co-recordings of cystometric changes and pelvic nerve activity in the *ex vivo* rat bladder.

Researchers initially used cystometry to demonstrate that intravesical L-menthol infusions resulted in significant reductions in both voided volumes and bladder capacity that were sensitive to the TRPM8 antagonist RO-00203078. The effects of TRPM8 activation on afferent nerve activity were then investigated. Intra-aortic infusion of RQ-00203078 resulted in a significant reduction in the frequency of single-unit mechanosensitive afferent activities (SAAs) in mechanosensitive C-fibres at bladder pressures of 30 mm H<sub>a</sub>O. In the same model, intravesical instillation of L-menthol resulted in a significant increase in SAA frequency, this effect was found to be sensitive to RQ-00203078, confirming that this effect is mediated by activation of TRPM8 receptors.

These findings demonstrate that TRPM8 receptors, either in the bladder or on afferent C-fibres, are activated by increases in pressure that occur during bladder filling, and that activation of TRPM8 receptors facilitates this effect. Igawa concludes "The SAA measurements suggest that TRPM8 channels, possibly located in the urinary bladder, have a facilitatory role in mechano-afferent transduction," adding, "these receptors have a modulatory role in bladder storage functions."

Igawa highlights that investigating these effects using animal models of OAB and/ or IC/BPS would be a logical next step toward the development of therapeutics that target TRPM8 receptors as a treatment of patients with these notoriously difficult-to-treat conditions.

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**Original article** Ito, H. *et al.* Functional role of the TRPM8 ion channel in the urinary bladder assessed by conscious cystometry and ex vivo measurements of single-unit mechanosensitive bladder afferent activities in the rat. *BJU Int.* doi:10.1111/bju.13225