Irritant sensing mechanisms in the bladder - novel targets for the treatment of bladder disorders

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Background: The sensory symptoms associated with overactive bladder syndrome and interstitial cystitis, including urinary urgency, frequency, and pain, are due to enhanced sensations of filling during normal bladder distension. The signalling pathways responsible for inducing and maintaining neuronal hypersensitivity of the bladder however, remain undefined. Irritant sensing mechanisms, both histaminergic and non-histaminergic, have recently been implicated as mediators of visceral and somatic pain pathologies, and may provide novel targets for the treatment of bladder disorders. The aim of this study was to determine the expression and function of irritant receptors within the bladder.

Methods: RT-PCR was performed on primary cultured urothelial cells and mucosal and detrusor layers of mouse bladders, as well as mouse lumbosacral (L5-S1) dorsal root ganglion (DRG) pairs. Retrogradely labelled bladder DRG neurons from mice were isolated and dissociated for single-cell RT-PCR and calcium imaging. Ex-vivo bladder afferent recordings determined the role of irritant receptors in bladder mechanosensitivity.

Results: RT-PCR revealed mRNA expression of histamine receptors Hrh1-3 and non-histaminergic irritant receptors TGR5, Mas-related G-Protein Coupled Receptor (Mrgpr) A3 and MrgprC11 in dissociated urothelium, bladder mucosa, and detrusor. Hrh1-3, TGR5, MrgprA3 and MrgprC11 mRNA expression was also found in lumbosacral DRG L5-S1. Hrh4 mRNA was undetected in all tissue. Single cell PCR revealed a subset of bladder innervating DRG neurons expressing Hrh1 (25%), TGR5 (12%), MrgprA3 (21%) and MrgprC11 (40%). Functionally, histamine induced calcium transients in 18% of dissociated bladder DRG neurons, which were abolished in DRG neurons from TRPV1-/− mice. Intra-bladder infusion of histamine induced pelvic afferent hypersensitivity to graded distension versus saline (p<0.01, n=6). TGR5 agonist CCDC, MrgprA3 agonist chloroquine, and MrgprC11 agonist BAM 8-22 were able to induce calcium transients in 60% of bladder neurons, with CCDC responses significantly attenuated in TRPV1-/− mice. Intra-bladder infusion of CCDC and BAM 8-22 into the bladder induced significant afferent hypersensitivity to bladder distension (p<0.001).

Conclusions: Irritant receptors are functionally present on bladder sensory structures and their activation induces calcium transients and enhances bladder mechanosensitivity. This work provides valuable insight into the action of irritant receptors in the bladder, unravelling potential novel mechanisms of pelvic pain pathology.