Adeno-associated viral vector (AAV)-mediated pharmacogenetic inhibition of lumbosacral sensory neurons alleviates visceral hypersensitivity in a mouse model of urological chronic pelvic pain syndrome (UCPPS)

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Background: Patients with UCPPS experience chronic pelvic pain (CPP) and overactive lower urinary tract symptoms (LUTS). The UCPPS symptoms are closely associated with nociceptive sensitization in the nervous system, which contributes to visceral hypersensitivity. Previous studies suggested that increased excitability of lumbosacral sensory neurons innervating pelvic organs plays an important role in the generation and maintenance of UCPPS symptoms, especially of bladder pain and urinary urgency. In this study, we tested the hypothesis whether inhibition of lumbosacral sensory neurons alleviate pelvic hypersensitivity and overactive LUTS in a mouse model of UCPPS.

Methods: To silence neuronal activity *in vivo*, Gi-coupled DREADDs (designer receptor exclusively activated by a designer drug, hM4Di) were expressed in lumbosacral sensory neurons via targeted AAV intrathecal injections. Transgenic mice expressing *Cre*-recombinase and fluorescent reporters in sensory neurons and afferent nerves were used to guide cellular expression of DREADDs, as well as to track potential nerve remodeling *via* neuroimaging. Intravesical instillation of $VEGF_A$ was used to induce bladder hypersensitivity and LUTS. Detrusor contractility recordings using isolated bladder strips were used to evaluate neuronal control of bladder functions. Spontaneous voiding spot assay, awake cystometry, and Von Frey filament testing were used to assess pelvic sensitivity and voiding function *in vivo*.

Results: Intravesical instillation of $VEGF_A$ induced sensory nerve remodeling in the bladder, visceral hypersensitivity, and increased responses to sensory nerve-mediated contractility of the detrusor in mice. The $VEGF_A$-induced symptoms were likely due to increased VEGF receptor 1 signaling in peripheral nerve terminals in the bladder wall, and subsequent up-regulation of bladder nociceptors. Pharmacogenetic inhibition of lumbosacral sensory pathways with Gi-DREADDs effectively reversed $VEGF_A$-induced pelvic hypersensitivity in mice. Awake cystometry revealed decreased number of non-voiding contractions in mice when their lumbosacral sensory afferent activity was inhibited.

Conclusions: Our data suggests that decreasing afferent neuronal excitability *in vivo* can serve as a potential therapeutic strategy for treating the symptoms of UCPPS in an animal model of upregulated VEGF signaling in the urinary bladder.

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