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THERAPEUTIC EFFECTS OF TRPV1TARGETING GENE THERAPY ON BLADDER OVERACTIVITY AND NOCICEPTION IN A RAT MODEL OF EXPERIMENTAL COLITIS

Hypothesis / aims of study

Pelvic organ neural cross-sensitization has been reported to be involved in overlapped pain symptoms in chronic pelvic pain syndrome (CPPS) including bladder pain syndrome/interstitial cystitis (BPS/IC) and irritable bowel syndrome (IBS). It has been reported that rats with experimental colitis exhibit enhanced bladder pain sensitivity [1,2]. Previous studies reported that transient receptor potential vanilloid-1 (TRPV1) receptors greatly contribute to the colon-to-bladder cross sensitization following colitis [1,2,3]. It has also previously shown that herpes simplex virus (HSV) vector-mediated gene delivery of poreless TRPV1, in which the segment in C terminus of TRPV1 receptor is deleted to suppress TRPV1 activation, or protein phosphate 1α (PP1α), which negatively modulates TRPV1 activation, had a therapeutic effect on TRPV1-mediated bladder overactivity and pain behavior in chronic cystitis rats. In the present study, we investigated the effect of gene therapy with HSV vectors encoding poreless TRPV1 or PP1α using a rat model of experimental colitis.

Study design, materials and methods

Replication-deficient HSV vectors encoding green fluorescent protein (GFP), poreless TRPV1 or PP1α were injected into the bladder wall of adult female Sprague-Dawley (SD) rats. One week later, following 24-hour-fasting, 2,4,6-Trinitrobenzenesulfonic acid (TNBS) (50mg/ml in 50% ethanol) or 50 % ethanol (vehicle) were administered into the distal colon through the anus (total volume 0.4ml each). Two weeks after viral injection, awake cystometry (CMG) was performed, nociceptive behavior such as licking (urethral pain) and freezing (bladder pain) induced by intravesical instillation of resiniferatoxin (RTX; 3μM for 1 min) was observed.

Results

GFP expression was seen in L6/S1 DRG and in the bladder after HSV-GFP vector injection into the bladder wall. In CMG, the GFP + TNBS (GFP/TNBS) group showed a significant decrease in intercontraction intervals (ICIs) compared to the GFP + ethanol (GFP/EtOH) group ($p<0.01$). Then, the reduced ICIs in the GFP/TNBS group were significantly prolonged by 43.6% and 49.0% in poreless TRPV1 + TNBS (PL/TNBS) and PP1α + TNBS (PP1α/TNBS) groups ($p<0.01$), respectively (Figure 1). The number of freezing behavior was significantly higher in GFP/TNBS group compared to GFP/EtOH group ($p<0.01$). It was then significantly reduced in both PL/TNBS and PP1α/TNBS groups by 87.3% and 87.2%, respectively, compared to the GFP/TNBS group (Figure 2). In contrast, the number of licking behavior was not significantly different among these four groups.

Interpretation of results

Rats with TNBS-induced colitis exhibited bladder overactivity shown by reduced ICIs, which was ameliorated in colitis rats treated with HSV-poreless TRV1 or PP1α vectors. Freezing behavior representing bladder pain was significantly increased in TNBS colitis rats, which was significantly reduced by both poreless TRPV1 and PP1α vector treatments. These results indicate that experimental colitis induced by TNBS demonstrated both bladder overactivity and bladder pain symptoms, and those symptoms were significantly reduced by HSV vectors-mediated gene delivery of poreless TRPV1 or PP1α. The results of the present study also suggest that the activation of TRPV1 receptors in the bladder could be an underlying mechanism of bladder overactivity and enhanced bladder pain sensitivity, which are induced by colon-to-bladder cross organ sensitization in CPPS.

Concluding message

HSV-mediated TRPV1-targeting gene therapy could be a novel and effective modality for the treatment of bladder pain and urinary frequency symptoms in CPPS patients who have overlapped symptoms of IC/BPS and IBS.

Figure 1: Intercontraction intervals in CMG

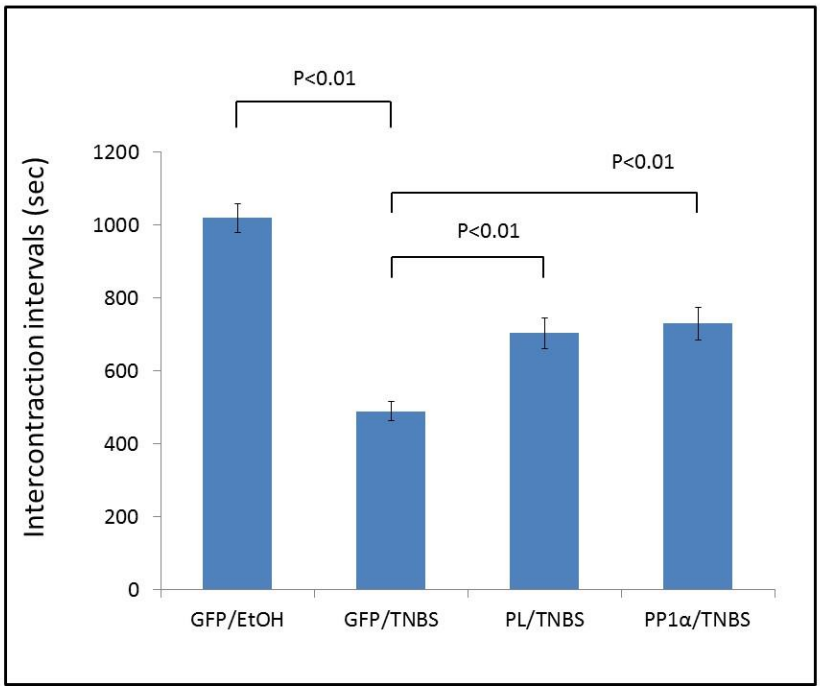
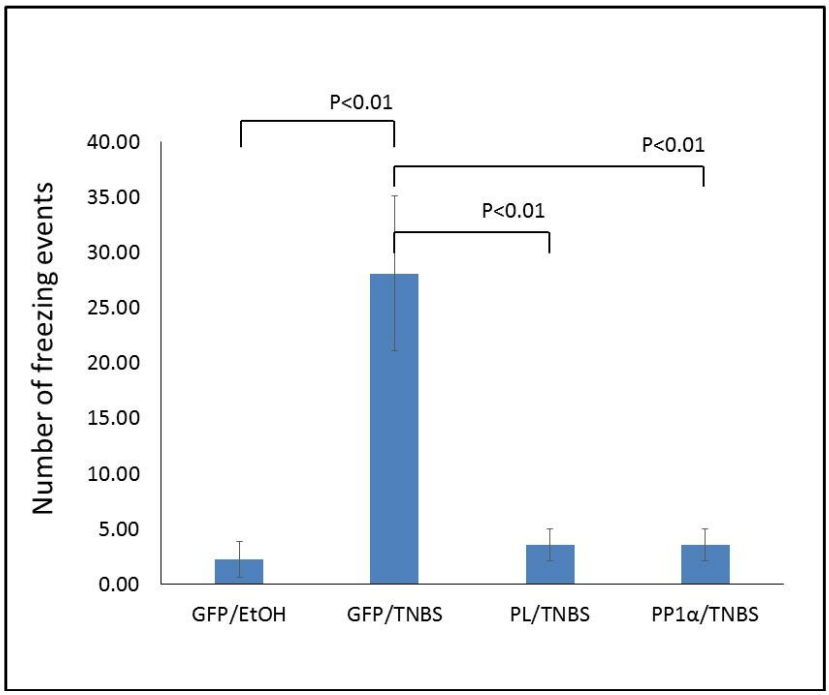


Figure 2: Freezing behavior in pain assessment



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Disclosures
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