

ACTIVATION OF TRANSCRIPTION FACTOR CAMP RESPONSE ELEMENT-BINDING PROTEIN (CREB) SIGNALLING IN AFFERENT PATHWAYS UNDERLIES NEUROGENIC BLADDER DYSFUNCTION AND CHRONIC PELVIC PAIN IN IC/BPS.

Hypothesis / aims of study

Chronic pelvic pain is a common symptom of many functional pelvic disorders including interstitial cystitis/bladder pain syndrome (IC/BPS). Recent studies suggest that bladder pain in IC/BPS could result from long-lasting sensitization in neural pathways induced by pathophysiological changes in neighbouring pelvic organs. Our previous work established that transient colitis triggers the development of a neurogenic bladder and chronic pelvic pain via release of pro-inflammatory neuropeptides such as calcitonin gene-related neuropeptide (CGRP) in the urinary bladder. CGRP gene expression is controlled by a transcription factor cAMP response element-binding protein (CREB), a critical modulator of neuronal plasticity. The goal of this work was to clarify the role of CREB in cross-sensitization in the pelvis and associated bladder pain.

Study design, materials and methods

Male Sprague-Dawley rats (N=16) were used for this study. Sensitization of neural pathways in the pelvis and neurogenic bladder dysfunction was induced by a single intracolonic instillation of 2,4,6-trinitrobenzene sulfonic acid (TNBS). Animals were sacrificed during acute (3 days post-TNBS) and recovery (30 days post-TNBS) stages. Lumbosacral (LS, L6-S2 levels) spinal cord and sensory dorsal root ganglia (DRG) were removed from control and experimental animals. Expression of CGRP, CREB, p-CREB and c-fos, a marker of neuronal activation, was assessed by immunohistochemical (IHC) staining and by Western blotting. Retrograde labeling technique was used to identify bladder-projecting DRG neurons.

Results

The results of IHC staining provide evidence that transient TNBS-induced colitis up-regulated expression of CREB in the dorsal horn of the spinal cord and nuclei of LS DRG neurons starting from 30 min and reaching maximal response at 1 and 2 h post-TNBS. Western blotting with antibodies against p-CREB (at S133) was performed on nuclear protein extracts and showed 20% increase in phosphorylation of CREB in LS DRG neurons at 1h and 2 h post-TNBS (N=6, $p \leq 0.05$ to control). IHC staining of the LS spinal cord identified the presence of p-CREB positive cells predominantly in the nuclei of the neurons located in the dorsal horn confirming their activation by nociceptive signalling. Staining of DRG sections containing retrogradely labelled bladder DRG neurons with p-CREB confirmed that CREB was activated by transient colitis in 40% of bladder afferent cell bodies (N=5, $p \leq 0.05$ to control).

Interpretation of results.

Our data suggest that activation of CREB signalling in bladder sensory and spinal neurons by noxious peripheral stimulation is important in programming the molecular changes underlying bladder discomfort and pain in neurogenic IC/BPS.

Concluding message.

Identification of the cellular and molecular mechanisms responsible for the functional interplay between the nervous and urological systems provides a scientific basis for the advancement of novel pharmacological therapies for the treatment of IC/BPS and chronic pelvic pain.

Disclosures

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