MP38-14

CONSTIPATION INDUCES OVERACTIVE BLADDER THROUGH ALTERATIONS OF NICOTINIC AND PURINERGIC PATHWAYS IN MOUSE BLADDERS

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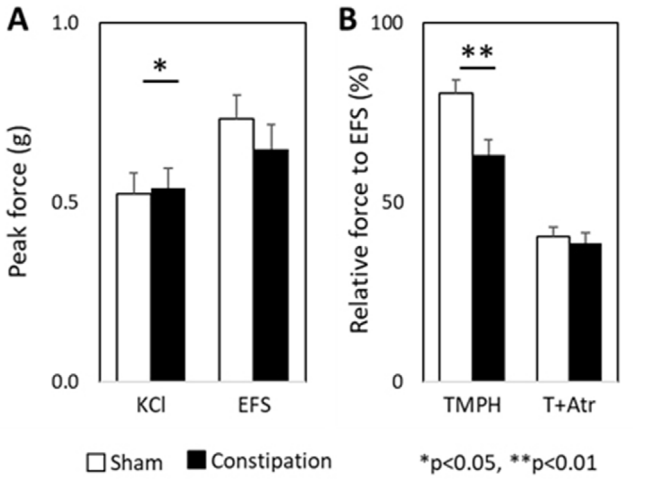
INTRODUCTION AND OBJECTIVES: It has been reported that lower urinary tract symptoms are more frequent in children with constipation and encopresis. The presence of inflammation and muscular hypertrophy in bladders in constipated children has also been reported. Although the impact of constipation on voiding function is undisputable, the etiology remains to be elucidated. We hypothesized that constipation would lead to a change in bladder function through neuronal cross talk.

METHODS: Male mice (C57BL/6J, 4-week old) underwent surgery to reduce external anal sphincter opening to induce constipation. Sham operated mice served as control. Bladder function was examined in vitro by physiological tests to evaluate detrusor contractility and baseline activity at 4 days post-op. Bladders were also subjected to histological and gene expression studies.

RESULTS: Detrusor contractility using bladder strips showed no difference in response to high potassium (KCl) and electrical field stimulation (EFS) (Fig A). Preincubation with a nicotinic receptor inhibitor, TMPH caused significantly larger decrease in EFS-evoked contractility in constipation group than in control (63 ± 4 vs. 80 ± 4 %, $p<0.01$, response to EFS without drugs taken as 100%), while no difference was observed with preincubation with a muscarinic receptor blocker, atropine, in addition to TMPH (T+Atr) (Fig B). This result suggests that constipation caused an enhanced excitatory effect of nicotinic receptor, and alteration of purinergic contribution on detrusor contractility. Calcium imaging with urothelium/mucosa-denuded detrusor strips showed a significant increase in spontaneous excitation of muscle in constipation group compared to control (frequency of 7 ± 2 vs. 3 ± 1/min, and amplitude of 0.8 ± 0.2 vs. 0.4 ± 0.2 F/F0), explaining the detrusor overactivity observed in micturition patterns evaluated by void spot assays in our previous study. Quantitative PCR demonstrated significant changes in expression levels of both nicotinic and purinergic receptors in bladders following constipation, consistent with the physiological phenotypes detected in bladders from constipation mice.

CONCLUSIONS: Our results indicate that acute phase of constipation caused detrusor overactivity through alteration of nicotinic and purinergic pathways in bladders.



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MP38-15

DIFFERENTIAL PROTEIN EXPRESSION IN PATIENTS WITH UCPPS: A MAPP STUDY

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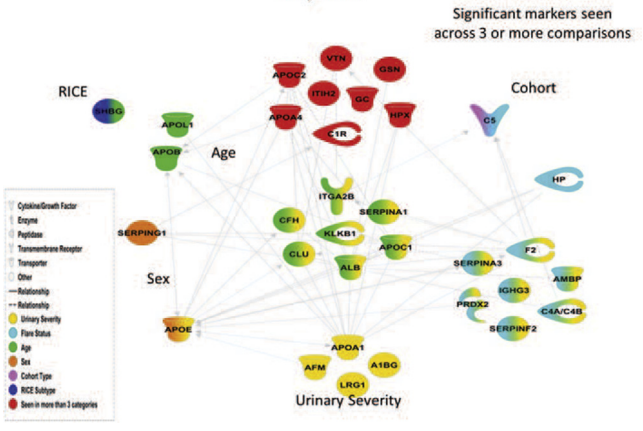
INTRODUCTION AND OBJECTIVES: Urologic chronic pelvic pain syndrome (UCPPS) encompasses both interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. A lack of understanding of the molecular mechanisms underlying UCPPS has been a challenge and dilemma for diagnosis and treatment leading to a delay in basic and translational research focused on biomarker and drug discovery, clinical therapy, and preventive strategies. Hoping to identify a specific diagnostic signature of UCPPS, our hypothesis is that UCPPS is associated with specific protein patterns in the blood.

METHODS: We collected serum samples from 400 patients who participated in the MAPP network. We applied multiple reaction monitoring mass spectrometry (MRM-MS) methods for 72 pre-selected targeted proteins that are involved in many diseases and inflammatory processes. The largest categories of study were control vs UCPPS. We also matched patients by pain severity, gender, pelvic pain vs. pelvic pain and beyond (widespread pain). These were processed and analyzed.

RESULTS: Proteins had significant differential expression across five categories, including age, sex, cohort (control vs. UCPPS), and urinary severity. One protein, sex hormone binding globulin, was differentially expressed in Rand Interstitial Cystitis Epidemiology (RICE) subtypes, specifically pain with bladder filling. We also identified interactions between proteins and their overlap across comparison groups (Figure 1). Many markers had overlap between, for example, urinary severity and the presence of UCPPS (vs. control). Some markers were seen across three or more comparisons.

CONCLUSIONS: Although validation studies are needed and underway, the targeted analysis of 72 proteins, which are involved in multiple pathways including inflammation, appears to distinguish patients with UCPPS vs. controls. Depending on the peptide it also distinguishes between sex, age, and urinary severity. Understanding the signaling networks perturbed in UCPPS will open new avenues to the identification of novel biomarkers and, equally important, drug targets.

Figure 1. Network showing interaction between proteins and their overlap across comparisons



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