

POSTER SESSION I ABSTRACTS

Poster #20

CHRONIC ORAL ADMINISTRATION OF THE GUANYLATE CYCLASE-C AGONIST LINALOTIDE ATTENUATES COLITIS INDUCED BLADDER AFFERENT HYPERACTIVITY

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Objective: A significant proportion of IBS patients also suffer from urological symptoms characteristic of overactive bladder syndrome and interstitial cystitis/bladder pain syndrome (IC/BPS). Rodents with active colitis exhibit bladder afferent sensitisation and altered cystometry. However, it remains to be determined if bladder overactivity persists following the resolution of colitis, in a model of chronic colonic hypersensitivity (CCH), or if reducing colonic nociception is able to alter bladder overactivity. Linaclotide, an FDA-approved guanylate cyclase-C (GC-C) agonist, reduces abdominal pain in IBS patients with constipation. In preclinical studies in vivo linaclotide administration reverses colonic mechanical hypersensitivity in CCH mice and reduces noxious signalling to the spinal cord. We hypothesized that oral linaclotide administration may also reduce bladder hypersensitivity.

Methods: We investigated healthy C57BL/6J mice and mice with CCH, 28 days after intra-colonic TNBS administration. CCH mice were randomly assigned to either chronic linaclotide (3µg/kg/day) or placebo (water) administration, consisting of a once daily oral gavage for 2 weeks prior to experimentation. In all four groups, whole cell patch clamp recordings from bladder retrogradely traced dorsal root ganglion (DRG) neurons determined neuronal excitability. Ex-vivo electrophysiological recordings determined bladder afferent and contractile sensitivity to ramp distension as well as muscarinic, purinergic and TRPV1 channel agonists. Micturition pattern analysis was performed by analysing in-vivo natural voiding behaviour. In situ hybridisation and qPCR determined GC-C expression in bladder and colon.

Results: Bladder innervating DRG neurons from CCH mice displayed significant hyperexcitability ($P < 0.01$). Bladder afferent responses to ramp distension ($P < 0.001$) and exogenous agonists ($P < 0.01$) were significantly increased in CCH mice, with no changes in muscle compliance or contraction responses evident. CCH mice also exhibited significant changes in bladder voiding frequency ($P < 0.01$). CCH mice treated with linaclotide displayed attenuated bladder DRG neuronal excitability ($P < 0.01$) with attenuated bladder afferent responses to distension ($P < 0.001$) compared with placebo. Chronic linaclotide treatment also restored natural bladder voiding behaviour ($p < 0.05$). The GC-C receptor is absent within the bladder, and, as expected, infusion of linaclotide into the bladder has no effect on bladder afferent mechanosensitivity.

Conclusion: Mice with CCH also demonstrate bladder afferent hypersensitivity and display abnormal bladder voiding behaviour, which is an example of viscerovisceral cross talk. Chronic oral administration of linaclotide, a gut-restricted GC-C agonist that inhibits colonic nociceptors, reverses these colitis-induced changes in bladder function and sensitivity. Our study suggests agents that reduce abdominal pain may be able to improve urological symptoms through common sensory innervation pathways.

Poster #21

EFFECT OF URINARY PH ON SYMPTOMS OF INTERSTITIAL CYSTITIS.

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Presented By: Shobha Sridhar, BS

Objective: Interstitial cystitis (IC) is a condition that is chronic and often debilitating in nature [1]. A common belief is that acidic food, exacerbates symptoms of IC; urine alkalization is proposed as treatment for IC [2] However, a double-blinded randomized cross-over study by Nguan et al showed no change in pain of IC patients from baseline after instillation of alkaline fluid [3,4]. A recent pilot study by Rosemary Catanzaro evaluating influence of diet on IC symptoms suggested a correlation between alkalinity of urine and increased symptoms of IC. Given these conflicting findings, this pilot study sets out to more closely examine the effect of urine pH on various IC symptoms.

Methods: Participants were recruited from the SLUCare OB/GYN urogynecology division. All participants have been clinically diagnosed with interstitial cystitis and have a O'Leary-Sant Pain Symptom and Problem Index questionnaire score ≥ 12 . Participants kept a 3-day voiding log, recording urine volume, pH, and specific gravity along with the type and severity of pain. Patients were asked to report on the presence of urgency, burning, bladder spasm, urethral spasm, and pressure with each void. A total of 12 patients, with a 260 voids total, completed the data sets and are included in this analysis.

Differences in individual and composite number of urinary symptoms by urinary pH were evaluated using chi-square, Kruskal-Wallis, and Mann-Whitney U tests. Differences in urinary pH between women having an individual urinary symptom and women not having the symptom were evaluated with the Mann-Whitney U test. Spearman's correlation was performed between the composite number of urinary symptoms and urinary pH. A p -value < 0.05 denoted significance.

Results: Of the 260 voids, 194 (74.6%) were acidic ($pH < 7$), 35 (13.5%) were neutral ($pH = 7$), and 31 (11.9%) were basic ($pH > 7$). A significantly higher proportion of neutral and basic voids had urgency ($p < 0.05$), burning ($p < 0.01$), and bladder spasm ($p < 0.001$) than acidic voids. Significantly higher urinary pH was found in women with urgency, burning, bladder spasm, and pressure than in women not having those symptoms. When categories represented acidic versus a range of neutral pH (< 6.5 , $> 6.5 - < 7.5$), a higher proportion of the range of neutral pH voids had burning ($p < 0.001$) and bladder spasm ($p < 0.001$) than acidic voids. When the analyses were restricted only to acidic voids (< 6.0 , $> 6.0 - < 7.0$), a significantly higher proportion of weaker acidic voids had burning ($p < 0.001$) than more strongly acidic voids. There was no statistically significant association between urinary pH and the urinary symptom of urethral spasm. A significant correlation was found between the composite number of urinary symptoms and urinary pH ($.246$, $p < 0.001$).

Conclusion: Individual and composite urinary symptoms are highly correlated with alkaline urinary pH in Interstitial Cystitis. In women diagnosed with IC, the symptoms of urgency, burning, and bladder spasm occur more often in urine with neutral or alkaline pH when compared to acidic pH. These findings challenge the putative benefits of alkalization of urine as a treatment of IC.