



(324) Bladder hypersensitivity and transcriptional regulation of potassium channel subunit mRNA expression in mice with cystitis

J DeBerry, K Albers, and B Davis; University of Pittsburgh, Pittsburgh, PA

Hyperexcitability in bladder primary afferents contributes to bladder overactivity and pain in pathological urological conditions. Target-derived growth factors can alter primary afferent expression of membrane-bound ion channels that regulate neuronal excitability, such as voltage-gated potassium (Kv) channels. Several Kv channels are expressed in primary afferent neurons and contain a binding site for repressor element-1-silencing transcription factor (REST). Growth factor-mediated, REST-induced, long-lasting downregulation of Kv channels may provide a mechanism through which persistent changes in bladder afferent sensitivity can occur. In the present study we used a model of cyclophosphamide (CYP)-induced cystitis to examine interactions between bladder-derived growth factors and REST-mediated regulation of Kv channel expression in lumbosacral (LS) bladder afferents. C57Bl/6 mice were administered CYP (100 mg/kg, i.p.) or vehicle every other day for five days. Visceromotor responses (VMR) to bladder distension, real-time PCR, and single cell PCR were used to examine nociception, bladder growth factor mRNA, and REST/Kv channel mRNA in LS bladder afferents, respectively. A significant increase in VMRs following CYP treatment was paralleled by increases in bladder growth factors (nerve growth factor (NGF), artemin (ARTN), and glial cell line-derived growth factor (GDNF)) and LS afferent expression of REST. These increases occurred in conjunction with a decrease in bladder afferent expression of Kv4.3 and Kv7.3. These results suggest that CYP-induced hypersensitivity may involve growth factor-mediated sensitization of primary afferents, at least in part via changes in Kv regulation of neuronal excitability as a result of transcriptional regulation by REST. Further preliminary data show that administration of the growth factor-sequestering antibody, anti-ARTN, can prevent behavioral sensitization following CYP. Ongoing studies will use additional sequestering antibodies to determine whether they also block changes in afferent expression of Kv4.3, Kv7.3, and REST and result in suppression of neuronal hyperexcitability, as well as examine similar changes in thoracolumbar bladder afferents.

(325) T13/L6 spinal nerve stimulation does not modify bladder-evoked visceromotor responses in rats

X Su, J Lynch Hill, A Randich, D Nelson, and T Ness; University of Alabama at Birmingham, Birmingham, AL

Urgency/frequency and pain are major sensations from the urinary bladder in interstitial cystitis (IC) patients. We have previously demonstrated an inhibitory effect of spinal nerve stimulation (SNS) on micturition reflexes.¹ The objective of this project was to investigate the effect of T13 or L6 SNS on visceromotor reflex (VMR) responses to urinary bladder distension (UBD) in rat models of bladder hypersensitivity produced by early-in-life (EIL) intravesical zymosan treatments, adult intravesical zymosan treatments or footshock-induced stress. All of these pretreatment groups have demonstrated bladder nociceptive hypersensitivity (increased VMRs to UBD), some with overactive bladder phenotype of increased frequency on cystometric testing and others with decreased frequency on cystometric testing.²⁻⁴ In urethane-anesthetized rats, monopolar stimulating electrodes were placed in T13/L1 or L6/S1 neuroforamina alongside the T13 or L6 spinal nerves bilaterally. Myoelectrical activity of abdominal muscles (external oblique) was quantified as rectified electromyograms. Neither T13 nor L6 SNS produced inhibitory effects on the VMRs to UBD at a wide range of frequencies tested (10 Hz, 50 Hz, and 100 Hz, $p > 0.01$, Two-way ANOVA) in any of the pretreatment groups. The present findings demonstrate a differential modulation of SNS on urgency/frequency and pain sensation. The pain sensation from urinary bladder seems insensitive to SNS, however may be improved indirectly by improvement of urodynamic functions. (1. Su X et al. *Am J. Physiol. Renal Physiol.* 302: F477-86, 2011; 2. DeBerry J et al. *J Pain*, 11: 247-255, 2010; 3. DeBerry J et al. *J Pain*, 8: 914-923, 2007; 4. Robbins MT and Ness TJ. *J. Pain* 9: 991-998, 2008.) Supported by a grant from Medtronic, Inc.

E28 Other

(326) Autonomic symptom profile and fibromyalgia

A Vincent, S McAllister, T Oh, and M Whipple; Mayo Clinic, Rochester, MN

Autonomic dysregulation is thought to play a role in the pathophysiology and symptoms of fibromyalgia (FM). The Autonomic Symptom Profile (ASP) is a validated self-report measure that comprehensively assesses autonomic symptoms in various domains namely - orthostatic intolerance, syncope, sexual dysfunction, bladder dysfunction, diarrhea, constipation, gastroparesis, secretomotor dysfunction, sleep dysfunction, vasomotor, and pupillomotor. The purpose of this study was to assess self-reported autonomic symptoms in patients with FM utilizing the ASP. Eight hundred fifty-eight of 1303 (66% response rate) randomly selected patients with FM who presented to a tertiary medical center between 1/1/2001 and 11/30/2011 completed the ASP and the Fibromyalgia Impact Questionnaire (FIQ-R). Association between ASP and FIQ-R were assessed using Pearson correlation and multivariate regression analysis. Though there were statistically significant ($p < .0001$) correlations between the FIQ-R-symptom subscale and 10 of the 11 autonomic symptom domains, only 9 of those remained significant in the multiple regression model (sleep $\beta = 1.33$, $p < 0.0001$; pupillomotor $\beta = .83$, $p < .0001$; bladder $\beta = .83$, $p < .0001$; constipation $\beta = .83$, $p < .0001$; diarrhea $\beta = .83$, $p < .0001$; gastroparesis $\beta = .83$, $p < .0001$; secretomotor $\beta = .83$, $p < .0001$; vasomotor $\beta = .83$, $p < .0001$; syncope $\beta = .33$, $p < .0001$). Our results indicate patients with FM report symptoms attributable to multiple autonomic domains. This is consistent with clinical observations and published literature where patients with FM report symptoms of heat intolerance, changes in sweating, dry eyes and mouth, difficulty focusing, photophobia, light sensitivity and visual blurring, bladder and bowel symptoms and sleep difficulties. Work is underway to corroborate self-report symptoms with objective physiologic autonomic measures. (Low, *Diabetes Care*, 2004; Suarez, *Neurology*, 1999.)

(327) NKTR-171: A novel, oral, sodium channel blocker that exhibits comparable analgesic efficacy to pregabalin with reduced Central Nervous System (CNS) side effects

H Gursahani, K Gogas, B Deng, G Kim, I Choi, J Evans, P Quach, M Guillon, R Jaladi, W Rubas, J Riggs-Sauthier, S Harrison, and S Doberstein; Nektar Therapeutics, San Francisco, CA

Sodium Channel (Nav) blockers provide a differentiated mechanism of action in the pharmacotherapy of neuropathic pain, but their use is currently limited by narrow therapeutic indices with respect to CNS side effects, and for some agents, their cardiovascular side effects. Nektar Therapeutics' technology has been applied to regulate CNS entry of a Nav-inhibitor pharmacophore with validated clinical efficacy and low cardiovascular liability. The in vitro pharmacology of NKTR-171 was characterized against recombinant human Navs and in native rat dorsal root ganglion cells, where NKTR-171 produces a state-dependent block. The analgesic efficacy of NKTR-171 was measured in rat models of persistent pain and neuropathic pain. In the rat formalin and Spinal Nerve Ligation models, acute oral administration of NKTR-171 (30-450 mg/kg) produces dose-dependent analgesic effects, with a maximal efficacy comparable to that of a 100 mg/kg oral dose of pregabalin in both models. However, NKTR-171 exhibited a favorable therapeutic window with respect to CNS side effects. The time spent on a rotarod was not impaired by a dose of NKTR-171 (200 mg/kg p.o.) that was maximally efficacious in the rat formalin model, whereas an equianalgesic dose of pregabalin (100 mg/kg p.o.) reduced the time spent on the rotarod to 30% of baseline values. Pharmacokinetic studies in rats show NKTR-171 to have a low brain:plasma ratio, compared to clinically used Nav blockers. The results of these preclinical studies show that NKTR-171 is a novel Nav blocker that demonstrates comparable analgesic efficacy to pregabalin with reduced CNS side effects. Disclosure: Authors are employees of Nektar Therapeutics.