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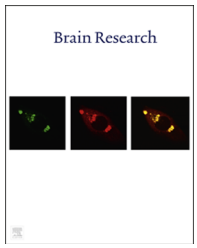

Research Report

The amygdala central nucleus is required for acute stress-induced bladder hyperalgesia in a rat visceral pain model

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ABSTRACT

Chronic stress has been implicated in the pathogenesis of chronic visceral pain conditions, such as interstitial cystitis (IC), and bouts of acute stress exacerbate clinical urological pain. Studies using animal models have shown that exposure to chronic footshock stress augments reflex responses to urinary bladder distension (UBD) in animal models, however acute effects in animal models are largely unknown, as are the central nervous system mechanisms of stress-related increases in nociception. The amygdala is a salient structure for integration of sensory and cognitive/emotional factors. The present study determined the role of the central nucleus of the amygdala (CeA) in stress-related bladder hypersensitivity. We examined the effects of CeA manipulations (lesions and chemical stimulation) on visceromotor responses (abdominal muscle contractions) to UBD in adult, female Sprague-Dawley rats. We report that acute footshock stress produces bladder hyperalgesia that can be prevented by bilateral CeA lesions, despite no effect of lesions on baseline somatic sensation, as indicated by flinch/jump thresholds to electrical shock. Further, acute glucocorticoid stimulation of the CeA recapitulated stress-induced hyperalgesia. Of note is that CeA lesions, but not chemical stimulation, significantly affected HPA axis activation, as indicated by measurements of circulating corticosterone. Our findings conclusively show that the CeA is necessary for the generation of bladder hyperalgesia in response to acute stress. The CeA may play multiple stress-related roles in nociceptive modulation, i.e., via direct facilitation of the HPA axis during acute stress, or via modulation of other systems that augment acute stress responsiveness.

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1. Introduction

Chronic bladder/pelvic pain associated with interstitial cystitis (IC) affects 3–8 million women in the United States (Berry et al., 2011). There is no single identified etiology of IC, although a prominent role for stress in its pathophysiology and presentation has been documented. Flares in bladder-related symptoms correlate with exposure to a laboratory stressor (Lutgendorf et al., 2000) and increased daily life stress (Rothrock et al., 2001). Those with a diagnosis of IC have a higher lifetime prevalence of panic disorder than healthy controls (Weissman et al., 2004), and patients with panic disorder are five times more likely than healthy controls to report IC symptoms (Talati et al., 2008).

We have previously shown that exposure to chronic footshock stress augments bladder nociceptive reflexes (Robbins and Ness, 2008), and both chronic and acute footshock alter spinal neuronal responses to noxious bladder stimulation and activate the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis (Robbins et al., 2011). Peripheral and spinal nociceptive mechanisms are required for enhanced pain during periods of stress or following exposure to an aversive event; however, the transformation of individual emotional states or cognitive factors into modulation of peripheral afferent input requires cortical function. The amygdala is a limbic forebrain structure integral to both stress responsiveness and nociceptive processing (LeDoux, 2007). Clinical studies have reported that individuals with IC exhibit elevated autonomic nervous system activity (Lutgendorf et al., 2004), hypothalamic pituitary adrenal (HPA) axis dysregulation (Dimitrakov et al., 2001; Lutgendorf et al., 2002), and exaggerated startle responses to a visceral threat (Twiss et al., 2009), all of which may be influenced by amygdala activity.

The amygdala central nucleus (CeA) densely expresses glucocorticoid receptors (Reul and de Kloet, 1985), which bind the endogenous ligand cortisol (in humans) and its rodent analog, corticosterone. In rats, direct administration of corticosterone to the CeA via a sustained-release micropellet augments HPA axis responses to stress (Shepard et al., 2003), increases indices of anxiety (Shepard et al., 2000), and enhances nociceptive reflexes (Greenwood-Van Meerveld et al., 2001) and neuronal responses (Qin et al., 2003b) to colorectal distension.

In this study, experimental manipulations involving the CeA were performed to examine its contribution bladder pain produced by acute footshock stress. Our results indicate that the CeA is required for the expression of acute footshock-induced bladder hyperalgesia, and that acute CeA activation is sufficient to drive bladder hyperalgesia in the absence of footshock. Given newly evolving clinical therapeutic options involving non-invasive modulation of deep brain structures, these results have implications for the management of stress-related flares in bladder pain.

2. Results

2.1. Acute footshock stress produces bladder hyperalgesia

We have previously shown that acute footshock exposure induces a significant increase in blood plasma corticosterone concentration (Robbins et al., 2011), indicative of HPA axis activation. In the current study, we assessed fecal pellet output during acute footshock exposure as an additional measure of stress responsiveness (Tache et al., 2004). Compared to rats in the no footshock (NFS) condition, those exposed to footshock (FS) had increased fecal pellet output (0.00 ± 0.0 versus 6.14 ± 0.4, respectively; $p < 0.001$; $N = 7$/group).

Abdominal EMG responses to graded bladder distension were quantified to determine whether acute footshock, like chronic footshock exposure, facilitates bladder nociceptive processing (Robbins et al., 2007). A repeated-measures ANOVA revealed significant effects of footshock ($p < 0.01$) and distension pressure ($p < 0.01$), and a significant interaction between these variables ($p < 0.01$). Post-hoc comparisons indicated significantly greater abdominal EMG responses to

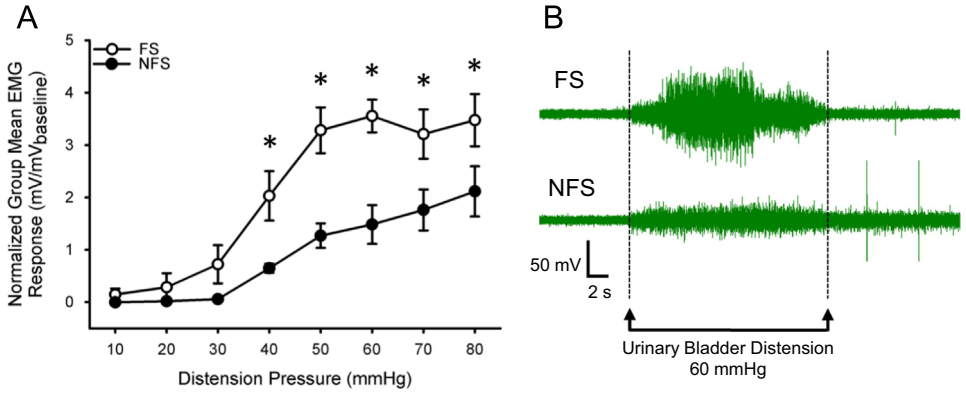

Fig. 1 – Acute footshock stress produces bladder hyperalgesia. (A) Abdominal EMG responses to graded UBD (10–80 mmHg) were quantified following acute exposure (1 mA, 1 s, 30 shocks in 15 min) to footshock (FS) or no footshock (NFS) after six accommodation sessions. Data are presented as group mean normalized responses; $N = 7$/group. A repeated-measures ANOVA revealed significant effects of footshock ($p < 0.01$) and distension pressure ($p < 0.01$), and a significant interaction between these variables ($p < 0.01$). * Indicates $p < 0.05$ acute footshock > no footshock at noxious distension pressures. (B) Raw EMG responses to bladder distension (60 mmHg; 20 s) are shown for a rat exposed to footshock (FS; *upper trace*) and a rat in the no footshock condition (NFS; *lower trace*).