BRAIN RESEARCH 1386 (2011) 118–126

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BRAIN RESEARCH

Research Report

Footshock stress differentially affects responses of two subpopulations of spinal dorsal horn neurons to urinary bladder distension in rats

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ARTICLE INFO

Article history:
Accepted 24 February 2011
Available online 2 March 2011

Keywords:
Visceral
Urinary bladder
Cystitis
Stress
Spinal

ABSTRACT

This investigation examined the effect of footshock on responses of 283 spinal dorsal horn neurons (DHNs) to urinary bladder distension (UBD). Female rats were treated with seven daily sessions of footshock (chronic footshock, CFS), six accommodation sessions followed by one exposure to footshock (acute footshock, AFS) or handled similarly without receiving any footshock (no footshock, NFS). After the final footshock or NFS session, rats were anesthetized, a laminectomy performed and extracellular single-unit recordings of L6–S1 DHNs obtained in intact or spinalized preparations. Neurons were classified as Type I—inhibited by heterotopic noxious conditioning stimuli (HNCS) or as Type II—not inhibited by HNCS—and characterized for spontaneous activity and for neuronal discharges evoked by graded UBD. A differential effect of footshock-induced stress was noted on neuronal subgroups. In intact preparations, Type I neurons were less responsive to UBD after either chronic or acute stress, while Type II neurons demonstrated significantly augmented responses to UBD. This enhanced neuronal responsiveness to UBD was present in spinalized preparations following exposure to CFS but not AFS. Type I neurons were still less responsive to stress in spinalized preparations following CFS and AFS. This study provides further evidence that (1) at least two populations of spinal neurons exist which encode for visceral stimuli and are likely to have distinct roles in visceral nociception, and that (2) the chronic stress-induced enhancement of DHN responses to UBD involves changes at the spinal level while the acute stress effects are dependent on a supraspinal substrate.

1. Introduction

Stress is one of the most common human experiences and one that modifies many other experiences, including pain. It is the rule rather than the exception that stressful life events, unless coupled with other major physiological events such as pregnancy, lead to an exacerbation of underlying pain disorders. A prominent role for stress in the pathophysiology and clinical

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Abbreviations: AFS, acute footshock; CeA, central nucleus of the amygdala; CFS, chronic footshock; CRF_2, corticotrophin releasing factor 2; DHN, dorsal horn neuron; HNCS, heterotopic noxious conditioning stimuli; HPA, hypothalamic–pituitary–adrenocortical; NFS, no footshock; NS, nociceptive-specific; OD, optical density; UBD, urinary bladder distension; WDR, wide dynamic range

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doi:10.1016/j.brainres.2011.02.081

expression of many pain states has been well-documented (Dancey et al., 1998; Farber et al., 1986; Garrett et al., 1991; Thomason et al., 1992; Zautra et al., 1997). Under normal conditions, acute stress induces transient release of stress-related hormones, which can act as pro-inflammatory mediators to produce short-term effects in peripheral tissue (e.g., Boucher et al., 2010; Theoharides et al., 1998). However, chronic stress can result in long-term and maladaptive physiological changes. For example, repeated large increases in the release of stress hormones can subsequently sensitize central stress system responsiveness (McCormick et al., 1998).

Stress is frequently reported as an exacerbator of pain symptoms in humans (Bennett et al., 1998; Rothrock et al., 2001; Zautra et al., 1997), and indeed, stress has been suggested to play a causative role in development of some functional disorders of visceral systems, including interstitial cystitis (IC). IC is a painful bladder syndrome (Bennett et al., 1998; Macaulay et al., 1987) that primarily affects the female population and is characterized by pelvic and/or perineal pain, urinary urgency and frequency, and nocturia. A majority of IC patients report symptom exacerbation during periods of clinical stress, and acute experimental stress increases bladder pain and urgency in these individuals (Koziol et al., 1993; Lutgendorf et al., 2000). As severity of the disease increases, the relationship between stress and symptom manifestation becomes even more evident (Rothrock et al., 2001).

Animal studies have demonstrated that acute (Schwetz et al., 2005; Bradesi et al., 2002) and chronic exposure to stressors such as restraint (Costa et al., 2005; Gamaro et al., 1998; Hirata et al., 2008; Toulouse et al., 2000), footshock (Robbins and Ness, 2008) and water avoidance (Bradesi et al., 2005; Mayer et al., 2001; Robbins et al., 2007) alters visceral nociceptive processing. Specifically, these manipulations produce a hypersensitive state reflected as augmented visceromotor responses to stimulation of the gut and urinary bladder. This hypersensitivity likely occurs via a combination of stress-induced cellular, molecular, neuroendocrine, and physiological changes (Imaki et al., 1991; Kuipers et al., 2003; Van Dijken et al., 1993). The current study examined whether exposure to intermittent footshock activates the hypothalamic–pituitary–adrenocortical (HPA) axis, thus supporting its utility as an experimental stressor, and whether intermittent footshock produces neurophysiological changes in the spinal dorsal horn. We have previously demonstrated that bladder inflammation differentially affects two subpopulations of DHNs that can be distinguished by their responses to the application of a heterosegmental noxious conditioning stimulus (HNCS) (Ness et al., 2009). Here, the modulatory effect of intermittent footshock was assessed by examining responses of DHNs to urinary bladder distension (UBD) following exposure to chronic and acute footshock in both intact and spinalized preparations.

2. Results

2.1. *Plasma corticosterone levels*

To verify that footshock exposure is a stressor, ELISA was used to quantify plasma corticosterone levels in rats exposed to the CFS, AFS and NFS conditions. A one-way ANOVA revealed a significant effect of group ($F(2,20)=23.13$; $p<0.01$). Post hoc contrasts indicated that compared to the NFS condition (3283.38 ± 758.53 pg/ml), plasma corticosterone was significantly increased following both AFS (12399.71 ± 1359.03 pg/ml; $p<0.01$) and CFS (7825.57 ± 897.45 pg/ml; $p=0.01$) (Fig. 1). Furthermore, AFS produced a significantly greater increase in circulating corticosterone than CFS ($p=0.023$).

2.2. *Intact animals*

2.2.1. *Description of neurons responsive to UBD*

UBD-evoked responses of 130 neurons were examined (Table 1). Using previously published criteria related to neurons excited by UBD (Ness and Castroman, 2001), approximately one-third ($n=49$) were designated as Type I neurons as a result of their observed inhibition to a HNCS. Most of these ($n=20$ for NFS condition; $n=16$ for AFS condition; $n=7$ for CFS condition) were of the class 2 (wide dynamic range; WDR) type, excited by both noxious and nonnoxious cutaneous stimuli. Assessment of cutaneous receptive fields demonstrated that half of the Type I neurons in the NFS condition had predominantly unilateral receptive fields, comprising 4 or 5 dermatomes, and half of the neurons had small receptive fields made up of only 1 or 2 dermatomes. Receptive fields of Type I neurons were similarly distributed in the footshock-exposed rats (62% medium, unilateral and 38% small for CFS condition; 58% medium unilateral and 42% small for AFS condition).

Most of the total neuronal sample in the intact preparations ($n=81$) were not inhibited by HNCS and were designated as Type II neurons. Cutaneous classification and receptive field characteristics of these neurons differed from Type I neurons. Approximately half of the Type II neurons examined were of the class 2/WDR type and half were designated as class 3 (nociceptive specific; NS), responding only to noxious cutaneous stimuli. Receptive fields were similar in the three groups of Type II neurons, with approximately half of neurons (41% in NFS and AFS conditions; 59% in CFS condition) exhibiting large, bilateral receptive fields. The other half of the Type II neurons examined had medium-sized, predominantly unilateral receptive fields (59%, 52% and 41% for NFS, AFS and CFS conditions,

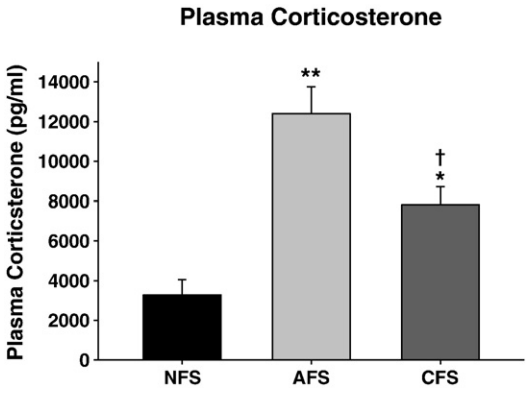

Fig. 1 – Plasma corticosterone concentrations measured immediately after exposure to the chronic footshock (CFS), acute footshock (AFS) or no footshock (NFS) conditions. * and ** indicate significantly different from the NFS condition with $p<0.05$ and $p<0.01$, respectively. † indicates significantly different from the AFS condition with $p<0.05$. N = 6–12/group.