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Chronic Psychological Stress Enhances Nociceptive Processing in the Urinary Bladder in High-Anxiety Rats

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Abstract

This study sought to determine whether acute and/or chronic psychological stress produce changes in urinary bladder nociception. Female Sprague-Dawley (SD; low/moderate anxiety) or Wistar-Kyoto (WK; high-anxiety) rats were exposed to either an acute (1 day) or a chronic (10 days) water avoidance stress paradigm or a sham stress paradigm. Paw withdrawal thresholds to mechanical and thermal stimuli and fecal pellet output, were quantified at baseline and after the final stress or sham stress exposure. Rats were then sedated, and visceromotor responses (VMRs) to urinary bladder distension (UBD) were recorded. While acute stress exposure did not significantly alter bladder nociceptive responses in either strain of rats, WK rats exposed to a chronic stress paradigm exhibited enhanced responses to UBD. These high-anxiety rats also exhibited somatic analgesia following acute, but not chronic, stress. Furthermore, WK rats had greater fecal pellet output than SD rats when stressed. Significant stress-induced changes in nociceptive responses to mechanical stimuli were observed in SD rats. That chronic psychological stress significantly enhanced bladder nociceptive responses only in high-anxiety rats provides further support for a critical role of genetics, stress and anxiety as exacerbating factors in painful urogenital disorders such as interstitial cystitis (IC).

Keywords

Bladder; Stress; Hyperalgesia; Visceral

1. Introduction

Stress is one of the most common human experiences and one that modifies many other experiences, including pain. Generally, the heightened anxiety and arousal accompanying the stress response is motivating rather than debilitating. For example, when placed in stressful situations, animals may exhibit antinociception to noxious cutaneous stimuli. This phenomenon, known as stress-induced analgesia (SIA), allows the animal to react (“fight or flight”) to a dangerous situation since pain is suppressed. However, when stress is either sustained or perceived as uncontrollable, the biological changes that, short-term, are usually adaptive, can have long-term pathophysiological consequences. Thus, instead of being inhibited, as in stress-induced analgesia, nociceptive responses may become augmented, with either a lowering of response threshold or a potentiation of suprathreshold responses, a phenomenon known as stress-induced hyperalgesia (SIH) [1,2].

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A prominent role for stress in the pathophysiology and presentation of clinical pain states, especially in functional gastrointestinal disorders characterized by visceral hypersensitivity has been well-documented [3,4,]. Recently, clinical observations have shown that anxiety and stress may generate and worsen urinary symptoms and functional urinary disorders [5,6], such as interstitial cystitis (IC). More than 60% of IC patients report symptom exacerbation by stress, and clinical studies have shown that acute stress increases bladder pain and urgency in these individuals [7,8]. Not only is there a significant positive relationship between stress and the IC symptoms of pain and urgency, but as severity of the disease increases, the relationship between stress and symptom manifestation become even more evident [9].

A number of laboratory studies have demonstrated SIH to colorectal stimulation [10,11,12, 13,14], and rats that are genetically predisposed to enhanced levels of anxiety exhibit exaggerated responses to colorectal distension [15]. In contrast, few laboratory reports exist about the relationship between stress and hypersensitivity of the urinary bladder. This study sought to determine whether psychological stress produces changes in urinary bladder nociception. Two different strains of rats were compared to examine whether stress effects were augmented in a stress-susceptible strain. Sprague-Dawley (SD) rats are generally considered to be a low/moderate-anxiety strain. Based on a number of lines of evidence, the Wistar-Kyoto (WK) rat, a high-anxiety strain, has been proposed as a model of stress vulnerability. These rats exhibit both neurochemical and behavioral differences in response to stress, including exaggerated hypothalamic pituitary adrenal (HPA) axis response, an attenuated brain noradrenergic system response, reduced locomotor activity in anxiety tests, and a higher reaction to adverse environments [16,17]. Furthermore, these rats have a much higher susceptibility to gastric ulceration in response to stress [18,19].

In the present study, both strains of rats were exposed to a water avoidance (WA) stress paradigm, either acutely (1 day) or chronically (10 days), which has been previously shown to increase anxiety-like behavior and visceral nociception in the colon [11]. We report the development of urinary bladder hyperalgesia following chronic psychological stress exposure in a high-anxiety strain of rats.

2. Materials and Methods

2.1. Animals

Female SD or WK rats 11-12 weeks of age (Harlan, Prattville, AL) were used in experiments. Female rats were chosen since disorders of the urinary bladder that are associated with pain are prevalent in and primarily affect the female population. Estrous cycle was not controlled for in these experiments. Food and water were available on an *ad libitum* basis. A 12:12-h light-dark cycle, where lights were off between 6:00 a.m. and 6:00 p.m., was maintained. There was one week between the time of the animals' arrival and the start of any experimental procedures. Rats exposed to either the chronic WA stress or chronic WA sham paradigm were housed individually in standard cages ($24 \times 45 \times 15$ cm^3). Naïve rats were housed in groups of 3-4 in standard cages. Animals were not exposed to any handling or cage habituation prior to the start of experimental procedures. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham.

2.2. WA Stress Paradigm

Rats were placed on a pedestal ($10 \times 8 \times 8$ cm^3) affixed to the center of the floor of a plexiglass tank ($45 \times 25 \times 25$ cm^3) for one hour. For the WA stress group, the tank was filled with water to within 1 cm of the top of the pedestal. WA sham animals were placed on the pedestal but the tank left waterless. Animals were exposed to the stress or sham condition between 9:00 a.m. and 12.00 p.m.

2.3. Assessment of Bladder Sensitivity

Under mask isoflurane anesthesia (3% isoflurane, 97% oxygen), a 22-gauge polytetrafluoroethylene angiocatheter was placed into the bladder via the urethra and held in place by a tight suture around the distal urethral orifice. Electrodes (silver wire) were inserted into the external oblique musculature immediately superior to the inguinal ligament. Following surgery, isoflurane anesthesia was lowered until flexion reflexes were present in the hind limbs, but spontaneous escape behaviors were absent (1-1.5% isoflurane). UBDs (20 sec) were produced using compressed air and a previously described distension control device [20], and intravesical pressure was monitored using an in-line, low volume pressure transducer. Contraction of the abdominal and hindlimb musculature, recorded as electromyographical (EMG) activity, was measured via the electrodes using standard differential amplification and rectification and saved on a computer. Approximately 15 min after initial anesthesia induction, EMG activity to three presentations of 60 mm Hg UBD at 3-minute intervals were recorded. Responses to graded stimuli (10-50 mm Hg; 1 min intertrial intervals) were then determined. Grass P511 amplifier settings were the following: EMG amplification factor=200; low frequency filter=10 Hz; high frequency filter=3 kHz; sample rate=10 kHz.

2.4. Assessment of somatic nociceptive responses

A set of calibrated von Frey nylon monofilaments was used in tests of mechanical sensitivity. Each rat was allowed to crawl into a glove. Once the rat was still, the tip of the nylon monofilament was applied to the lateral edge of the hindpaw. Mechanical stimuli were increased in a graded manner until the paw was withdrawn. The paw withdrawal threshold was defined as the mechanical stimulus that elicited a withdrawal reflex in two out of three applications. Paw withdrawal threshold was determined for both hindpaws, and these values were averaged to obtain a single measure of mechanical sensitivity. There was approximately a 5 min interval between measures of mechanical and thermal somatic sensitivity.

The method described by Hargreaves et al. [21] was used in tests of thermal sensitivity. Rats were confined within a clear plexiglass cage ($24 \times 45 \times 15$ cm^3) placed on an elevated piece of glass 3 mm thick. A radiant heat source consisting of a high-intensity projector lamp (50 W) was positioned 6 mm under the glass floor. The beam was projected through an 11×11 mm^2 aperture and positioned so that it struck the glaborous skin and toe pads of the hindpaw. The latency to withdraw the hindpaw was measured. Three trials were conducted on each hindpaw, with an intertrial interval of 3 min, and averaged to obtain the mean response latency for each hindpaw. These values were averaged to obtain a single measure of thermal sensitivity.

2.5. Measurement of Fecal Pellet Output

Fecal pellets were counted at the end of each WA stress or WA sham exposure. Fecal pellet output is a reliable measure of autonomic system modulation of colonic motility.

2.6. General Experimental Protocol

2.6.1. Acute WA stress—Paw withdrawal thresholds to mechanical stimuli and paw withdrawal latencies to a thermal stimulus were determined. Approximately 5 min later, rats were exposured to either WA stress or WA sham stress for 1 hour. Somatic nociceptive responses were reassessed approximately 5 min after stress or sham stress exposure, and 15 min later, VMRs to UBD were measured. Naïve animals were not exposed to the tank and did not have somatic nociceptive responses assessed but did have responses to UBD determined.

2.6.2. Chronic WA stress—On day 0, before any pretreatment, paw withdrawal thresholds to mechanical stimuli and paw withdrawal latencies to a thermal stimulus were determined. SD and WK rats were exposed to either the WA stress paradigm or WA sham stress paradigm

for 1 hour/day for 10 days. Approximately 5 min after their exposure on day 10, mechanical and thermal nociceptive responses were reassessed, and 15 min later, VMRs to UBD were measured.

2.7. Statistical analysis

EMG activity was quantified as a response (change) score which represents a signal-to-noise ratio. In this case, baseline mean rectified myoelectrical activity measured prior to the presentation of UBD was treated a “noise” (in mV), and the evoked response (the rectified myoelectrical activity during UBD that exceeded the ongoing activity level immediately prior to UBD) represents the “signal” (in mV). Creating a ratio (signal divided by noise) yields a quantified measure of the vigor of the UBD-evoked physiological response that is independent of other measures. The vigor of the response is thereby represented by a signal-to-noise ratio. All of the groups contained at least one animal that was a “low responder”, i.e. did not exhibit a signal-to-noise ratio of ≥ 1 at UBD pressures ≤ 60 mm Hg. A Pearson correlation analysis was performed on responses of these animals to determine whether EMG activity at 20-60 mm Hg UBD was correlated with distension pressure. Animals were excluded only if VMRs did not correlate with distension pressure ($p>0.05$). There were approximately equal numbers of “low responders” across all groups that fit the exclusion criteria (1 or 2 animals in each of the 10 groups). Nineteen out of a total of 118 animals were therefore excluded. Data were analyzed by repeated measures analysis of variance (ANOVA). Post-hoc tests were performed using Fisher's LSD.

Mechanical and thermal withdrawal responses were quantified as change from baseline. Specifically, baseline responses were subtracted from those obtained on the last day of WA stress or WA sham stress exposure. This was done for every animal, and then the mean change in threshold/latency for a particular group was determined by averaging changes of all the individual animals in that group. Changes in mechanical and thermal withdrawal responses were analyzed using ANOVA.

Significant differences in fecal pellet output were analyzed using the nonparametric Kruskal-Wallis ANOVA. In all tests, $p < 0.05$ was considered statistically significant. All data are presented as mean ± SEM.

3. Results

3.1. Effect of stress on bladder nociception

Chronic WA stress produced bladder hyperalgesia in high-anxiety WK rats, manifested as significantly more vigorous VMRs to UBD compared to those exposed to the WA sham condition (Fig. 1A) ($F(1,16)=5.351$, $p=0.034$). Post hoc tests revealed significant differences at UBD pressures of 10-40 mmHg. SIH was not evident in the low-anxiety SD rats following 10 days WA stress (Fig. 1B). VMRs in WK rats measured after acute WA stress or WA sham exposure were increased slightly relative to responses of naïve rats (Figure 1C), but statistical analyses revealed no significant between group differences (stress vs. naïve: $F(1,21)=1.621$, $p=0.217$; sham vs. naïve: $F(1,19)=4.125$, $p=0.056$). A similar trend toward enhanced VMRs to UBD after acute stress exposure was also observed in SD rats (Figure 1D), but again, this difference was not statistically significant (stress vs. naïve: $F(1,25)=3.32$, $p=0.08$; sham vs. naïve: $F(1,24)=0.639$, $p=0.432$). Statistical analyses also revealed that UBD-evoked VMRs of sham WK rats were not different from those of SD rats ($F(1,14)=0.562$; $p=0.466$). Similarly, VMRs of naïve WK rats were not different from those of naïve SD rats ($F(1,21)=2.078$, $p=0.164$).

3.2. Effect of stress on somatic nociception

Stress-induced analgesia to somatic stimuli was observed after acute WA stress exposure, as shown in Fig. 2. Mechanical paw withdrawal thresholds of WK ($F(1,18)=10.335$, $p=0.005$) and SD ($F(1,25)=4.932$, $p=0.036$) rats in the WA stress condition were significantly elevated compared to animals in the WA sham condition (Fig. 2, A and C). Stress-induced thermal analgesia was evident in high-anxiety ($F(1,18)=9.551$, $p=0.006$) but not low-anxiety rats (Fig. 2, B and D, respectively). No significant changes in mechanical (Fig. 3A) or thermal (Fig. 3B) paw withdrawal responses were observed either WK or SD rats following chronic stress.

3.3. Effect of stress on fecal pellet output

In the chronic stress paradigm, WA stress rats of both strains had significantly higher fecal pellet output after the first day of stress exposure than their sham stress counterparts (Fig. 4; WK-$p=0.021$; SD-$p=0.006$), but there were no statistically significant differences between WA stress and WA sham animals in their respective groups by day 10 (Fig. 4; WK-$p=0.056$; SD-$p=0.05$). On day 1, fecal pellet output of WA stress animals did not differ between SD and WK rats, but WK rats in the sham condition had significantly greater fecal pellet output than did SD rats. However, by day 10, the high-anxiety WK rats in the WA stress group had significantly greater fecal pellet output relative to the corresponding group of SD rats ($p=.037$), and there were no differences between the sham groups ($p=0.218$). Compared to the WA sham groups, rats exposed to acute WA stress had significantly greater fecal pellet output (WK-sham=0.0 ± 0.0 pellets, stress=2.73 ± 0.84 pellets, Mann-Whitney $U=85.50$, $p=0.017$; SD-sham=0.0 ± 0.0 pellets, stress=1.93 ± 0.44 pellets, Mann-Whitney $U=162.50$, $p<0.01$).

4. Discussion

The results of the present study indicate that chronic exposure to a psychological stressor augments nociceptive responses of the urinary bladder in high-anxiety WK rats. These findings are similar to those of a previous report of gastrointestinal hyperalgesia, as evidenced by enhanced VMRs to colorectal distension, using the same WA stress paradigm [11]. These data provide further support for a role of chronic stress in the modulation of bladder nociception.

SIA to somatic stimuli was observed in both strains of rats but only as a consequence of acute stress exposure. That chronic psychological stress does not modulate somatic nociception is in contrast to the findings of Bradesi et al. [11], who reported a significant increase from baseline tail-flick latency immediately after the stress exposure on day 10. In the present study, paw withdrawal latency to a thermal stimulus and paw withdrawal threshold to a mechanical stimulus were used as indices of somatic nociception. These are supraspinally-mediated reflexes, while the tail flick response, as measured by Bradesi et al. [11] is spinally-mediated, which may account for the discrepancy in SIA in the two studies. Twenty-four hours later, the analgesic effect of stress reported by Bradesi et al [11] was no longer evident, which is consistent with the bulk of the existing literature on stress-induced analgesia, describing it as a transient phenomenon, primarily induced by exposure to acute, rather than chronic, stress.

Stress can have differential effects on gastrointestinal motor responses – delaying gastric emptying while simultaneously accelerating large bowel transit, and there are numerous reports, both clinical and experimental, implicating stress as a significant modulator of gastrointestinal motor function [22]. Since defecation responses are a reliable measure of autonomic nervous system modulation of colonic motility, fecal pellet output was recorded to see if the stress paradigm utilized in the present study affected gastrointestinal motor function in high- and/or low-anxiety rats. Regardless of strain and duration of WA stress, rats in the stress condition had greater fecal pellet output than their WA sham counterparts. Furthermore, a decrease in the magnitude of the stress response in the SD stress group and in WK stress and

sham groups during the chronic WA paradigm was evident, as indicated by the significantly greater number of fecal pellets after the first day of stress or sham stress compared to the tenth day. The high-anxiety WK rats in the WA sham group also had significantly greater fecal pellet output than the low/moderate-anxiety SD rats on the first day of the experiment. By day 10, this difference was no longer apparent, but WK rats exposed to WA stress had significantly greater defecation responses than the corresponding SD rats. These data support that WK rats are indeed a higher-anxiety strain of rats than SD rats, and WA stress exacerbated this difference.

Not only do individuals with IC report higher levels of daily stress than healthy individuals, but the relationship between stress and symptoms of pain and urgency in IC patients becomes more pronounced as severity of the disease increases [9]. Exposure to stress in a laboratory setting also increases bladder pain in these IC patients [8]. A genetic linkage study reported that individuals with IC had more than a four-fold higher incidence of panic disorder compared to individuals without IC [23]. Furthermore, first degree relatives of IC patients showed a significantly increased risk of panic disorder. Taken together with the results of the present study that chronic psychological stress enhances bladder nociception in a strain of rats predisposed to be more anxious, these data suggest that there may be a genetic component to the relationship between stress and the exacerbation of bladder pain in functional urinary disorders.

There are a number of different, and likely interrelated, mechanisms by which stress may worsen and/or cause painful urinary bladder disorders. One of these mechanisms involves the sympathetic nervous system (SNS), an integral component of the stress response. IC patients exhibit abnormal vasomotor tone, increased density and activity of sympathetic nerves supplying the bladder and increased urine norepinephrine (NE) excretion, all of which suggest overactivity of the SNS [24,25]. In addition, there is a positive correlation between the number of sympathetic fibers supplying the bladder and severity of IC symptoms [26]. Similar findings have been reported in laboratory studies of cats with feline interstitial cystitis; these animals have elevated bladder tissue content and release of NE and higher concentrations of plasma NE [27].

Sympathetic activation has been shown to increase mast call degranulation, one of the morphological criteria for defining IC [28]. Both clinical and laboratory studies indicate that stress not only enhances the activation and number of granulated mast cells in the bladder [29,30], but is also associated with increases in substance P (SP) containing nerve fibers. Ercan et al. [31] reported that cold-immobilization stress or i.c.v. administration of SP not only increases the number of granulated and degranulated mast cells in the bladder, but also induces urothelial degeneration. These stress-induced morphological changes are prevented by central and peripheral administration of an NK-1 receptor antagonist. Together with the observations that mast cells are closely apposed to SP-containing nerve terminals and that mast cell secretion is elicited by SP [26,32,33], this evidence suggests that stress-induced release of SP may induce morphological changes in the bladder wall that are characteristic of IC.

The corticotropin-releasing factor (CRF) family of peptides may also contribute to stress-related symptoms in IC. CRF acts not only peripherally, as a hormone, but also centrally on various brain regions that mediate the central stress response (i.e., amygdala, locus ceruleus, dorsal raphe nucleus, and hippocampus). That the amygdala is a relay center for emotional stress and visceral pain and the dorsal raphe is involved in major depression strongly suggests a link between stress and/or anxiety and CRF-related peptides.

Stress delays gastric emptying and accelerates large bowel transit, and administration of CRF or urocortins (Ucns) produces analogous effects [34,35,36]. A number of studies suggest that

the CRF system might also be modulating visceral sensitivity related to stress [12,13,14,37]. With regard to the bladder, CRF is abundantly expressed in areas involved in the control of micturition (i.e., Barrington's nucleus, lumbosacral areas of the spinal cord) and administration of various CRF receptor agonists and antagonists alters cystometric parameters [38,39,40]. Following stress or bladder inflammation, increases in CRF-IR and/or CRF2 receptor expression have been detected in these areas and in the bladder itself [41,42]. These converging lines of evidence implicate the CRF system as a potential mediator of stress-induced bladder hyperalgesia as well.

5. Conclusions

In summary, the present study demonstrated enhanced nociceptive processing related to the urinary bladder following exposure to a chronic psychological stressor in a high-anxiety strain of rats. These data provide further support for a role not only of chronic stress in the exacerbation of bladder pain in functional urinary disorders such as IC, but also for a genetic component to this relationship, since chronic stress effects were only observed in high-anxiety rats. Stress may influence a variety of factors, which then directly or indirectly affect the bladder to produce hyperalgesia and other characteristic symptoms of IC.

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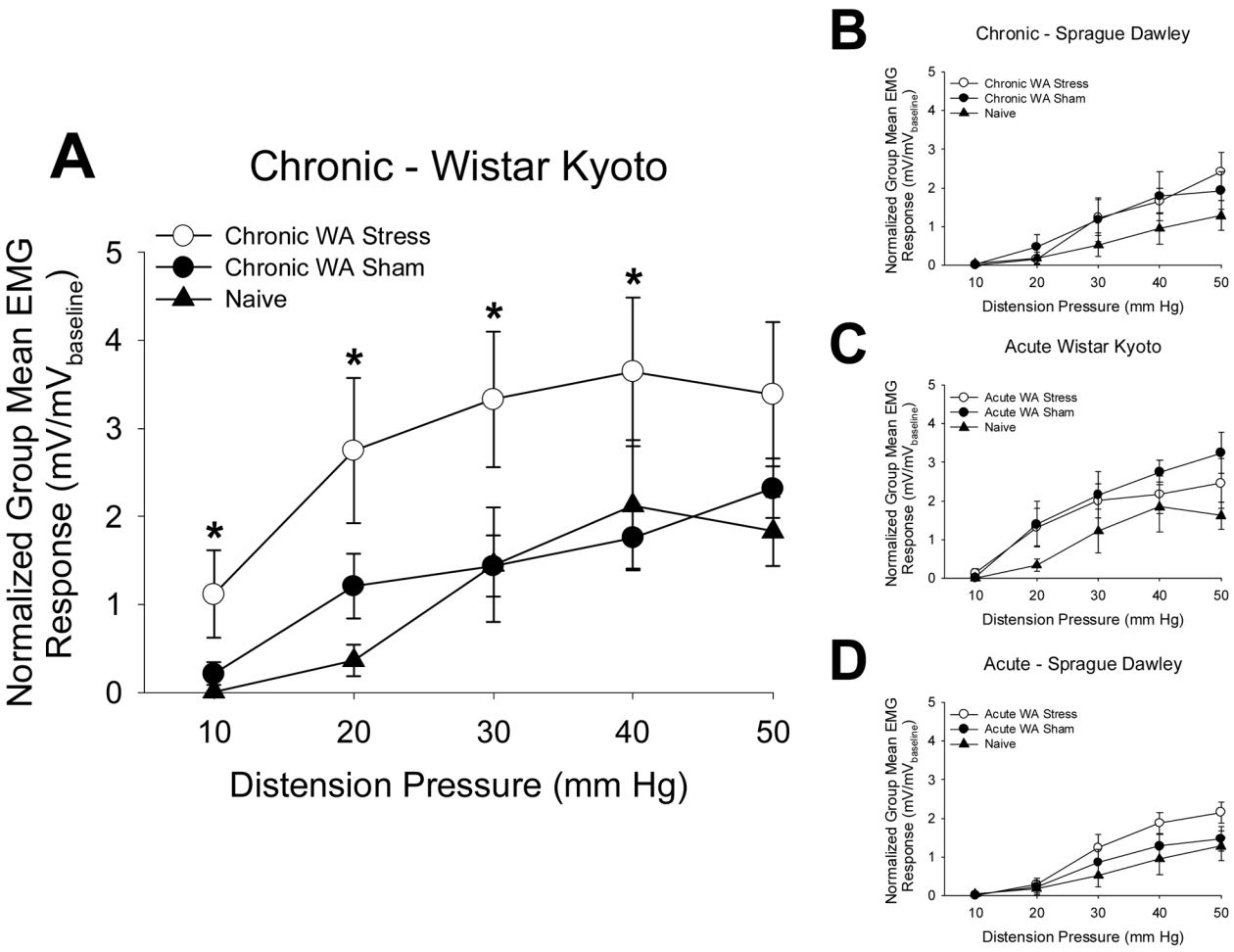

Figure 1.

Chronic WA stress (○; N=8) induced bladder hyperalgesia in high-anxiety WK rats (A), manifested as significantly enhanced VMRs compared to those evoked by UBD after chronic WA sham exposure (●; N=10). Nociceptive responses were the same in SD rats, whether they were exposed to the chronic WA stress (○; N=5) or the chronic WA sham (●; N=6) condition (B). Acute WA stress did not significantly alter bladder nociceptive responses in either WK (C) or SD (D) rats. Rats exposed to the WA stress (○; N=11 for WK; N=14 for SD) or WA sham (●; N=9 for WK; N=13 for SD) conditions demonstrated similar responses as naïve animals (▲; N=10 for WK; N=13 for SD). * indicates significantly different from WA sham condition ($p<0.05$).

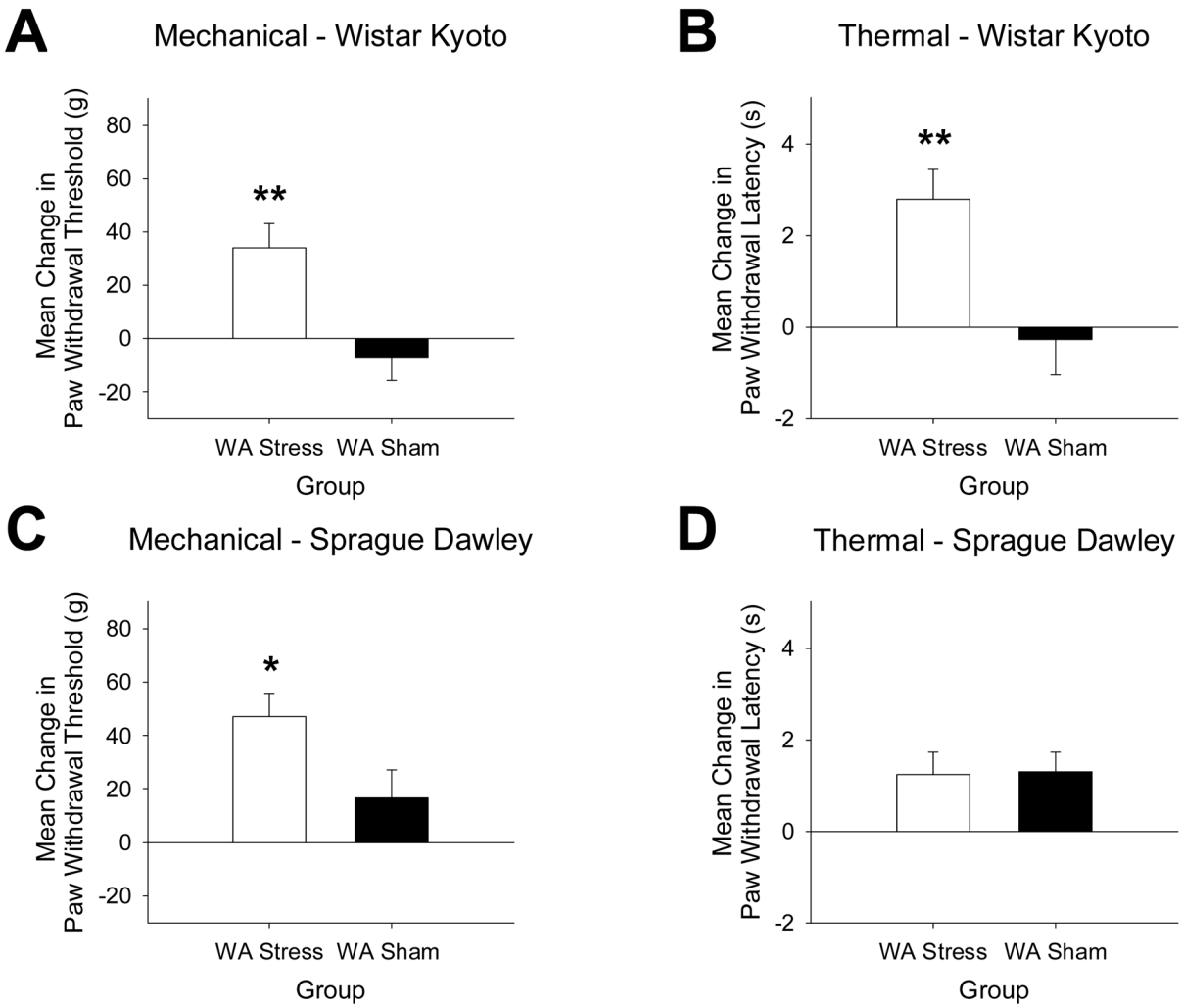

Figure 2.

Immediately following 1 hour of WA stress, mechanical (A) and thermal (B) nociceptive responses were significantly attenuated in WK rats. Acute WA stress induced mechanical (C), but not thermal (D) analgesia in SD rats. N=9-14/group. * and ** indicate $p<0.05$ and $p<0.01$, respectively.

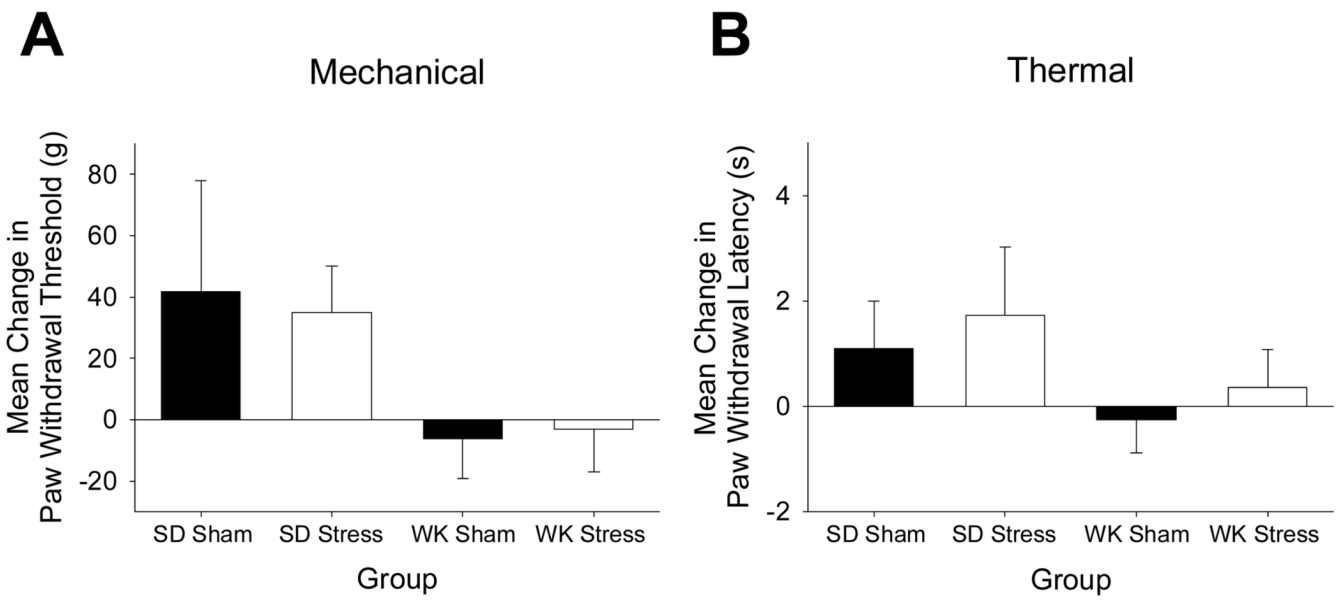

Figure 3.
Neither mechanical (A) nor thermal (B) nociceptive responses were significantly altered following 10 days of WA stress. N=5-12/group.

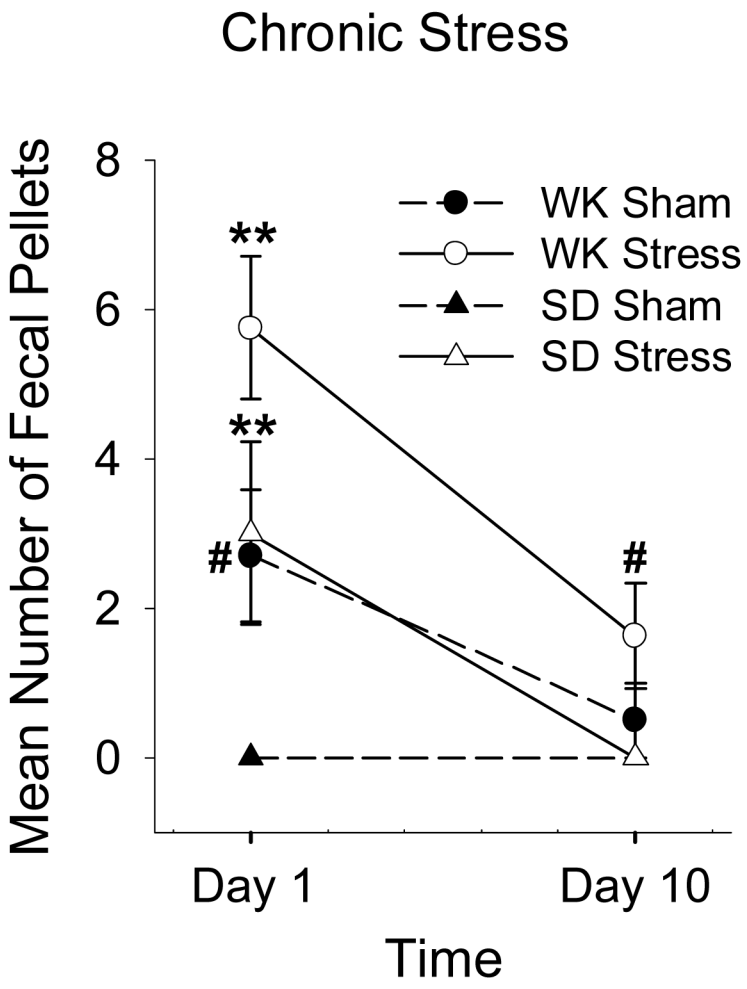

Figure 4.

On day 1 of the chronic stress paradigm, fecal pellet output of both strains of WA stress rats was significantly enhanced relative to their WA sham counterparts (WK: Mann-Whitney U=62.50, p=0.021, SD: Mann-Whitney U=27.00, p=0.006). Furthermore, sham WK rats had significantly greater fecal pellet output than sham SD rats on day 1 (Mann-Whitney U=48.00, p=.0125), but there were no significant differences between groups in the stress condition (Mann-Whitney U=30.50, p=0.06). However, by day 10, WK rats in the stress condition had significantly greater fecal pellet output than did SD rats in the same condition (Mann-Whitney U=30.00, p=.037), but there were no differences in the sham groups (Mann-Whitney U=33.00, p=0.218). N=5-12/group. ** indicates significantly different from WA sham stress at $p<0.05$. # indicates significantly different from corresponding SD group.