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Effects of Oxytocin and Prolactin on Stress-Induced Bladder Hypersensitivity in Female Rats

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Abstract

Anecdotal evidence suggests that chronic bladder pain improves while breastfeeding. The present study sought to identify potential mechanisms for such a phenomenon by investigating the effects of the lactogenic hormones prolactin (PL) and oxytocin (OXY) in a rat model of bladder nociception. Lactating rats were less sensitive to urinary bladder distension (UBD) than controls. In investigating potential antinociceptive and anxiolytic roles for these hormones, we found exposure to a footshock paradigm (STRESS groups) produced bladder hypersensitivity in saline-treated rats, manifested as significantly higher electromyographical (EMG) responses to UBD, compared to rats exposed to a non-footshock paradigm (SHAM groups). This hypersensitivity was attenuated by the intraperitoneal administration of OXY prior to footshock in the STRESS-OXY group. The administration of PL augmented EMG responses in the SHAM-PL group but had no effect on the responses of the STRESS-PL group. In the absence of behavioral pretreatment, OXY attenuated UBD-evoked responses while PL had no effect. Moreover, OXY-treated rats spent more time in the open arm of an elevated plus maze compared to saline-treated rats suggesting anxiolysis. These studies suggest the potential for systemic OXY, but not PL, as an analgesic and anxiolytic treatment for painful bladder disorders such as interstitial cystitis.

Keywords

oxytocin; prolactin; nociception; pain; stress; anxiety; bladder

Introduction

Anecdotal evidence suggests patients with the painful bladder disorder interstitial cystitis can experience a significant attenuation of their symptoms while breastfeeding.¹⁴ This observation led us to hypothesize that hormones involved in postpartum lactation, namely oxytocin (OXY) and prolactin (PL), would attenuate bladder nociception. There are multiple physiological effects of PL and OXY. PL is secreted by the anterior pituitary gland and is regulated by the hypothalamus. It stimulates the mammary glands to produce milk. OXY, which is synthesized in the hypothalamus and released by the posterior pituitary gland in response to both psychic

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processes and breast stimulation, is responsible for milk “letdown” and ejection. It is also responsible for stimulating uterine contractions during childbirth. It is the other physiological and psychological effects of PL and OXY that may serve as mechanisms for symptom reduction in painful disorders. In a study by Heinrichs and associates, women reported elevated mood, enhanced calmness and reduced anxiety while breastfeeding.²¹ Lactation is associated with a hypothalamic-pituitary-adrenocortical (HPA) axis hyporesponsiveness to physical and psychological stressors. Moreover, during the period of lactation, OXY and PL receptor expression and binding are enhanced in hypothalamic and limbic areas of the brain that are involved in the regulation of HPA axis activity.^{15,19,25,35} In the rat, lactation is associated with an activation of central OXY pathways and a down-regulation of the endocrine responses to stress.^{28,36,42} OXY has also been demonstrated to have analgesic effects in rats when administered centrally,^{53–54} and in humans, it has been shown to promote positive couple interactions when administered intranasally.¹³

Stress is one of the most common human experiences and there is extensive clinical and basic science evidence that it alters pain sensations. Generally, the heightened anxiety and arousal accompanying the stress response is motivating rather than debilitating, a phenomenon known as stress-induced analgesia (SIA). However, when pain is either sustained or perceived as uncontrollable, the biological changes that in the short term are usually adaptive acquire long-term pathophysiological consequences. Thus, instead of being inhibited, as in SIA, nociceptive responses, particularly those associated with deep tissue sensations, may become augmented, a phenomenon known as stress-induced hyperalgesia.^{31,32} Previous studies by our group have shown that chronic stress augments nociceptive responses in a rat model of bladder hypersensitivity.^{44–45}

A prominent role for stress in the pathophysiology of clinical pain syndromes has been well documented.^{20,48,55} For example, clinical observations have shown that stress and anxiety can worsen the symptoms associated with interstitial cystitis.^{26,29} This relatively common chronic, debilitating visceral pain syndrome primarily affects the female population and is characterized predominately by pelvic and/or perineal pain, urinary urgency and frequency, and nocturia.^{11,23,37,47} To determine whether there is a potential therapeutic role for the lactogenic hormones in the treatment of painful bladder disorders, the present studies sought to determine whether lactating rats had any alterations in bladder nociception and then assessed the analgesic/anxiolytic effects of OXY and PL in rat models of pain, anxiety and stress-induced bladder hypersensitivity.

Materials and Methods

Animal Subjects

Female Sprague Dawley rats (Harlan, Prattville, AL) were used in the following experiments. Female rats were chosen since disorders of the urinary bladder associated with pain primarily affect the female population. Food and water were available on an *ad libitum* basis. A 12:12-h light-dark cycle, where lights were off between 6:00 p.m. and 6:00 a.m., was maintained. One group of rats (Experiment 1-Lactating) was used at the time of weaning from pups 2–4 weeks postpartum. A separate group of parous rats (Experiment 1-Non-Lactating) was utilized 3–4 weeks after weaning from their pups. All other female rats were virgins which were allowed a period of one week between the time of the animals’ arrival and the start of any experimental procedures in order to recover from the stressful effects of transport from the animal supplier. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham and adhered to the guidelines of the International Association for the Study of Pain.

General Procedures

Footshock Paradigm

Electrical footshock is an established and readily controlled stressor that has been used to produce behavioral and neurochemical changes in a variety of experiments.^{24,43} Factors such as timing, predictability, frequency, intensity and duration of exposure to the footshock determine the characteristics of the resultant stress response. We chose to use a chronic intermittent footshock paradigm described by Imaki et al. which produced activation of the HPA axis evidenced by upregulation of corticotrophin-releasing factor mRNA in the brain.²² This same paradigm has also been shown by our group to produce bladder hypersensitivity.^{44–45} Rats that received the footshock treatments (STRESS groups) were placed in operant conditioning chambers enclosed in sound-attenuating cubicles and received daily intermittent footshocks (15 min/day, 1.0 mA, 1s duration, total of 30 shocks each day) administered via a grid floor under a variable-interval schedule for 7 days. Rats in the non-footshock treatment groups (SHAM groups) were treated in an identical manner except they did not receive any footshocks while in the operant conditioning chambers.

Elevated Plus Maze

The elevated plus maze is a widely used behavioral assay for rodents. It has been validated to assess the anxiolytic effects of pharmacological agents and steroid hormones and to define brain regions and mechanisms underlying anxiety-related behaviors. Briefly, rats are placed at the junction of the open and closed arms facing the open arm and entries/duration in each arm is recorded simultaneously by a video-tracking system and observer for 5 minutes. Other ethological parameters (i.e., rears, head dips and stretch-attend postures) can also be observed. An increase in open arm activity (duration and/or entries) reflects an anxiolytic effect.^{39,50}

Urinary Bladder Distension (UBD)-Evoked Electromyographic (EMG) Responses

Under mask isoflurane anesthesia (1–3% isoflurane in 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. Silver wire electrodes were inserted into the external oblique musculature immediately superior to the inguinal ligament. Following surgery, the isoflurane anesthesia was lowered until flexion reflexes were present in the hind limbs, but spontaneous escape behaviors were absent (~1% isoflurane). Urinary bladder distensions (UBDs; 20 sec) were performed using compressed air generated via a previously described distension control device.² Intravesical pressure was monitored using an in-line, low volume pressure transducer. Visceromotor responses (VMRs; contraction of the abdominal and hind limb musculature), recorded as electromyographical (EMG) activity, were measured via the electrodes using standard differential amplification and rectification and saved on a computer using Spike-2 software and associated hardware (Micro 1401; CED, Cambridge, UK). Approximately 15 min after initial anesthesia induction, EMG activity to three presentations of 60 mmHg UBD at 3-minute intervals were recorded to overcome a period of bladder sensitization that occurs before demonstration of vigorous and reliable VMRs.⁸ Responses to graded stimuli (10–60 mmHg, 20 s, 1 minute inter-trial intervals) were then determined.

This animal model has been validated in previous studies of bladder nociception by our group and others. Cardiovascular and visceromotor responses to UBD in the anesthetized rat have been demonstrated to be useful endpoints in that they are reliable, reproducible, and inhibited in a dose-dependent fashion by analgesics such as morphine, fentanyl, lidocaine, and ketamine. Furthermore, we have shown that these responses are augmented in the presence of inflammation and become more vigorous after the presentation of repeated trials of UBD, reflecting a phenomenon of sensitization.^{4,9,33–34}

Drugs

Prolactin salt (PL) was obtained from Sigma-Aldrich (St Louis, MO). Oxytocin salt (OXY) and vasotocin salt were obtained from Bachem (Torrance, CA). PL and OXY were dissolved in saline. Vasotocin was dissolved in sterile water. Doses of these agents were based on previous reports.^{3,6,38}

Statistical Analysis

Similar to our previous studies^{44–45}, 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 as “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 data are presented as group mean $\pm$ SEM. Data from the UBDs were analyzed by repeated measures analysis of variance (ANOVA). Post-hoc tests were performed using Fisher’s LSD. Statistical analysis of the elevated plus maze experiments were performed via independent samples T-test.

Specific Experimental Protocols

Experiment 1: UBD-Evoked EMG Responses in Lactating vs. Non-Lactating Rats—To determine whether lactation alters bladder nociception, female Sprague-Dawley rats that were actively lactating (Lactating rats) were anesthetized with isoflurane and UBDs were performed to evoke EMG responses as described above. The same procedure was performed in a separate cohort of parous Non-Lactating rats.

Experiment 2: The Effects of OXY and PL on UBD-Evoked EMG Responses Following Stress (Stress-Induced Bladder Hypersensitivity)—To determine whether OXY and PL had effects on stress-induced bladder hypersensitivity, female Sprague-Dawley rats were divided into STRESS and SHAM groups. STRESS rats were placed in an operant conditioning chamber where they received seven daily intermittent footshock treatments as described above. SHAM rats were treated in an identical manner except they did not receive footshock treatments while in the operant conditioning chamber. Rats in both paradigms received daily single-dose intraperitoneal (i.p.) injections of PL (0.5 mg in 0.2 ml), OXY (0.5 mg in 0.2 ml), or an equivalent volume of saline (SAL) on days 3–7 prior to being placed in the chambers. On day 7 following treatment, rats were anesthetized with isoflurane and UBDs were administered to evoke EMG responses as described above. Following the UBDs, subgroups of animals initially injected with OXY were then injected with vasotocin (0.5 mg in 0.5 ml, i.p.), an OXY-receptor antagonist, and a second set of UBD-evoked EMG responses were obtained.

Experiment 3: The Effects of OXY and PL on UBD-Evoked EMG Responses in the Absence of Stress—In order to determine whether OXY and PL affect bladder nociception in the absence of stress, female Sprague-Dawley rats were given i.p. injections of OXY (0.5 mg or 0.25 mg, both in 0.2 ml), PL (0.5 mg in 0.2 ml), or an equivalent volume of SAL. Thirty minutes later, rats were anesthetized with isoflurane and UBD-evoked EMG responses were obtained as previously described.

Experiment 4: The Effects of OXY and PL on Anxiety Independent of UBD—In order to determine whether OXY and PL had any anxiolytic effects, female Sprague-Dawley rats were given i.p. injections of OXY (0.5 mg in 0.2 ml), PL (0.5 mg in 0.2 ml), or an equivalent

volume of SAL. Fifteen minutes later, the rats were placed in an elevated plus maze for 5 minutes. Duration of time in the open vs. closed arms was recorded as well as the number of exploratory behaviors. All observations were recorded by a single investigator in an unblinded fashion.

Results

Experiment 1: UBD-Evoked EMG Responses in Lactating vs. Non-Lactating Rats

Lactating rats had significantly decreased EMG responses to UBD as compared to Non-Lactating rats ($F=35.5$, $p<0.01$). Post hoc tests revealed significant differences in the UBD-evoked EMG responses at intensities of 40, 50, and 60 mm Hg (Figure 1). These results suggest the period of lactation is a hypoalgesic state in this animal model of bladder nociception consistent with clinical observations related to bladder pain.^{14,18}

Experiment 2: The Effects of OXY and PL on UBD-Evoked EMG Responses Following Stress (Stress-Induced Bladder Hypersensitivity)

The rats treated with SAL that experienced 7 days of footshock (STRESS-SAL group) experienced evidence of stress-induced bladder hypersensitivity manifested as significantly enhanced EMG responses to UBD as compared to the rats that were treated with SAL but did not receive footshock (SHAM-SAL; $F=7.12$, $p<0.05$). Post hoc tests revealed significant differences at intensities of 20, 30, 40, 50, and 60 mm Hg (Figure 2A). The effects of stress-induced bladder hypersensitivity were abolished in the rats treated with OXY on days 3–7 (Figure 2B) evidenced by the fact that STRESS-OXY rats had significantly decreased UBD-evoked EMG responses as compared to the STRESS-SAL rats ($F=3.38$, $p<0.05$). There was no difference between the SHAM-OXY and SHAM-SAL groups ($F=1.49$, $p=0.12$). Since this is a model of stress-induced bladder hypersensitivity, the lack of augmented EMG responses in the OXY-treated group could indicate that OXY has either an analgesic and/or anxiolytic effect. As shown in Figure 3, rats treated with OXY had enhanced UBD-evoked EMG responses after the administration of vasotocin in both the STRESS-OXY and SHAM-OXY subgroups ($F=13.2$, $p<0.01$). This provides further evidence that the attenuated EMG responses in the STRESS-OXY rats were in fact a result of the OXY administration.

In evaluating the effects of PL on stress-induced bladder hypersensitivity, Figure 2C shows that the SHAM-PL group had significantly enhanced UBD-evoked EMG responses compared to the SHAM-SAL group ($F=4.66$, $p<0.05$). There was no difference in EMG responses between the STRESS-PL and STRESS-SAL groups ($F=1$, $p=0.33$). There was also no difference in EMG responses between the STRESS-SAL and SHAM-PL groups ($F=0.69$, $p=0.42$). These results suggest that PL treatment produced enhanced bladder hypersensitivity through augmentation of either stress or nociception.

Experiment 3: The Effects of OXY and PL on UBD-Evoked EMG Responses in the Absence of Stress

As shown in Figure 4A, rats treated with OXY had significantly lower UBD-evoked EMG responses than rats treated with SAL ($F=8.92$, $p<0.05$). This difference was less pronounced with a lower dose of OXY (Figure 4B). When 0.25 mg of OXY was used instead of 0.5 mg of OXY, there was no statistical difference in EMG responses to UBD between the lower dose of OXY and the SAL groups ($F=2.6$, $p=0.13$). Since there was no preceding stressor in this series of experiments, the results argue that OXY does in fact have an analgesic effect in this model of visceral nociception. While there appeared to be some slight increase in EMG responses to suggest a nociceptive-enhancing effect of PL (Figure 4A), this difference was not statistically significant ($F=0.91$, $p=0.36$).

Experiment 4: The Effects of OXY and PL on Anxiety Independent of UBD

This series of experiments was designed to evaluate the effects of OXY and PL on anxiety independent of nociception. Even though there was some variability in these measurements, the OXY group spent significantly more time in the open arm of the elevated plus maze compared to the SAL-treated group ($45 \pm 35\%$ vs. $10 \pm 7.5\%$, $p < 0.01$). In contrast to the SAL-treated group, the PL-treated group spent significantly less time in the open arm of the elevated plus maze ($10 \pm 7.5\%$ vs. $1 \pm 1.7\%$, $p < 0.05$). These results suggest that OXY has an anxiolytic effect and further suggest that PL may have an anxiogenic effect.

Discussion

These experiments provide valuable insight into the effects of the lactogenic hormones OXY and PL on stress and bladder nociception. Experiment 1 showed that Lactating rats had significantly decreased EMG responses to UBD in a previously validated model of bladder nociception.^{8,33–34,44–45} This suggests a hypoalgesic state associated with breastfeeding. The basic science and clinical literature has shown postpartum lactation is associated with both decreased levels of anxiety²¹ and a HPA axis hyporesponsiveness to stressors.^{7,27} Coupled with the subsequent findings of the present study, we assert that this hypoalgesia is the result of a combination of analgesic and anxiolytic effects of the hormone OXY, but not PL, despite the fact that both are involved in postpartum lactation. Support for this assertion is given below.

The effects of stress-induced hyperalgesia have been well documented in both the basic science and clinical literature.^{12,16,20} From such reports, it is known that stress can exacerbate chronic pain conditions.^{26,29} Experiment 2 evaluated the effects of OXY and PL on stress-induced bladder hypersensitivity. In the SAL treated groups, a 7 day exposure to footshock (a well characterized experimental stressor^{22,45}) produced bladder hypersensitivity as measured by augmented EMG responses to UBD. However, rats pretreated with OXY prior to the footshock exposure did not have any differences in their EMG responses to UBD as compared to rats who did not receive footshock. In this model of stress-induced bladder hypersensitivity, such a finding implies an analgesic or anxiolytic effect of OXY. Results related to OXY in Experiments 3 and 4 suggest both effects were occurring. Experiment 3 was a measure purely of analgesia, Experiment 4 was a measure purely of anxiolysis, and OXY had positive effects in both. In Experiment 2, we also found that after the administration of vasotocin, an OXY receptor antagonist, augmented responses to UBD were restored. This provides strong pharmacological evidence that the inhibition of augmented EMG responses was a result of OXY-receptor activation as opposed to a nonspecific drug effect.

Experiment 2 also showed that after pretreatment with PL, rats which had not received 7 days of footshock (SHAM-PL rats) had UBD-evoked EMG responses similar to rats which had received 7 days of footshock, whether they received PL or SAL. This finding suggests that PL augments nociception, possibly via angiogenesis. Results related to the effects of PL in Experiments 3 and 4 support this theory. A caveat to this statement is that the elevated plus maze test which was used in Experiment 4 for measurements of anxiety has been validated as a tool for demonstrating anxiolysis, but is less definitive as a measure of angiogenesis.^{1,30,39}

Taken together, these experiments argue for analgesic and anxiolytic efficacy of OXY in modulating bladder nociception. Analgesic effects of OXY are further implicated in this process as animal studies have shown female rats have higher pain thresholds around the time of childbirth, which is also a time associated with peaks in oxytocin levels.¹⁸ Other studies have documented analgesic^{53–54} and anxiolytic^{1,30,51} effects of the central administration of OXY in separate animal models. There has also been evidence to imply that OXY has a role in the blunting of the HPA axis response seen with postpartum lactation.^{17,52} The results of the present experiments are novel in that they evaluate the results of the *peripheral*

administration of OXY and determined the effects of OXY on *both* nociception and stress in a visceral nociceptive model. These findings suggest that systemically administered OXY may be a potentially useful agent for patients suffering from stress-exacerbated chronic visceral pain syndromes like interstitial cystitis.

Experiment 1 utilized parous and actively lactating rats. Virgin rats were used for subsequent experiments to minimize the potential variability induced with parity. In analyzing the collective data from all four experiments, it would appear that rats in the Non-Lactating group of Experiment 1 (Figure 1A) have higher UBD-evoked EMG responses compared to rats in the SHAM-SAL group of Experiment 2 (Figure 2A) and rats in the SAL group of Experiment 3 (Figure 4). Such a finding would suggest the possibility of enhanced degrees of nociception post lactation. However, these experiments are usually conducted by a single investigator in a carefully paired fashion to reduce the potential for variability by nonspecific factors such as differences in baseline “noise” levels. For example, in Experiment 2, UBD-evoked EMG responses were obtained from the same number of animals in each treatment group daily. Therefore, it is difficult to compare data from different experiments since they were done at different points in time. Thus, such conclusions regarding nociception in the post-lactation period cannot be made from these studies.

Further studies are warranted to better define the exact mechanisms of analgesia and anxiolysis documented in these studies. Since there is an anxiolytic effect, this implies central nervous system sites of action, but because these agents were injected peripherally, the central sites of activation must either allow penetration of the drug despite poor permeability through the blood-brain barrier or must be activated by a peripheral input, such as vagal afferents, which in turn would have to be activated by OXY. Further study is also needed to define whether or not peripheral OXY has analgesic effects in other types of nociception. Given the regular use of systemic OXY in obstetrics, there is good safety data related to its use, so the demonstration of analgesic utility could have rapid translation to clinical use.

Contrary to our initial hypotheses, our studies did not support an analgesic or anxiolytic effect associated with PL. Previous studies have documented such effects of centrally-administered PL in rats.^{40–41,46,49} However, in patients with PL-secreting pituitary adenomas, it has been shown patients with higher PL levels have worse headaches⁵ and a poorer overall quality of life.¹⁰ It is also possible that perhaps, at least in regards to postpartum lactation, an anxiogenic effect of PL is advantageous. Since PL is responsible for stimulating the mammary glands to produce milk, it is feasible it could also be responsible for encouraging the mother to breastfeed through a slightly heightened state of anxiety. This heightened anxiety could be relieved through breastfeeding via the anxiolytic effects of OXY release, which is associated with suckling. The analgesic effect of OXY is also likely advantageous in promoting this interaction between the mother and infant.

In summary, our results indicate that OXY has both analgesic and anxiolytic properties which potentially make it a useful agent for the treatment of stress-induced pain exacerbations in women with interstitial cystitis. PL may have an anxiogenic effect. This needs to be further studied, as does the effects of PL on nociception independent of stress.

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Figure 1.

A, Rats that were actively lactating had decreased EMG responses to UBD as compared to rats that were not lactating, implying an analgesic effect associated with postpartum lactation. **B**, Typical examples of EMG activity in response to a 50 mm Hg UBD in a Non-Lactating (upper) and Lactating (lower) rat. ** $p < 0.01$. $n = 6$ per group.

Figure 2.

A, STRESS (footshock-treated) rats exhibited significantly enhanced EMG responses to UBD as compared to SHAM (no footshock) rats in the SAL treated groups. **B**, OXY significantly attenuated stress-induced bladder hypersensitivity. The STRESS-OXY group had significantly lower EMG responses to UBD compared to the STRESS-SAL group. There was no difference between the SHAM-OXY and SHAM-SAL groups. **C**, SHAM-PL rats had augmented responses to UBD compared to SHAM-SAL rats. Responses of STRESS-PL and STRESS-SAL rats did not differ. ** $p < 0.01$. $n = 8-12$ per group.

Figure 3.

The analgesic effects of OXY were reversed by vasotocin, an OXY receptor antagonist, in both the SHAM (**A**) and STRESS (**B**) groups ($p < 0.05$ for figures 3A and 3B with a combined $p < 0.01$ for the OXY vs. vasotocin EMG responses). * $p < 0.05$, ** $p < 0.01$. $n = 6$ per group.

Figure 4.

A, In the absence of footshock, OXY significantly attenuated UBD-evoked EMG responses, while PL had no significant effect. **B**, Compared to SAL-treated rats, OXY 0.5 mg significantly attenuated EMG responses to UBD. The difference was less pronounced with an OXY dose of 0.25 mg suggesting that it is analgesic in a dose-dependent manner. * $p < 0.05$ (OXY 0.5 mg vs. the SAL-treated group), ** $p < 0.01$ (OXY 0.5 mg vs. the SAL-treated group). $n = 8$ per group.