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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 nonfootshock 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.**

Perspective: ***This study presents evidence that systemic oxytocin has both analgesic and anxiolytic properties which may make it a potentially useful agent for patients with stress-exacerbated chronic-pain syndromes such as interstitial cystitis. These studies do not suggest a similar role for prolactin.***

Key words: *Oxytocin, prolactin, nociception, pain, stress, anxiety, bladder.*

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 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 et al,[21] women reported elevated mood, enhanced calmness and reduced anxiety while breastfeeding. 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]

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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.

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-hour light-dark cycle, where lights were off between 6:00 pm and 6:00 am, was maintained. One group of rats (Experiment 1-lactating) was used at the time of weaning from pups 2 to 4 weeks postpartum. A separate group of parous rats (Experiment 1-nonlactating) was utilized 3 to 4 weeks after weaning from their pups. All other female rats were virgins which were allowed a period of 1 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[22] which produced activation of the HPA axis evidenced by upregulation of corticotrophin-releasing factor mRNA in the brain. 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 minutes/day, 1 mA, 1-second duration, total of 30 shocks each day) administered via a grid floor under a variable interval schedule for 7 days. Rats in the nonfootshock 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 (ie, 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 to 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 secconds) 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 minutes after