Reversal of Peripheral Nerve Injury-induced Hypersensitivity in the Postpartum Period

Role of Spinal Oxytocin

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ABSTRACT

Background: Physical injury, including surgery, can result in chronic pain; yet chronic pain following childbirth, including cesarean delivery in women, is rare. The mechanisms involved in this protection by pregnancy or delivery have not been explored.

Methods: We examined the effect of pregnancy and delivery on hypersensitivity to mechanical stimuli of the rat hindpaw induced by peripheral nerve injury (spinal nerve ligation) and after intrathecal oxytocin, atosiban, and naloxone. Additionally, oxytocin concentration in lumbar spinal cerebrospinal fluid was determined.

Results: Spinal nerve ligation performed at mid-pregnancy resulted in similar hypersensitivity to nonpregnant controls, but hypersensitivity partially resolved beginning after delivery. Removal of pups after delivery prevented this partial resolution. Cerebrospinal fluid concentrations of oxytocin were greater in normal postpartum rats prior to weaning. To examine the effect of injury at the time of delivery rather than during pregnancy, spinal nerve ligation was performed within 24 h of delivery. This resulted in acute hypersensitivity that partially resolved over the next 2–3 weeks. Weaning of pups resulted only in a temporary return of hypersensitivity. Intrathecal oxytocin effectively reversed the hypersensitivity following separation of the pups. Postpartum resolution of hypersensitivity was transiently abolished by intrathecal injection of the oxytocin receptor antagonist, atosiban.

Conclusions: These results suggest that the postpartum period rather than pregnancy protects against chronic hypersensitivity from peripheral nerve injury and that this protection may reflect sustained oxytocin signaling in the central nervous system during this period.

What We Already Know about This Topic

- Chronic pain develops after many surgeries
- The prevalence of chronic pain depends on the particular type of surgery

What This Article Tells Us That Is New

- There is a low incidence of chronic pain after cesarean delivery; this could be related to hormones regulated during pregnancy or after delivery
- Increased postpartum oxytocin reduces mechanosensitivity after nerve injury and may be part of a protective mechanism against the development of chronic pain after cesarean delivery

PHYSICAL injury can result in chronic pain, usually with neuropathic characteristics, and occurs in 5–50% of patients undergoing surgery, depending on the surgical procedure.[1] For example, chest wall pain is present in nearly half of women 2 yr after mastectomy for cancer, and half of these women rate their pain as moderate to severe with interference of activities of daily living and utilization of healthcare resources.[2] Although many patient and surgical factors are associated with increased risk for chronic pain after surgery, the mechanisms underlying the lack of resolution of pain in these individuals are unknown. Peripheral nerve injury in rodents results in long lasting hypersensitivity to mechanical stimuli,[3] a surrogate for allodynia in patients that can accompany chronic pain after surgery.[4] This hypersensitivity is associated with multiple changes in neuronal function and neuronal-glial interactions in the spinal cord, and pharmacologic blockade of many of these changes results in temporary resolution of hypersensitivity.[5,6] Social interactions also modulate hypersensitivity in rodents with peripheral nerve injury, with hypersensitivity reduced in pair-housed mice compared with isolated animals by a mechanism that involves oxytocin.[7]

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In contrast to chronic pain after surgery, childbirth is not associated with such a high incidence of chronic pain. Thus, chronic pain related to surgery is nearly ten-fold greater in incidence following abdominal hysterectomy for non-cancer indications compared with cesarean delivery.[8–11] This could reflect a lesser degree of injury to peripheral nerves from cesarean delivery, which typically is of shorter duration than abdominal hysterectomy, although peripheral nerve injury from cesarean delivery has been documented to produce chronic pain.[12,13] Alternatively, psychological factors or active protection from pregnancy or delivery could be responsible for this low incidence of chronic pain. The primary purpose of the current study was to determine whether protection occurs also in rodents during the peripartum period from hypersensitivity induced by spinal nerve ligation, a surgical model of chronic neuropathic pain. We observed a protective effect which was related to the postpartum period, but not during pregnancy.

A protective effect in the post-, but not prepartum period, is not consistent with an etiology dependent on circulating progesterone and estrogen, which decline rapidly following delivery. We therefore focused our initial mechanistic studies on oxytocin. Oxytocin is released from the pituitary into the systemic circulation to accomplish multiple functions during labor and thereafter.[14–16] In addition, oxytocin is also released in the central nervous system, as evidenced by increased concentrations in cerebrospinal fluid (CSF) during labor.[17] Because oxytocin does not cross the blood brain barrier[18] this increase likely reflects sustained activation of oxytocin containing neurons in the central nervous system. In addition to its effects on maternal-neonatal bonding, oxytocin, released in the spinal cord from descending projections from the paraventricular nucleus, is analgesic.[19] A secondary purpose of this study was to probe the role of spinal oxytocin receptor signaling in protection from surgery-induced hypersensitivity.

Material and Methods

Animals

Female Sprague-Dawley rats (250–350 g) from Harlan Industries (Indianapolis, IN), housed under a 12-h light-dark cycle with food and water ad libitum, were used. All experiments were approved by Animal Care and Use Committee at Wake Forest University (Winston Salem, North Carolina).

Surgical Preparations

One week before delivery or the day of delivery, animals were anesthetized with 2% isoflurane in oxygen and spinal nerve ligation (SNL) or sham surgery was performed. For SNL, the right L6 transverse process was removed and the right L5 and L6 spinal nerves were tightly ligated using 5.0 silk sutures as previously described.[3] Sham surgery consisted of exposure of the L5 and L6 spinal nerves, but no ligation. After surgery, animals were housed individually with or without their pups according to the study design in plastic cages in a climate-controlled room under a 12 h/12 h light-dark cycle, with free access to food and water.

Behavioral Testing

Withdrawal threshold to punctuate mechanical stimulation was determined before and after SNL or sham surgery by the application of calibrated von Frey filaments (Stoelting, Wood Dale, IL) to the hindpaw. Animals were separated from pups, if present, and placed on a plastic mesh floor in individual clear plastic boxes and allowed to accommodate to their environment for at least 30 min. Filaments were applied to the bending point for 5 s, and a brisk paw withdrawal was considered a positive response. Withdrawal threshold was determined by application of filaments of different bending strengths using an up–down statistical method.[20] Behavioral testing was performed prior to surgery and commencing 3 days thereafter. The person performing the behavioral test was blinded to surgery and treatment.

A total of 168 animals were tested in these protocols. All animals recovered from surgery without evidence of infection, and all deliveries occurred spontaneously with an average litter size of 11.

Timing of Surgery and Behavioral Measures

To investigate the effect of pregnancy and postpartum over the SNL-induced hypersensitivity, SNL surgery was performed one week before delivery in a total of 37 pregnant rats. In a group of these (20/37), the pups were housed with the dam until weaning and their withdrawal thresholds were monitored and compared with nonpregnant animals with SNL (n = 17). The other group of the pregnant rats with SNL (n = 17/37) were separated from the pups within 24 h of delivery. Their withdrawal thresholds were monitored and compared as well with controls (nonpregnant rats with SNL, n = 6).

To study the resolution of SNL-induced hypersensitivity during postpartum period and after weaning, surgery was performed in 30 animals (15 SNL and 15 sham) within 24 h after delivery and compared with virgin controls (SNL or sham, n = 13 each).

Withdrawal threshold was determined prior to surgery and 3, 10, 14, and 17 days afterwards. In addition, in 18/30 animals with surgery within 24 h of delivery (9 Sham and 9 SNL), their withdrawal thresholds were monitored also at 22, 28, 31, and 34 days after surgery.

Oxytocin Concentration in Lumbar Spinal Cerebrospinal Fluid

In 11 animals without previous surgery (four nonpregnant, four with pups 22 days after delivery, and three, also 22 days after delivery, but with pups removed 24 h previously), anesthesia was induced with 2% isoflurane and a T13-L1 laminectomy was performed. A sharp glass pipette with connection to a microinjection syringe was used to penetrate

into the intrathecal space corresponding to L4-L5 segments. Approximately 100 μl of CSF was withdrawn for oxytocin assay, using a commercially available ELISA kit (Assay Designs Inc., Ann Arbor, MI) as previously reported.[21]

Intrathecal Drug Administration

Rats were briefly anesthetized with isoflurane in oxygen on day 21 following delivery and 12 μl containing 12 μg of the oxytocin receptor antagonist atosiban (1-deamino-2D-Tyr(O-ethyl)-4-Thr-8-Orn-oxytocin (n = 7 for SNL, n = 8 for no surgery), the opioid receptor antagonist naloxone (10 μg, n = 7 for SNL), or 12 μl saline (n = 6 for SNL) were injected intrathecally by acute puncture between L3 and L4 vertebrae of the spine using a 30-gauge half-inch needle as previously described.[22] Needle insertion was assumed by a brief tail flick. Prior training using this method and injection of local anesthetic in other rats resulted reliably (> 95%) in temporary hindlimb paralysis, indicative of intrathecal injection. Behavioral testing was conducted before and at hourly intervals after injection. On day 22 following delivery, the day after weaning, another group of animals received 10 μl containing 120 ng of oxytocin (n = 7) or μl saline (n = 6) by the similar procedure.

Statistical Analysis

To examine our hypotheses we used generalized estimating equations. Generalized estimating equations are a method for analyzing multilevel longitudinal data.[23] Because both the nature of the outcome as well as the correlation structure of the repeated measures can be specified, generalized estimating equations provide accurate estimates of the standard errors, allowing for precise estimation of confidence intervals. In general, we utilized two-factor models with experimental groups (or sides) as a between subjects factor and time as a repeated measures factor. A normal distribution with identity link was specified for the outcomes and repeated measures modeled with an independent covariance structure. For these models, time is expressed as days since surgery, injury, or delivery as appropriate. We report the main effects (group, time) and interactions (group × time) for all models. Only where indicated by either a statistically significant main effect or group × time interaction (for group differences across time) was *post hoc* testing conducted. To control the error rate for each effect, Bonferroni corrected *post hoc* tests were conducted on *a priori* designated pairs (*e.g.*, groups at synchronous times). Because of the modest sample size and heterogeneous variance, we conducted a Kruskal-Wallis test on CSF oxytocin levels by experimental group with post hoc Mann-Whitney U tests and Bonferroni corrections. Data are presented as mean ± SD, except for CSF oxytocin concentrations that exhibited considerable heterogeneity of variances so these data are presented using scatter plots. All analyses were conducted using SPSS 18.0 (IBM, Chicago, IL). Where appropriate, all hypothesis testing is two-tailed with P value less than 0.05 considered statistically significant.

Results

The Postpartum Period, but Not Pregnancy, Alleviates SNL Hypersensitivity

SNL 1 week before delivery resulted in slightly less hypersensitivity in pregnant animals compared with nonpregnant animals (fig. 1A), whereas sham surgery was without effect on paw withdrawal threshold in either group (data not shown). Overall pregnant rats were less sensitive as compared to nonpregnant rats (Group $P < 0.0001$) with both groups exhibiting a similar sharp drop in withdrawal thresholds after injury (Time: $P < 0.001$), but following delivery there were increasing thresholds among postpartum rats, whereas it was relatively unchanged over a similar time period in nonpregnant animals (fig. 1A: Group × Time: $P < 0.001$). Separation of the pups on the first day after delivery prevented the postpartum decrease in hypersensitivity (fig. 1B, Group: $P = 0.131$) with both groups exhibiting similar drop in withdrawal thresholds after injury (Time: $P < 0.001$, Group × Time: $P < 0.001$).

Hypersensitivity from SNL Is also Alleviated When the Injury Occurs at the Time of Delivery

When SNL injury was performed on the day of delivery, ipsilateral tactile hypersensitivity developed rapidly and to a similar degree compared with nonpregnant rats (fig. 2A). However, hypersensitivity diminished thereafter in postpartum, but not in nonpregnant rats (Group: $P < 0.0001$, Group × Time: $P < 0.0001$). A much lesser degree of hypersensitivity was observed after sham surgery in both groups (fig. 2A, Time: $P < 0.0001$), and as in SNL, with lesser hypersensitivity overall in postpartum than nonpregnant animals. There were small reductions in withdrawal threshold contralateral to surgery in both sham and SNL groups (fig. 2B; Time: $P < 0.001$, Group: $P = 0.002$; Group × Time: $P = 0.001$), with overall differences between the groups.

Weaning of Pups Produces Temporary Hypersensitivity

Weaning of pups 21 days after delivery resulted in a temporary reduction in withdrawal threshold regardless of whether SNL or sham surgery had been performed (fig. 3; Time: $P < 0.0001$, Side × Group $P = 0.004$) and this effect was greater ipsilateral to surgery in SNL than sham animals (fig. 3; Group: $P < 0.001$)

Role of Spinal Oxytocin in Postpartum Action on SNL-induced Hypersensitivity

Three results suggested a prominent role of spinal oxytocin release on the resolving effect of the postpartum period on SNL-induced hypersensitivity. First, there were significant differences among postpartum rats that were kept with or separated from their pups 24 h earlier and the controls in the oxytocin concentration in lumbar CSF 22 days after delivery (fig. 4A, Group $P = 0.036$). Second, acute administration of intrathecal oxytocin, but not vehicle, one day after separation

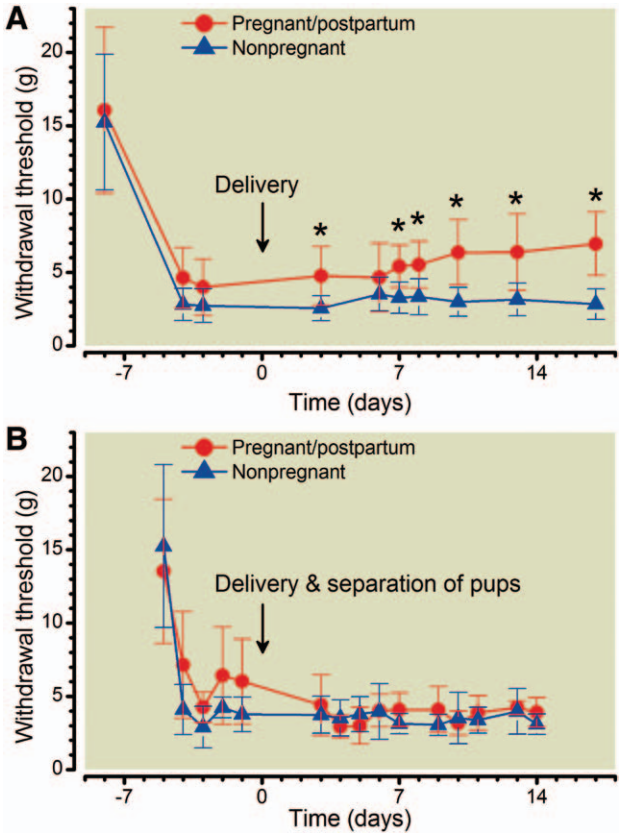

Fig. 1. Effect of spinal nerve ligation surgery, when performed during pregnancy, on withdrawal threshold. *A*, Withdrawal threshold over time in pregnant and nonpregnant rats, with surgery performed one week prior to delivery. *B*, Withdrawal threshold over time in pregnant and nonpregnant rats, with surgery performed 1 week prior to delivery and pups removed within 24 h of delivery. Data are presented as mean ± SD, Bonferroni's Multiple Comparison Test: *$P < 0.05$ compared with nonpregnant.

from pups produced an antihypersensitivity effect (fig. 4B, Group $P < 0.001$, Time: $P < 0.001$, Group × Time $P < 0.001$). Finally, in rats with SNL performed 1 week before delivery, the partial resolution of tactile hypersensitivity 3 weeks after delivery was reversed by the acute lumbar intrathecal injection of the oxytocin receptor antagonist, atosiban, but not by the opioid receptor antagonist, naloxone (fig. 4C; Group: $P < 0.001$; Time: $P < 0.001$; Group × Time: $P < 0.001$).

Discussion

Chronic pain after major physical injury, including surgery, affects as many as 50 million individuals globally each year, yet little is known regarding the processes which result in resolution or lack of resolution of acute pain following injury. Although backache and headache are common pain complaints following childbirth, these usually predate the delivery itself[24] and pain in the perineum, pelvis, or site of cesarean delivery scar 1 yr after delivery is remarkably low.[11] This observation suggests that the puerperium may alter processes of pain resolution and thereby influence the trajectory of recovery from pain following physical injury. The current study provides an animal correlate to these clinical observations and an initial examination of the mechanisms for this protection. We employed a surgical injury of peripheral nerves resulting in hypersensitivity to mechanical stimuli rather than an abdominal incision such as would occur with cesarean delivery in order to more rigorously examine our hypothesis that factors during pregnancy or the puerperium protect against chronic pain after neuropathic surgical injury.

Hypersensitivity to tactile stimuli after peripheral nerve injury in rodents is used as a surrogate for allodynia[3,24] which occurs in many patients with chronic neuropathic pain. Although patients suffer and seek medical treatment for chronic neuropathic pain because of spontaneous pain rather than allodynia *per se*, allodynia nonetheless may exacerbate pain during activities of daily living, resulting in fear of pain and curtailment of normal activities. In addition, there is a strong correlation between the area of tactile allodynia surrounding the surgical wound following surgery and the risk for chronic pain,[25] suggesting that this measure is meaningful in the study of mechanisms of resolution of pain following injury.

Using this model of neuropathic hypersensitivity, we observed a very minor protective effect of pregnancy on resolution, at least over the last 7 days of pregnancy. Although it is conceivable that resolution took more than 7 days to become evident, the reduction in hypersensitivity which occurred within a few days of delivery, whether neuropathic injury occurred at the time of delivery of 7 days previously, argues strongly against a primary effect of factors present during pregnancy on this resolution. Gestational hormones and neurosteroids can produce antinociceptive and antihypersensitivity effects when acutely administered,[26–28] and we did not probe the role of these hormones using selective antagonists, so we cannot completely exclude their role in the resolution of hypersensitivity observed.

Minimal resolution of hypersensitivity was observed over a 3-week period following SNL in virgin female rats, consistent with the very shallow recovery observed after this surgical nerve injury, typically requiring 3–6 months for resolution, with many animals showing no resolution at all.[3,29] In contrast, hypersensitivity began to recover starting 3 days after delivery with continued improvement over the subsequent month, although complete recovery was not observed in all animals at this time period.

The presence of pups was important for this recovery, because it did not occur in animals whose pups had been removed shortly after delivery in agreement with previous studies that suggest that social isolation increases mechanical allodynia.[30]

Although many factors could affect central nervous system plasticity during the puerperium, we focused our initial studies on oxytocin. This neuropeptide, classically examined

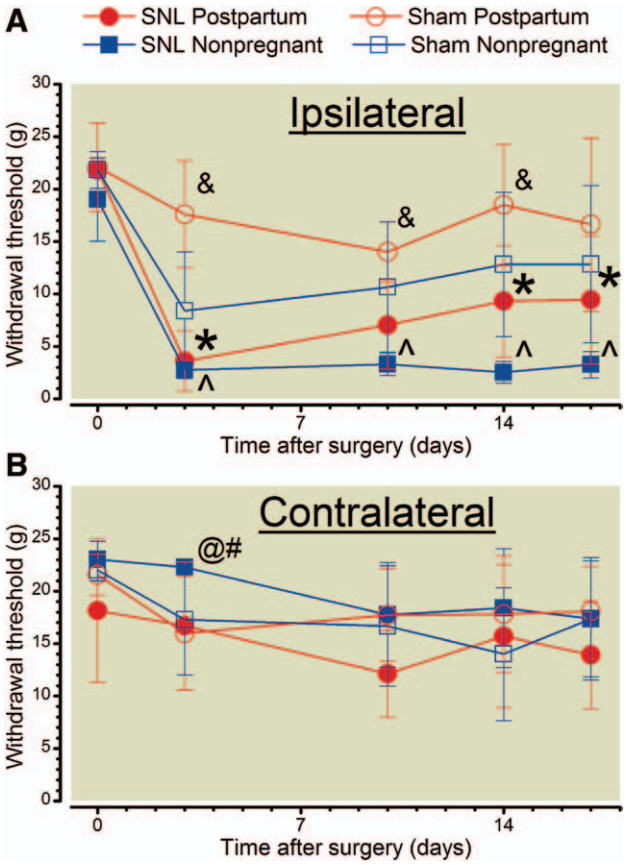

Fig. 2. Effect of SNL or sham surgery, when performed within 24 h of delivery, on withdrawal threshold. Withdrawal threshold ipsilateral (*A*) or contralateral (*B*) to SNL or sham surgery in virgin, nonpregnant and in postpartum rats when surgery was performed within 24 h of delivery. Data are presented as mean ± SD, Bonferroni's Multiple Comparison Test: $^{*}P < 0.05$ comparing postpartum SNL with nonpregnant SNL; $^{\wedge}P < 0.05$ comparing postpartum SNL with postpartum Sham, $^{\&}P < 0.05$ comparing postpartum SNL with nonpregnant Sham; $^{\wedge}P < 0.05$ comparing nonpregnant SNL with nonpregnant Sham, $^{@}P < 0.05$ comparing nonpregnant Sham with postpartum Sham, $^{\#}P < 0.05$ comparing nonpregnant Sham with postpartum SNL. SNL = spinal nerve ligation.

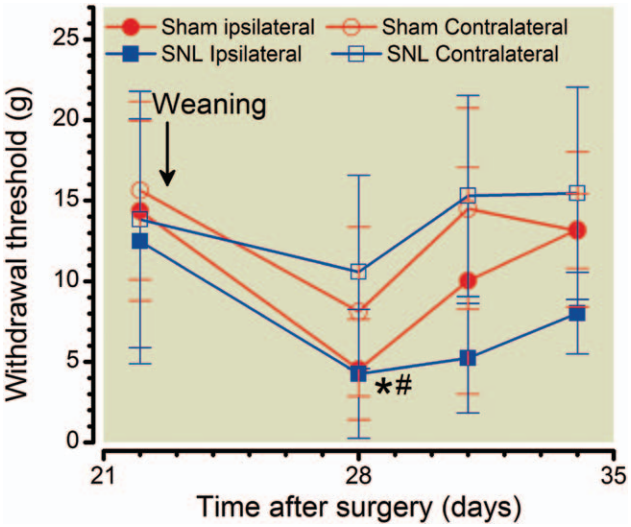

Fig. 3. Effect of pups separation at the time of weaning on withdrawal threshold. Withdrawal threshold over time before and after weaning and separation of pups 22 days after delivery and with SNL or sham surgery performed within 24 h of delivery. Data are presented as mean ± SD, Bonferroni's Multiple Comparison Test: $^{*}P < 0.05$ comparing nonpregnant Sham with postpartum Sham; $^{\#}P < 0.05$ comparing nonpregnant Sham with postpartum SNL. SNL = spinal nerve ligation.

for its effect on the labor process and lactation after release from the pituitary, has more recently received attention as a neurotransmitter within the central nervous system important to social interactions. Oxytocin containing neurons in the paraventricular and supraoptic regions of the hypothalamus send diffuse projections to the forebrain, limbic structures, brainstem, and spinal cord. Of special importance to pain are oxytocin's effects in the amygdala, a key center regarding negative emotional experiences and reaction to pain, and the spinal cord, the initial site of pain neurotransmission. Others have shown that this paraventricular nucleus—spinal cord oxytocin pathway, when stimulated, produces acute antinociception and acutely reduces hypersensitivity after peripheral nerve injury.[19,31,32]

Several experiments in the current study support a role for spinally released oxytocin in the resolution of injury-induced tactile hypersensitivity during the puerperium. Lumbar CSF concentrations of oxytocin were increased during this time period, rapidly decreasing after removal of pups in normal animals and coincident with a transient return of hypersensitivity in both normal and injured animals. We did not measure CSF concentrations of oxytocin in injured animals and our sample size was small, both factors limiting the interpretation of our data, yet it is consistent with the known effects of lactation to stimulate release of oxytocin[33] not only in the blood, but also in the central nervous system, and is consistent with the reliance on the presence of pups, and hence lactation for the resolution of hypersensitivity in postpartum animals. The observation that pregnancy did not alleviate SNL-induced hypersensitivity is consistent with the fact that oxytocin released in the paraventricular hypothalamic nucleus of pregnant rats did not differ from that of nonpregnant animals.[34,35] Following labor, there is a significant but transient increment of oxytocin in the paraventricular hypothalamic nucleus (3-fold) and during lactation central oxytocin remains high during the postpartum period.[34] It is also consistent with the very transient reduction in withdrawal threshold, even in normal animals, when the pups were weaned at the normal time after delivery. Lumbar intrathecal injection of oxytocin shortly after weaning reinstated the antihypersensitivity effect. Finally, intrathecal injection of the oxytocin receptor preferring antagonist, atosiban, prior to weaning transiently reversed the postpartum antihypersensitivity effect. Atosiban also reduced withdrawal

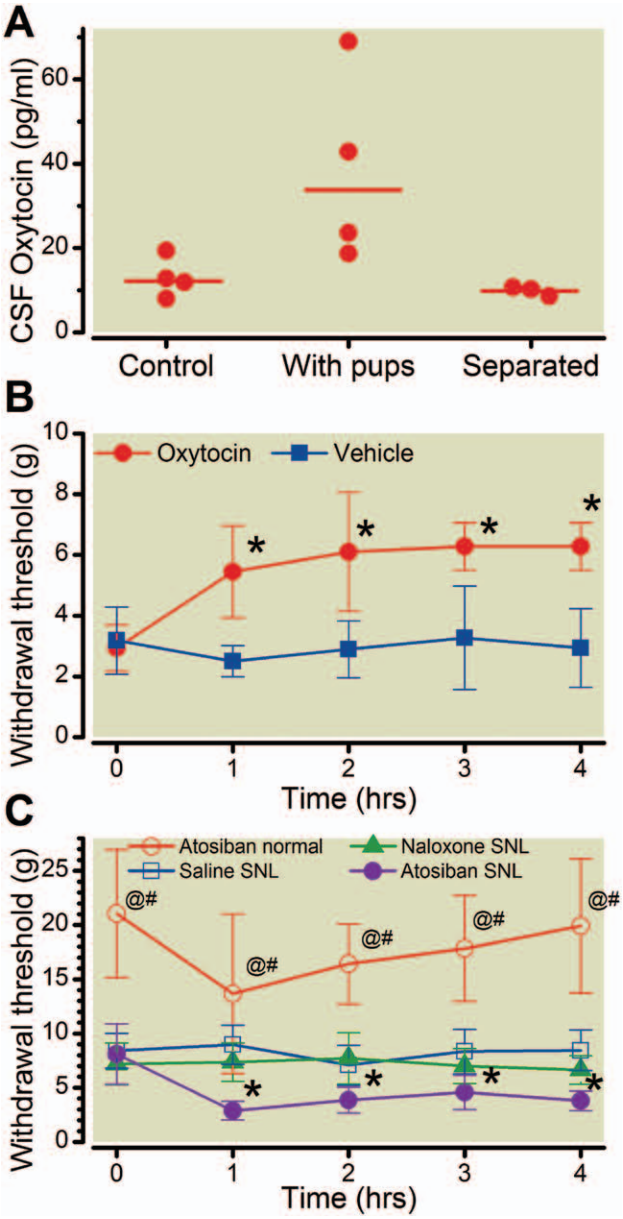

Fig. 4. Role of spinal oxytocin in postpartum antihypersensitivity. *A*, CSF concentrations of oxytocin in nonpregnant animals (control), postpartum rats 22 days after delivery (With pups) or those 22 days after delivery with pups separated 24 h earlier (Separated). The *bar* represents the mean. *B*, Withdrawal threshold over time in postpartum rats with SNL following separation of pups and after intrathecal injection, at time 0, of oxytocin or vehicle. $^{*}P < 0.05$ compared with vehicle. *C*, Withdrawal threshold over time in postpartum rats 3 weeks after SNL at the time of delivery and receiving intrathecal injection of saline, the oxytocin receptor antagonist atosiban, or the opioid receptor antagonist, naloxone. For comparison, the effect of intrathecal atosiban in nonpregnant, non-postpartum rats is also shown. Data are presented as mean ± SD. Bonferroni's Multiple Comparison Test: $^{*}P < 0.05$ comparing atosiban SNL with saline SNL; $^{@}P < 0.05$ comparing atosiban normal with atosiban SNL; $^{\#}P < 0.05$ comparing atosiban normal with saline SNL. CSF = cerebrospinal fluid; SNL = spinal nerve ligation.

threshold in normal animals, and although this decrease was not statistically significant it was not specific to the nerve injury state and is consistent with tonic oxytocinergic tone in the spinal cord which affects response to peripheral stimuli. Additionally, we recognize that a weakness of these pharmacologic studies is that oxytocin and atosiban act on both oxytocin and vasopressin receptors and, antinociception from systemically administered oxytocin is dependent on vasopressin-1A receptor signaling.[36] We cannot conclude from the current experiments which of these receptors are primarily responsible for these effects.

Endogenous opioids modulate the antinociceptive effect of oxytocin in normal rats.[37] However, intrathecal naloxone failed in the current study to reverse the postpartum alleviation of SNL-induced hypersensitivity suggesting that oxytocin may act by a mechanism different than the opioids during the postpartum period and in chronic pain condition. The mechanisms by which oxytocin might prevent the development of SNL-induced hypersensitivity in rats after delivery were not otherwise examined in these studies. Others have shown that oxytocin reduces behavioral hypersensitivity in male rats by stimulating γ-amino-butyric acid release from spinal interneurons[38] and by preventing long-term potentiation in wide dynamic range neurons in the spinal cord.[32] It is conceivable that oxytocin released onto the spinal cord during the postpartum period acts by similar mechanisms to prevent the sensitization of superficial spinal cord neurons.

The current work has limitations in its interpretation. For one, it focuses on spinal mechanisms of oxytocin action, although other sites may also be relevant to analgesia. For instance, injection of oxytocin into the periaqueductal gray and nucleus raphe magnus produces antinociception in normal rats[39,40] and oxytocin signaling is also important in modulating nociception in the central nucleus of the amygdala[41] and the nucleus accumbens,[42] the latter dependent on opioid receptor activation. It is conceivable that part of the enhanced resolution of hypersensitivity observed in the current study could be attributable to increased oxytocin signaling at these and other supraspinal sites. Another limitation is that, like most mechanistic studies in rodents, it relies on evoked response to mechanical stimuli and hypersensitivity following nerve injury as an important reflection of chronic pain in humans. Allodynia is far from universally present in patients with chronic pain after surgery, and its importance to the subjective experience of pain may often be small.

In conclusion, clinical experience suggests the likelihood of chronic pain after childbirth is small, and we show here a gradual, partial resolution of tactile hypersensitivity from peripheral surgical trauma during the puerperium in rats. This protective effect requires the presence of pups but outlasts weaning if the injury occurs near the time of delivery. Reversal of this protective effect by lumbar intrathecal delivery of an oxytocin, but not opioid-receptor antagonist,

and its association with increased CSF concentrations of oxytocin are consistent with a hypothesis that supraspinal-spinal oxytocin drive increases after delivery and is at least partially responsible. A better elucidation of the causes of puerperal protection from hypersensitivity after peripheral nerve injury could provide important targets for prevention and treatment of chronic neuropathic pain.

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