Effects of intramuscular oxytocin on sensory function in healthy volunteers with ultraviolet burn injury to the skin
IRB00056660

NCT03935399

Version Date: 10/17/2019

BACKGROUND

A large body of evidence in animals and in humans suggest that oxytocin can produce analgesia to experimental pain stimuli and relieve pain in acute and chronic clinical pain states. For the past 8 years we have, under an NIH MERIT award, tested the role of the spinal cord in oxytocin's actions by studies in rodents and clinical trials, 3 of which are ongoing, of spinally injected oxytocin.

The Pain Mechanisms Laboratory at Wake Forest is now in the process of assembling an NIH program project grant (P01) on the topic of oxytocin sites, mechanisms, and clinical applications for analgesia, and Dr. Eisenach will lead the clinical project in that proposal. The goal of this IRB protocol is to test whether effects of oxytocin on peripheral nerves observed in physiology experiments in rodents might be applicable to humans and worthy of study more completely in the NIH P01 application in September, 2019.

ANIMAL DATA SUPPORTING THE UNDERLYING PREMISE

Following acute peripheral injury and in many chronic pain states there are changes in sensory response to mechanical stimulation in and surrounding areas of pain. Patients and investigators focus understandably on hypersensitivity, resulting in increased pain to a normally painful stimulus (hyperalgesia) and pain from light touch which is normally not painful (allodynia). Yet, hyposensitivity is as or more prevalent in chronic neuropathic pain, and many chronic pain patients experience both hyper- and hyposensitivity [9; 19; 24]. Gate control theory posits that Aβ, touch sensitive fiber input acts to reduce Aδ and C nociceptor input [18], so loss of Aβ input could play an important role in the setting of pain.

Over the past 7 years we have recorded from Aβ and Aδ neurons *in vivo*, showing that both are altered after injury and that oxytocin acutely returns their function towards normal [2; 4-6; 23]. Within minutes of peripheral skin incision, during recovery from surgery, and in a model of chronic nerve injury pain, Aδ are sensitized, as evidenced by larger receptive fields, lower mechanical threshold in the receptive field for activation, shift in response to a tonic mechanical stimulus from a rapidly adapting, on-

off response to a sustained or slowly adapting response, and ability to respond to repeated stimuli at higher frequency than before. In contrast, opposite effects are seen in the Aβ touch-sensitive neurons, with smaller or non-existent receptive fields, higher mechanical threshold for activation, hyperpolarized resting membrane potential (Em), and reduction in the frequency of stimuli they can respond to. Experimental constraints precluded the study of all of these outcomes during acute peripheral oxytocin exposure, but oxytocin depolarizes Em in Aβ fibers towards normal by hyperpolarizing Em in Aδ fibers, which should render them less responsive to peripheral stimuli.

In summary, these animal data support the concept that oxytocin may act in the periphery to reset the balance of touch and nociceptor mechanical input towards normal after injury. They suggest that treatment of oxytocin in humans with peripheral injury will affect touch-sensitive Aβ fibers by restoring their response to high frequency, vibration stimuli and will reduce the sensitivity of Aδ nociceptors, thereby increasing the pain detection threshold for mechanical stimuli.

RATIONALE FOR USE OF THE UV-BURN PLUS HEAT MODEL OF PERIPHERAL INJURY

For our primary goal – to examine the effects of oxytocin peripheral nerves after tissue injury – we chose the controlled ultraviolet sunburn model. This is a model that we have previously used at Wake Forest in healthy volunteers [8]. It utilizes an FDA approved device which is designed and marketed to evaluate sunscreens in people, is titrated to the individual's response to UV radiation, and results in a subscribed area of redness and sensitivity to light touch that lasts 2-3 days, with minimal or no spontaneous pain and no lasting changes in the skin. The area of sensitivity can be expanded beyond the area of UV radiation exposure temporarily by heating the area with a non-painful stimulus (40°C) for 5 min, and this expanded area and sensitivity within the area of UV exposure can be maintained by repeating this heating at 40 min intervals. As in our previous use of this method and as used by others [8; 16], we propose to expose the skin to 3 levels of irradiation to determine the minimum erythematous dose (MED) defined on inspection the following day characterized by marked redness with well demarcated borders [1]. On a subsequent day the skin on the volar aspect of the dominant wrist will be irradiated at the 2 MED dose and the subject

will return twice for testing, first on the day after irradiation and second the following day. At each testing session the area of UV radiation will be heated to 40°C twice separated by 40 minutes.

RANDOMIZED TREATMENT

We propose to take advantage of the stable nature of this model of peripheral injury for 2-3 days in order to apply a randomized, blinded, cross over design with treatment with oxytocin one day and placebo on another. Following baseline measures on each of the two study days, subjects will receive an intramuscular injection of oxytocin (Pitocin®) in its indicated dose of 10 IU (17 µg) or an equivalent volume of saline. In the absence of pregnancy or the postpartum period, doses of oxytocin much greater than this (24-80 IU) produces no physiologic adverse effects when administered intranasally, which produces rapid systemic absorption [15; 17; 21; 27; 32].

RATIONALE FOR PRIMARY OUTCOME MEASURES AND TIMING OF MEASUREMENTS

We will determine thresholds to perception of vibration at a frequency of 256 Hz, pain within the area of UV burn, and area of hypersensitivity to von Frey filament testing before and at the following times after intramuscular study drug injection: 5 minutes, 45 minutes, and 65 minutes. We will also perform a vibration threshold at 30 minutes after the intramuscular injection. These primary outcome measures will assess both Aβ and Aδ/C fiber sensitivity in the area of injury and these times will capture the time of peak plasma oxytocin concentration after intramuscular injection [20].

TEST OF Aβ FIBER SENSITIVITY

Light touch is subserved by a group of myelinated peripheral nerves with fast conduction in the Aβ range and which are capable of following high frequencies, being responsible for the sensation of vibration. This capability of individual nerve fibers to respond with high frequency also underlies our ability to sense a light touch moving across the body surface as in brushing.

As noted, preclinical studies show that following injury these light touch fibers become less sensitive to repeated stimulation as occurs with a vibration [2]. Oxytocin,

when perfused around the neuronal cell bodies of these Aβ nerve fibers, partially restores their function, including their sensitivity to low intensity stimulation.

In order to determine the threshold for perception of vibration, we have created a simple device that produces an oscillatory / vibratory stimulus which can be used on the skin. The subject places the area of interest on the device and the device is set to slowly increase the intensity of vibration at 256Hz until the subject first perceives this. This is repeated twice in the areas of interest. More details on the device are provided in the Appendix.

We anticipate that oxytocin will have no effect on normal Aβ fibers with testing in normal skin but will decrease the detection threshold for vibration intensity towards normal in the area of UV radiation exposure .

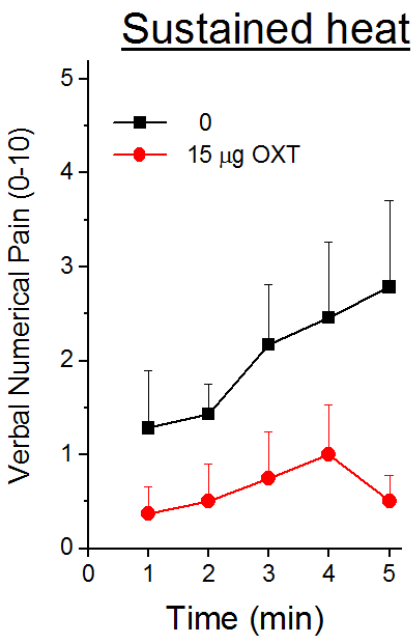
TEST OF Aδ FIBER SENSITIVITY

Pain threshold to punctate stimulation within the area of irradiation will be determined using calibrated von Frey filaments and an up-down sequential method which efficiently estimates median thresholds [7].

SECONDARY OUTCOME MEASURE: SUSTAINED HEAT

As part of a protocol used by us in several studies, the surface of the skin of the forearm opposite to the area of irradiation is heated to 45°C using an FDA approved, Peltier-controlled thermode for a period of 5 minutes (TSA®, Medoc, Ramat Yishai, Israel). This typically results in a slowly increasing pain experience, peaking at 5 minutes in the mild to low moderate range and has been tolerated by more than 150 subjects in studies over the past 14 years.

In an interim analysis of an ongoing clinical study in volunteers, we noted that spinal injection of oxytocin, 15 µg (equivalent to 9 IU), that pain from this sustained heat was dramatically reduced over the 5 minutes of stimulus presentation (figure). In contrast, spinal oxytocin had no effect on the stimulus-response relationship of pain to noxious heat over a 42-50°C range when the stimuli were presented for only 5 seconds. These data suggest that oxytocin reduces C-fiber mediated signaling of sustained heat pain, likely through a spinal site of action.



Drugs administered spinally have a much higher concentration in cerebrospinal fluid than plasma. Nonetheless, spinally administered drugs are typically absorbed to an extent and with a time course similar to that after intramuscular injection, and it is conceivable that the effect on sustained heat pain we are seeing in the spinal study reflect peripheral effects via systemic absorption. Thus, if we see a similar reduction in response to sustained heat in this protocol of intramuscular administration, we will conclude that oxytocin is more likely activing peripherally than spinally.

Protocol

Effects of intramuscular oxytocin on sensory function in healthy volunteers with ultraviolet burn injury to the skin

PRIMARY GOAL: Provide an estimate of effect size of intramuscular oxytocin on a test of Aβ and of Aδ fiber sensitivity in injured skin following ultraviolet B burned skin.

GENERAL METHODS: Equal numbers of healthy adult men and women will be recruited (ten total) and will have 5 visits in the Clinical Research Unit (CRU) at Wake Forest Baptist Medical Center or Piedmont Plaza 2. In the first visit they will be trained in the experimental procedures to assess pain and perception of vibration and they will receive 3 ultraviolet radiation exposures on the calf of differing intensities surrounding the anticipated minimal erythematous dose (MED). They will return one day later for examination of these sites and determining the MED. At least 5 days later they will return, sensory tests will be repeated and ultraviolet radiation at two times the MED will be exposed to the volar wrist of the dominant hand. The following day and the day thereafter they will return and, after heating the area of the burn to 40°C for 5 min and baseline sensory tests in the area of burn, they will receive an intramuscular injection of either oxytocin (Pitocin®), 10 IU, or saline. The study will be randomized and double blind and all subjects will receive both treatments.

STUDY DESIGN

Inclusion Criteria: We request permission to study up to 12 subjects so that we will have 10 evaluable subjects who have completed all 5 visits.

1. Male or female > 18 and < 60 years of age, Body Mass Index (BMI) <40.
2. Generally in good health as determined by the Principal Investigator based on prior medical history, American Society of Anesthesiologists physical status I
3. Normal blood pressure (systolic 90-140 mmHg; diastolic 50-90 mmHg) resting heart rate 45-100 beats per minute) without medication
4. Female subjects of child-bearing potential and those < 1 year post-menopausal, must be practicing highly effective methods of birth control such as hormonal methods (e.g., combined oral, implantable, injectable, or transdermal contraceptives), double

barrier methods (e.g., condoms, sponge, diaphragm, or vaginal ring plus spermicidal jellies or cream), or total abstinence from heterosexual intercourse for a minimum of 1 full cycle before study drug administration.

Exclusion Criteria:

1. Hypersensitivity, allergy, or significant reaction to any ingredient of Pitocin®

2. Any disease, diagnosis, or condition (medical or surgical) that, in the opinion of the Principal Investigator, would place the subject at increased risk (active gynecologic disease in which increased tone would be detrimental e.g., uterine fibroids with ongoing bleeding), compromise the subject's compliance with study procedures, or compromise the quality of the data

3. Women who are pregnant (positive result for urine pregnancy test at screening visit), women who are currently nursing or lactating, women that have been pregnant within 2 years.

4. Subjects with neuropathy, chronic pain, diabetes mellitus, or taking benzodiazepines or pain medications on a daily basis.

Study Visit 1: The participant will report to the CRU or Piedmont Plaza 2. The participant will review and sign the Informed Consent. After informed consent is adequately obtained, a detailed medical history will be obtained from the participant, female participants will provide a urine sample to determine pregnancy status. The research nurse will train the participants to estimate pain quantitatively using a 2 cm^2 Peltier controlled thermode (TSA®) applied to a forearm with 5 sec presentation of stimuli at 39, 41, 43, 45, 47, 49, and 50°C, using a 11 point numerical verbal scale (NRS) anchored at 0 for no pain and 10 for the worst pain imaginable . Typically, the participant is exposed to temperatures between 38^0 and 51^0 C using a random staircase method. After this training, we will ask them to report pain intensity on the 0-10 NRS scale every minute for 5 minutes upon exposure to a 4 cm^2 Peltier controlled thermode at 45°C to the lateral calf. Finally, the subject will place the palmar aspect of the wrist of their dominant hand on a device and report when they first perceive a sensation as the intensity of vibration at a fixed frequency of 256 Hz is slowly increased. We have found

this training session significantly reduces anxiety and variability in pain and hypersensitivity ratings on subsequent study days.

Ultraviolet-B light exposure will be controlled by a commercially available solar simulator and dose control system that meets specifications for FDA sunscreen testing (Solar Light Co., Inc). The solar simulator consists of a 150-watt xenon bulb that produces the full range of solar ultraviolet energy (290-400 nm) without exposing subjects to thermal energy. Exposure is limited to a 3 cm^2 diameter circle of skin and, after an individualized determination of dose, produces moderate erythema that is sensitive to thermal and mechanical stimulation. During this visit three areas of skin on the subject's calf will be exposed to ultraviolet light for different lengths of time not to exceed 200 seconds. This procedure is not painful, and this burn does not produce spontaneous pain as the burn injury resolves over the next several days.

Study Visit 2

The subject will return to the CRU or Piedmont Plaza 2 24 hours later and the exposed areas evaluated for UV-induced erythema. The purpose of this procedure is to determine each subject's MED, defined as the dose of UV light that produces clear redness with sharply demarcated borders.

Study Visit 3

The subject will report to the CRU or Piedmont Plaza 2 at least 5 days after study visit 2. After determination of vibration frequency perception threshold on the dominant arm volar aspect of the wrist, the center of the volar aspect of the wrist will be irradiated with an ultraviolet exposure of 2 times the subject's MED. Subjects will be instructed that they can take acetaminophen as needed, but not NSAIDs, over the next 2 days, but that they should not take acetaminophen within 6 hours of study visits 4 and 5.

Study Visit 4

The subject will report to the CRU the day after Study Visit 3. Baseline blood pressure, heart rate and respiratory rate will be measured. Baseline measures will be obtained to include 5 minute presentation of a 45°C stimulus to the lateral calf, perception threshold of vibration intensity on the dominant arm site of ultraviolet burn, and pain threshold using application of calibrated von Frey filaments to the site of ultraviolet burn. Finally, we will map the area of hypersensitivity surrounding the burn

site using a 225mN von Frey filament. Following baseline measurements we will apply the Peltier controlled thermode to the burn site and increase the probe temperature to 40°C for 5 min. Immediately after removing the probe the subject will receive an intramuscular injection of oxytocin (Pitocin®), 10 IU or the same volume (1 ml) of saline. Thresholds to perception of vibration and pain within the area of UV burn and areas of hypersensitivity surrounding the burn area will be determined 5 minutes, 45 minutes, and 65 minutes after injection. A vibratory threshold will also be determined at 30 minutes after the injection. Pain report to a 5 minute presentation of the 45°C stimulus to the lateral calf will be determined at the 20 and 60 min time period after injection. The area of the burn site will be heated to 40°C for 5 min a second time, 40 min after the first.

Study Visit 5

All procedures from Study Visit 4 will be repeated with the cross-over study drug solution.

Safety and Monitoring: Given that oxytocin is available over the counter in much larger systemic doses than proposed in this application and since multiple scientific reports have examined much larger systemic doses than in this application using only subjective reporting, we propose to only request subjects to report any unusual sensations and query them at the end of each drug administration study day if they experienced any unusual sensations. UV protective glasses will be worn by study staff administering the UV exposure. The subject will be shielded with a barrier so there will be no exposure to their eyes.

Blood pressure, heart rate and respiratory rate will be measured on study visits 4 and 5 at baseline and then at 30 and 60 minutes after the injection.

RISKS

Risks of intramuscular injection include pain and bruising. Risks from the FDA approved heat stimulus device are pain, and the subject can stop testing at any time if the pain they perceive is such that they do not want to continue. Please note that these devices are used in many pain clinics routinely and have multiple fail-safe designs to

avoid thermal burn. Risks from the non-regulatory vibratory device are related only to microshock and are addressed in the Appendix. Risks from the Electromechanical Risks from the UV radiation causes mild sunburn, and may blister or hurt for a few days. The sunburned skin will almost always tan in normal individuals, and may tan more darkly than the surrounding skin for several weeks to several months. It is possible that the darker patches of skin may be present for up to a year. Long-term darkening (discoloration) or scarring is possible, but rare in people with normal skin and a history of normal tanning. Repeated exposure of the skin to UV light is known to produce photoaging (aging of the skin in response to sunlight) and carries the risk of photo carcinogenesis (skin cancer). However, the few exposures in this study, equivalent perhaps to one hour of casual sun exposure during the summer, produces an insignificant increase in lifetime risk.

Risks of oxytocin are primarily restricted to uterine contraction in the presence of pregnancy, since oxytocin receptors are not present in the non-pregnant uterus (Package insert attached). Additionally there is the possibility of a feeling of being flushed, headache and increased heart rate with no significant change in blood pressure during or immediately after the infusion. These events have been reported by previous participants but were short lived, lasting approximately 12-15 minutes.

Data Safety Monitoring Plan

Although the use of oxytocin in this protocol is outside FDA approval for oxytocin administration during the postpartum period, the dose to be studied is similar to or less than that of multiple recent studies in healthy volunteers with intranasal oxytocin purchased over the counter in the US [10; 12-15; 17; 20-22; 25-32] and without description of adverse events. For these reasons, we do not propose a data safety monitoring committee or special safety evaluation beyond those required by IRB regulations.

Minority, Gender, and Children Participation

Both sexes and races and ethnicities will be actively recruited in this small study. Children under age 18 are not included in these protocols because this protocol because the safety of this product has not been established in children.

Volunteer Payment

Participants will be paid a total of $500 according to the following payment schedule which we have used throughout the last 2 cycles of this grant's protocols. We believe that this payment schedule is fair and appropriate, paying for each procedure attempted and an additional payment for completion of the entire study.

Completion of study visit 1: $50

Completion of study visit 2: $25

Completion of study visit 3: $25

Completion of study visit 4: $50

Completion of study visit 5: $350

Long-term Follow-up

Volunteers will be contacted daily within the following week after the last study visit and questioned about adverse events from the study.

STATISTICAL RATIONALE

Co-Primary outcome measures are the vibration intensity detection threshold, the punctate stimulus pain detection threshold in the burned area, and the area of hypersensitivity surrounding the UVB area. We request a convenience sample of the remaining 5 subjects in this protocol under this amendment for the purpose of preliminary data to provide variance and effect size estimates that will inform federal grant submission for use of this model to a larger sample size to adequately test the plasma concentration response of computer controlled infusions of oxytocin to targeted plasma concentrations with intravenous infusions. Thus, we propose descriptive statistics as the primary analysis of this pilot study.

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