Published in final edited form as:

Menopause. 2015 December ; 22(12): 1328–1334. doi:10.1097/GME.0000000000000476.

Kappa Agonists as a Novel Therapy for Menopausal Hot Flashes

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Abstract

Objective—Postmenopausal hot flash etiology is poorly understood, making it difficult to develop and target ideal therapies. A network of hypothalamic estrogen-sensitive neurons producing Kisspeptin, Neurokinin B, and Dynorphin (KNDy neurons), located adjacent to the thermoregulatory center, regulate pulsatile secretion of GnRH and LH. Dynorphin may inhibit this system by binding kappa opioid receptors within the vicinity of KNDy neurons. We hypothesize that hot flashes are reduced by KNDy neuron manipulation.

Methods—A double-blind, cross-over, placebo-controlled pilot study evaluated the effect of a kappa agonist (KA). Hot flash frequency was the primary outcome. Twelve healthy postmenopausal women with moderate-severe hot flashes, ages 48–60 years, were randomized. Eight women with sufficient baseline hot flashes for statistical analysis completed all 3 interventions: placebo, standard Pentazocine/Naloxone (50/0.5 mg) or low-dose Pentazocine/Naloxone (25/0.25 mg). In an inpatient research setting, each participant received the 3 interventions, in randomized order, on 3 separate days. On each day, an intravenous catheter was inserted for luteinizing hormone (LH) blood sampling, and skin conductance and Holter monitors were placed. Subjective hot flash frequency and severity were recorded.

Results—Mean hot flash frequency 2–7 hours following therapy initiation was lower than that for placebo (KA standard-dose: 4.75 ± 0.67 ; KA low-dose: 4.50 ± 0.57 ; and placebo: 5.94 ± 0.78 hot flashes/5 hours; $p = 0.025$). Hot flash intensity did not vary between interventions. LH pulsatility mirrored objective hot flashes in some, but not all women.

Conclusions—This pilot suggests that kappa agonists may affect menopausal vasomotor symptoms.

Keywords

hot flash etiology; LH pulses; kisspeptin; kappa agonist; KNDy neurons

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Disclosure Statement: S.R., C.C., D.C., and R.S. are holders of International Patent Application #PCT/US13/72772, titled, “Methods and Compositions for Treating Vasomotor Symptoms.” The other authors (A.O., L. F.) declare that they have no competing interests.

Trial registration: ClinicalTrials.gov NCT02070718.

Introduction

The neuroendocrine factors that trigger hot flashes are not well understood, but estrogen-sensitive circuits in the brain generate these phenomena.¹ Research in the late 1970s suggested that hot flashes temporally correlate with pulses of luteinizing hormone (LH); it was hypothesized that the same mechanism that drives hot flashes also triggers episodic LH secretion.² Pulsatile LH secretion from the pituitary is itself driven by intermittent secretion of gonadotropin-releasing hormone (GnRH) from the brain.^{3,4} However, hot flashes are clearly not dependent on pulsatile LH itself since they occur even in its absence.⁵ Rather, it seems the same upstream afferent input responsible for driving GnRH neurons is responsible for triggering hot flashes. We hypothesize that hot flashes and LH pulses have the same source generator, but they are not causally linked to one another.

Recent evidence suggests that pulsatile GnRH secretion itself is governed by a network of estrogen-sensitive neurons in the hypothalamic arcuate (infundibular) nucleus, which express **Kisspeptin (Kiss1)**, **Neurokinin B (NKB)**, and **Dynorphin**.^{6,7} These so-called **KNDy** neurons also express the key isoform of the estrogen receptor, ER α ,⁸ and KNDy neurons are the primary targets for the estrogen-dependent regulation of GnRH and gonadotropin secretion.⁹⁻¹¹ Moreover, it appears likely that KNDy neurons drive the pulsatile secretion of GnRH and LH—as evidenced by the fact that blockade of kisspeptin signaling in the brain inhibits GnRH pulses.¹² If bursts of KNDy neuronal activity evoke the pulsatile release of GnRH and LH, it is plausible that they also drive hot flashes.^{13,14}

The pulsatile activity of KNDy neurons is controlled by an interplay of NKB and dynorphin, the principle endogenous hypothalamic kappa agonist, acting in a reciprocal fashion to generate pulsatile events—intermittently stimulated by NKB and suppressed by dynorphin (Figure 1).¹⁵⁻¹⁸ Several recent lines of evidence support this model. First, NKB provides stimulatory, regenerative feedback via NK3R (the NKB receptor) located on KNDy neurons that forces a rapid activation of GnRH and LH.¹⁷ Second, kappa agonists bind the dynorphin receptor (also referred to as kappa opioid receptor (KOR), and inhibit LH pulses, presumably by interfering with kisspeptin and GnRH signaling.¹⁵ Third, KOR receptor antagonists stimulate LH pulse frequency, likely mediated through increased kisspeptin and GnRH release.¹⁹⁻²¹ In addition, it has been our clinical observation that women chronically treated with opioids, like methadone, are amenorrheic and rarely complain of hot flashes at menopause (SR). Importantly, the network of KNDy neurons governing pulsatile GnRH secretion also project to hypothalamic areas containing circuits that control thermoregulation.^{14,22} Thus, it is conceivable that if KNDy neurons were in a state of superactivation—as is the case in menopause,²³ they could disrupt baseline thermoregulation and trigger hot flashes, as has been proposed.^{14,24} If Kiss1 neurons trigger hot flashes, it might be possible to inhibit hot flashes pharmacologically with kappa agonists, by inhibiting the neuronal activity of KNDy neurons.¹⁵

Unfortunately, when administered systemically to humans, pure kappa agonists cause dysphoria and nausea,²⁵ making them suboptimal choices for the treatment of hot flashes. But fortunately, a new class of peripherally restricted kappa agonists (PRKAs), whose

access to the brain is restricted by the blood brain barrier,²⁶ are in development for management of peripheral pain disorders. KNDy neurons reside in the arcuate (or infundibular) nucleus, an area of the hypothalamus which lies at the junction of the blood brain barrier.²⁷ Thus, it may be possible to extinguish KNDy neuronal activity (and hot flashes) with peripherally-restricted kappa agonists (PRKAs) and avoid unwanted central side effects.²⁸ However, these agents are not yet FDA approved. Several PRKAs are undergoing phase 2 trials for irritable bowel syndrome²⁹ and post-surgical pain management,^{30,31} and have an excellent side effect profile, but were not yet available for our pilot study.

As an alternative, we investigated whether a *non*-peripherally-restricted kappa agonist used for pain, pentazocine, could reduce hot flashes in menopausal women. Although a pure kappa agonist is not an ideal treatment for women with menopausal symptoms due to side effects, a decrease in the frequency of hot flashes in women treated with a kappa agonist would provide a proof of concept that kappa signaling is important in the regulation of human thermoregulation—and that blockade of kappa receptors with a more ideal molecule (e.g. PRKA) might well decrease hot flashes without untoward side effects. Using an inpatient, double-blind, randomized placebo-controlled cross-over pilot study, we administered a low-dose kappa agonist, standard-dose kappa agonist, or placebo to women with hot flashes.

Materials and Methods

Study Design, Inclusions, Exclusions, and Primary Endpoint

Women were eligible if they were healthy with no major medical illnesses, between 45-60 years of age, > 12 months amenorrhea, had a uterus and ovaries, had > 56 moderate to severe hot flashes during one week of baseline monitoring using daily diaries, and had a family member or friend available to drive them home following clinic visits. Women were excluded if they were using hormonal prescription medication or supplements for vasomotor symptoms; took narcotics, serotonergic medications, gabapentin, MAOI, anti-epileptics, anti-cholinergics, or sedatives; had a history of polycystic ovarian syndrome; had depression; or had any chronic or acute medical illnesses including renal, hepatic, pulmonary diseases, or seizures. They were excluded if they had FSH < 20 IU/mL, current substance abuse, severe corn allergy, or known allergic reaction to pentazocine or naloxone. Data collected from women who were accepted into the study were excluded from analysis if 0-2 hot flashes occurred during the 7 hours of monitoring on the day of placebo treatment. The primary endpoint was the frequency of hot flashes between 2-7 hours following ingestion of the first dose of study drug.

Study recruitment

Women were recruited via flyers placed at community centers, local markets, gyms, and at the University of Washington Medical Center following University of Washington IRB approval. Interested women called the study hotline and scheduled a screening visit with the study coordinator (Figure 2). At the telephone screening, verbal consent was obtained and demographic information (including date of birth, gender, race) was recorded. The study

coordinator received calls from 65 interested women. Of those, 39 were potentially eligible and were mailed hot flash diaries to complete at home.

Consent and randomization

Written consent was obtained from each woman on the day of her first study visit, and her treatments were randomized to Pentazocine/Naloxone 50/0.5 mg (standard-dose), Pentazocine/Naloxone 25/0.25 mg (low-dose), or placebo in a 1:1:1 ratio. Each participant served as her own control and the study drugs were given in random order on 3 separate days. Randomization was achieved using a scheme developed by the University of Washington Investigational Drug Service employing the Excel random number generator. Access to the randomization code was strictly controlled by the research pharmacy and packaging and labeling of test and control treatments were identical so as to maintain double-blind conditions. All randomization occurred between January 1, 2013 and June 1, 2013.

Study drug

An Investigational New Drug application was filed with the FDA and approved with a treatment indication of menopausal hot flashes (IND number 116715). Pentazocine 50 mg/ Naloxone 0.5 mg (generic Talwin NX), manufactured by Watson Labs in Corona CA, is used as an oral analgesic. For blinding purposes, the pentazocine/naloxone tablet or half tablet was over-encapsulated by University of Washington Investigational Drug Services in an opaque gelatin capsule (Gallipot capsules, size 1, green). The capsules containing placebo or half tablet were backfilled with cornstarch NF. Analgesic onset is 15-30 minutes after oral administration with mean plasma half-life of 3.6 hours. Typical doses for pain are one to two 50/0.5 mg tablets every 3- 4 hours. Peak concentrations are 1-3 hours after administration.

Data collection

Demographic and health data were collected during eligibility screening. Blood pressure, heart rate, temperature, height, weight, and blood for follicle stimulating hormone (FSH) and estradiol serum concentrations were obtained at the first study visit. Participants were monitored in an inpatient research clinic setting on 3 separate days for each intervention (mean of 6.8 ± 2.2 days between visits 1 and 2; 4.6 ± 0.9 days between visits 2 and 3; overall range 1-21 days between visits). At each study visit, the participant had an intravenous catheter inserted, blood samples were drawn (3 cc), and a Bahr skin conductance monitor³² and a Holter monitor were placed. The first drug dose (active or placebo) was administered (at $08:59 \pm 12$ min) and blood samples (24 samples at 1.5 cc each) were collected for LH measurements at 20-minute intervals. A second dose of the same study drug initially administered was given approximately 3.5 h after the first. In addition, each participant pushed a button on the Bahr monitor when she sensed a hot flash, and she recorded the occurrence and the severity of the flash in a diary. Adverse events were recorded by the RN and were also reported by the study participant at each subsequent visit or via phone message to the study coordinator.

Outcomes

Primary outcome – hot flash frequency—Hot flash occurrences were assigned by investigators (AEO, SDR, and RAS) without knowledge of the intervention arm. Only the last 5 hours of hot flash data during the sampling window was analyzed, as it was assumed 2 hours would be required for the study drug to reach steady state after the first treatment (based on pharmacokinetic). A hot flash was defined by a combination of subjective and objective criteria. If no subjective indication was identified by participant diary, but there was a clear increase in skin conductance, we assumed that the participant either fell asleep or failed to report the hot flash. If there was a presumed hot flash by defined subjective and objective criteria, but the investigators were not unanimous in the assignment of a hot flash, additional evidence on LH pulse occurrence was used in the deliberations.

Secondary Outcomes – LH pulse frequency, Hot flash intensity—LH samples were taken over the 7-hour study period, and the frequency of pulses was analyzed in the 2-7 hour period after study drug was given. The DC3 algorithm was used to detect the occurrences of LH pulses.³³ Hot flash intensity was rated by the participant in the hot flash diary at the time of the hot flash occurrence using a scale of 0-3 (0= “not at all”, 1= “a little”, 2= “moderately” 3= “a lot”).

Radioimmunoassays (RIA)—All hormone assays were performed in duplicate by the University of Virginia Ligand Assay Laboratory (Charlottesville, VA), with kits from Siemens Medical Solutions Diagnostics (Los Angeles, CA): 1) IMMULITE Human LH (catalog #LKLH5); 2) IMMULITE Human FSH (catalog #LKFS1); and 3) RIA Human Estradiol (catalog #TKE21). Reportable human hormone assay ranges were as follows: LH 0.1-200 mIU/mL, intra-assay coefficient of variation (CV) 4% (3 assays); FSH 0.1-170 mIU/mL; and estradiol 12.3-1700.0 pg/nL.

Statistical analysis—Because hot flashes and LH pulses are discrete events, their frequencies over short intervals cannot be expected to be normally distributed. To circumvent this problem, we analyzed the results using Friedman analysis of variance, which provides a nonparametric repeated measures test across treatments. We tested the effect of generic pentazocine/naloxone on the frequency of hot flashes and the frequency of LH pulses. Standard parametric analysis of variance with repeated measures was used to test for effects of generic pentazocine/naloxone treatment on hot flash intensity and mean levels of LH. P-values < 0.05 were considered statistically significant.

Results

Sixteen women completed hot flash diaries for a week and mailed them back to the study coordinator (Figure 2). Three of the 16 women did not enroll due to study time commitment or concern about side effects of the drug. One of the 16 women was ineligible because she did not meet the inclusion criteria of ≥ 5 moderate-to-severe hot flashes per week. Of the 12 randomized women, one was found to be ineligible after consent and randomization (only following consent did the research nurse have permission to look at her medical record, which revealed substance abuse). Two women provided data on study drug

tolerance, but were not included in the hot flash analysis because of low baseline hot flashes on placebo. A fourth woman provided data for one study visit, but withdrew due to side effects from the study drug, leaving 8 women that completed the 3 interventions (placebo, low and standard-dose pentazocine/naloxone) with sufficient baseline hot flashes for analyses while on placebo.

Of the 8 eligible and randomized women who completed all visits, the mean age was 55 years (range 50-60 years); 50% were white; all were postmenopausal with > 12 months amenorrhea, with FSH > 35 mIU/mL (mean 77 ± 10 mIU/mL). Seven of the women had estradiol below the detectable limit of the assay (12.3 pg/nL) and one had estradiol of 17.0 pg/nL. Baseline LH was 24.6 ng/mL (standard error 3.4 ng/mL). Median BMI was 27.4 kg/m² (range 22.9 –52.3 4 kg/m²).

There was a strong association between increased skin conductance and the subjective occurrence of a hot flash, and these parameters were frequently associated with pulses of LH in some, but not all women (Figure 3). In some women, particularly those with very high LH levels and/or very frequent hot flashes, the putative association between LH pulses and hot flashes was not apparent. Treatment with pentazocine/naloxone significantly reduced the frequency of hot flashes by approximately 1 hot flash per 5 hours (~20%) relative to the placebo ($p = 0.025$) in the 2-7 h period after ingestion of either the low or standard-dose of the study drug (Figure 4). Pooled analyses of all women taking pentazocine/naloxone showed benefit of hot flash frequency over placebo ($p < 0.05$). There were no significant effects of pentazocine/naloxone on mean LH serum concentrations, or the reported intensity of hot flashes (data not shown). The treatment effect, LH baseline and LH pulsatility did not appear to vary by age, the number of years from final menstrual period, or BMI, though with such small numbers, no conclusions can be drawn.

Side effects of pentazocine/naloxone were noted in some women, but 5 of the 6 adverse events occurred in association with the standard-dose. Emesis and dysphoria side effects were most common among women with lower BMIs. Low-dose generic pentazocine/naloxone was relatively well-tolerated, with only one woman reporting mild headache.

Discussion

We demonstrated that a brief exposure to a kappa agonist, pentazocine/naloxone, appears to reduce hot flash frequency in menopausal women, providing empirical rationale that peripherally restricted kappa agonists—a new class of drugs, not yet FDA approved—may provide relief for menopausal hot flashes. We propose that PRKAs, particularly when given for a longer duration of time than the kappa agonists used in this study, may prove beneficial for menopausal hot flashes.

Administration of a kappa agonist appears to immediately reduce hot flashes – the effect was modest (20% reduction) — yet, statistically significant within the 2-7 hour time-frame from the time of the initial dose. One would not anticipate an immediate large effect, since it takes standard-dose estrogen therapy (the gold standard for hot flash treatment) several weeks to reduce hot flashes by 60-80%. Full effect for lower doses is not achieved for at

least 5-6 and sometimes even up to 8 weeks.³⁴ SSRIs may act more rapidly but have lower efficacy than standard-dose hormonal therapy.³⁵ We would infer that more prolonged treatment with any kappa agonist might likewise be necessary to exert its full potency. Some of the participants in our study had hot flashes for up to 5 years. Such women can be presumed to have hypertrophied KNDy neurons,²³ and by inference, it may require sustained inhibition over days (or weeks) to diminish hot flashes under these circumstances.

We do not promote the use of pure kappa agonists for hot flashes, because side effects preclude their use. However, the untoward effects from PRKAs, in human studies thus far, appear small. Comparatively, non-hormonal medications to treat hot flashes such as clonidine, selective serotonin and norepinephrine reuptake inhibitors (SSRIs) (*e.g.*, paroxetine, venlafaxine, desvenlafaxine, citalopram and escitalopram), gabapentin, and pregabalin may elicit intolerable side effects, leading to discontinuation in less than 5% of women, including drowsiness, nausea, diarrhea, headaches, dizziness, sleep disturbances, agitation or anxiety, and fatigue.^{1,36-41} However, in non-depressed postmenopausal women, recent trials of venlafaxine and escitalopram did not show side effect profiles statistically different from placebo.^{35,42}

We anticipated finding reduced LH pulse frequency associated with pentazocine/naloxone treatment in all women; however, that was not the case. There was a strong association between increased skin conductance and the subjective occurrence of a hot flash, and these parameters were frequently associated with pulses of LH in some, but not all women, as reported previously.⁴³ This apparent coupling was either obscured by a higher LH baseline or simply did not exist. Given the relatively small number of participants studied, we may have lacked sufficient statistical power to identify an effect. It is also conceivable that in women with high frequency hot flashes, there may have been insufficient time to observe hormone decay given the half-life of LH (20 minutes). Additionally, it may be difficult to immediately suppress LH levels in individuals in whom there has been unrestrained gonadotropin secretion and gonadotropic hypertrophy. And finally, although we propose the primary driver of menopausal hot flashes is via the KNDy neuron pathway, as with other complex physiologic processes, there may be several pathways governing this process.

There are strengths and limitations to this pilot study. The study was rigorously executed with hypotheses, outcomes, inclusion and exclusion criteria, and power determined prior to analysis. Pentazocine is a relatively pure selective KOR agonist. Naloxone is added to all FDA approved formulations of oral pentazocine to discourage inappropriate intravenous injection abuse.⁴⁴ Naloxone, a μ -opioid receptor antagonist, produces rapid onset of withdrawal symptoms, and perhaps menopausal hot flashes⁴⁵ when delivered intravenously. However, delivered at the oral doses used in this study, it is essentially biologically inert. Unlike intravenous naloxone, which has CNS effects, the effects of oral naloxone are primarily limited to the gut because marked metabolism of oral naloxone during hepatic first pass results in low systemic bioavailability⁴⁶ and precludes a CNS effect. Randomization was securely executed, and blinding of participants, study nurses, and analysts to treatment arms was assured. The use of modern hot flash monitoring techniques and serum LH sampling at 20 min intervals in 8 postmenopausal women permitted corroboration of previously published reports that hot flashes frequently occur in association with pulses of

LH secretion;^{2,5} LH sampling at 10 minute intervals might have improved detection of LH pulsatility. Subjective and objective hot flashes did not always correlate, suggesting either insensitivity of the monitor or lack of hot flash recognition by the participant; however assignment of whether a hot flash occurred was done blinded to treatment arm. If misclassification occurred, it would have been unbiased. Importantly, the study was performed only during the day, thus the effect on night sweats was not assessed and the duration was short (7 hours)—a time period far short of the weeks required by the FDA to show clinical efficacy of medications for hot flashes.³⁴ Though our results are promising, and indeed surprising, it is unclear if longer treatment duration would achieve the desired effect of at least a 60%, and preferably 80% reduction in bothersome hot flash frequency. Ideally, all randomized women in our study would be included in the analyses, regardless of hot flash frequency on placebo day; however, given that this was a pilot study, including women without hot flashes at baseline might have diminished our ability to detect a signal if it existed. A post hoc analysis, including all women, did not change our findings. Small sample size may have precluded the ability to detect an effect of the kappa agonist on LH secretion. Poor tolerance of a standard-dose of the study drug resulted in the drop out of one participant. Lastly, we chose a pure kappa agonist, but evidence suggests even “pure” kappa agonists have mu effects.

Conclusions

The physiologic effect of currently used nonhormonal therapies on thermoregulation is poorly understood and their effect on hot flashes is modest at best in studies up to 12 weeks. Hormone therapies for hot flashes preclude use for certain populations of at risk women. We propose a model (Figure 1) that weaves together the finding that LH pulses are coincident with hot flashes in some women, together with the emerging idea that KNDy neurons form an oscillatory neuronal network that drives GnRH and LH neuron pulsatility and perhaps affects postmenopausal hot flashes via cross talk with the adjacent thermoregulatory center. Efforts to fully understand the etiology of postmenopausal hot flashes that guide the development of other highly targeted nonhormonal agents that can inhibit hot flashes without side effects should be engaged. Peripherally restricted kappa agonists might have adequate efficacy, present relatively few side effects, and add to the therapeutic arsenal for hot flash treatments.

Acknowledgments

We gratefully acknowledge Sheree Miller (research pharmacist) and John Amory (study medical monitor); Ryutaro Moriyama, Simina M. Popa, Ashley E. Angell, Jessica Falksen Lancaster, Lee W. Organick, and Paige E. Haas for technical assistance and thoughtful discussions; and Genevieve Neal-Perry for editorial comments. We are grateful to Aleisha Schoenfelder, Beth Marcinko, and Lisa Geddis for performing the RIAs and to Core Director Daniel Haisenleder at the University of Virginia Center for Research in Reproduction Ligand Assay and Analysis Core.

Funding: This research was supported by National Institutes of Health (NIH) Grant 2 R01 HD049651; by a cooperative agreement issued by the National Institute of Aging (NIA), in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Research and Women's Health (ORWH), grants NIA U01 AG032699 and NIA U01 AG03268; the NIH National Center for Advancing Translational Research Grant UL1TR000423; and a research pilot award from the Department of Obstetrics and Gynecology at the University of Washington. The University of Virginia Center for Research in Reproduction Ligand Assay and Analysis Core is

supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH—Specialized Cooperative Centers Program in Reproduction and Infertility Research Grant U54-HD28934.

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Figure 1.

A model of the GnRH/LH pulse generator, which comprises KNDy and other neurons within the arcuate nucleus. According to this model, those KNDy neurons also connect to warm-sensing (WS) neurons in the median preoptic nucleus to drive hot flashes. Activation of kappa opiate receptor signaling in the arcuate nucleus with a kappa agonist could block both GnRH/LH pulses and hot flashes.

Figure 2.
Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram.

Figure 3. LH pulse patterns with skin conductance (objective) hot flashes in a menopausal woman treated with placebo with 20-minute blood samples assayed for LH (closed circles) and subjective hot flashes indicated with arrows.

Figure 4. Hot flash frequency 2-7 hours following initiation of generic Talwin NX (kappa agonist) treatment (mean $\pm$ SEM) among menopausal women with moderate to severe hot flashes. Frequencies of hot flashes differed between placebo, low-dose and standard-dose kappa agonist groups, $p=0.025$. Analyses were performed using Friedman analysis of variance.