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Published in:
Scandinavian Journal of Pain

DOI (link to publication from Publisher):
10.1515/sjpain-2023-0034

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Original Experimental

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https://doi.org/10.1515/sjpain-2023-0034
Received March 16, 2023; accepted August 28, 2023;
published online September 15, 2023

Abstract

Objectives: Pain and itch share similar neuronal networks; hence, it is difficult to explain why opioids can relieve pain but provoke itching. The present human volunteer study aimed to investigate the similarities and differences in responses to experimentally provoked pain and itching to explore the underlying fundamental mechanisms.

Methods: Twenty-four healthy volunteers were enrolled in this single-center, randomized, double-blind, placebo-controlled, parallel-group trial. Three volar forearms and two mandibular areas were marked, and participants randomly received morphine (20 mg) or identical placebo tablets. Heat, cold, and pressure pain thresholds, and vasomotor responses were assessed at baseline and after oral morphine administration. Itch provocations were induced by intradermal application of 1 % histamine or a topical cowhage (non-histaminergic itch) to a marked area of the skin. The participants were subsequently asked to rate their itching and pain intensities. The assessments were repeated for all marked areas.

Results: Morphine caused analgesia, as assessed by the significant modulation of cold and pressure pain thresholds ($p<0.05$). There were no significant differences in histaminergic or non-histaminergic itch or pain intensity between the morphine and placebo groups. Superficial blood perfusion (vasomotor response) following histamine provocation was significantly increased by morphine ($p<0.05$) in both areas. No correlation was found between the provoked itch intensity and analgesic efficacy in any area or group.

Conclusions: Oral administration of morphine caused analgesia without modulating itch intensities but increased neurogenic inflammation in response to histamine, suggesting that different opioid mechanisms in histaminergic and non-histaminergic neurons evoke neurogenic inflammation.

Keywords: pain; analgesia; opioid-induced itch; experimentally evoked itch; histamine; cowhage

Introduction

Opioids are effective analgesics for selected pain conditions and short-term use [1–5]. However, they frequently cause pruritus as a side effect in 5–20 % of patients. Approximately 60–80 % of patients report itching after intrathecal opioid administration [1–4, 6]. Both itch and pain rely on signaling along the same groups of afferent C-fibers [7–9]; hence, it is difficult to explain why opioids relieve pain but evoke itching [10–12]. Although the mechanisms underlying opioid-induced itch have not been fully elucidated, two main hypotheses have been proposed [11]. Opioids may cause itching by a spinal disinhibition mechanism (central nervous system model) [10, 12, 13] or through a cutaneous mast cell destabilizing effect, leading to histamine and tryptase release (peripheral model) [14–17]. To the best of our knowledge,

The current manuscript, in abstract form, was presented at the IASP 2021 Virtual World Congress of Pain from June 9 to June 11 and from June 16 to June 18, 2021.

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these hypotheses have not been explored in fundamental, mechanistic, human, or experimental studies, including histaminergic and non-histaminergic evoked itch.

This present human volunteer study aimed to explore the effect of oral morphine (1) on experimentally provoked histaminergic and non-histaminergic itch intensities and associated neurogenic inflammation, and (2) examine the effects of experimentally provoked itch and pain (thermal and mechanical experimental pain stimulations).

Methods

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group human volunteer trial. The regional ethics committee approved the study (N-20190049), and was registered at ClinicalTrials.gov (NCT04115462) before the enrollment of the first participant.

Twenty-four healthy participants participated in this study. The exclusion criteria were clinically significant abnormalities, pregnancy or lactation, drug addiction, use of medication (e.g., antihistamines and analgesics), alcohol consumption 24 h before the study, previous or present neurological, musculoskeletal, mental illness, pain and itch, or psychiatric disorders, inability to cooperate, participation in previous drug studies, and allergy/discomfort to morphine. All participants provided written and verbal informed consent. This study is in accordance with the Declaration of Helsinki. One investigator (HO) performed all outcome assessments to minimize variation. Finally, 12 participants were assigned to each group and analyzed (Figure 1).

Study procedure

Cold (CPT), heat (HPT), and pressure pain threshold (PPT) were measured at baseline. Five 4×4 cm areas were marked: three volar forearm areas and two mandibular areas were selected based on previous publications reporting topographical differences in provoked itch and pain [18]. Vasomotor reactions were assessed using full-field laser perfusion imaging (FLPI) as a baseline assessment (first FLPI).

The study was double-blinded with balanced randomization of either morphine (morphine hydrochloride 20 mg; Takeda Pharma, Łyszkowice, Poland) or identical placebo pills (lactose monohydrate; "Region Hovedstadens Apotek," Copenhagen, Denmark). One hour after drug administration, pain thresholds and vasomotor reactions were re-assessed (second FLPI). Subsequently, itch was randomly induced by histamine (1 %) or cowhage (non-histaminergic itch) immediately after the participants evaluated itch and pain for 10 min.

The final measurement of vasomotor response was conducted (third FLPI). All procedures were repeated five times every 15 min at each provocation area (70, 85, 100, 115, and 130 min after dosing) (Appendix S1). Study procedures are shown in Figure 2.

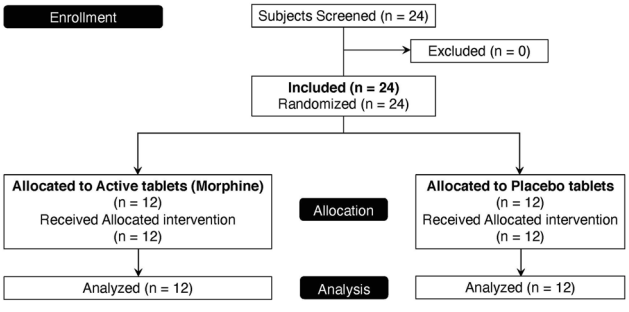

Figure 1: Enrollment and allocation of participants. The diagram shows the numbers of screened, excluded, included, and completed participants. All the participants were included in the primary data analysis.

Itch induction

Histaminergic itch was evoked using histamine dihydrochloride solution (1 %) with standard 1-mm skin prick test (SPT) lancets (Allergopharma, Hamburg, Germany). A droplet of histamine solution was placed on a predetermined area, and the SPT lancet was pierced through histamine into the epidermis using a 120-g weight-calibrated device (Aalborg University, Aalborg, Denmark) for 1–2 s. A droplet of saline (0.9 %) was placed in another area and pierced in a manner similar to the control. Non-histaminergic itch was evoked using cowhage spicules (approximately 25) inserted at the center of the predefined area. The spicules were gently rubbed for 15–20 s to facilitate epidermal penetration. The volume of mucunain delivered using this method was calculated to be 8–15 ng [19]. These human surrogate models have been proven to be reliable [20, 21].

Itch and pain assessments

Participants were instructed to rate itch and pain intensities continuously for 10 min following itch provocation using two computerized visual analog scales (VAS) (eVAS Software: Aalborg University, Aalborg, Denmark) ranging from 0 to 100, whereby 0 represented "no itch/pain" and 100 "worst imaginable itch/pain," installed on a Samsung Note tablet (Samsung, Seoul, South Korea). Temporal itch and pain intensity profiles were generated from VAS/time data. Mean and individual peak itching and pain intensities were calculated.

Outcomes

The primary endpoints were changes in the provoked itch/pain intensities (VAS parameters) and vasomotor responses (FLPI parameters). The secondary endpoints were changes in CPT, HPT, and PPT and associations between itch sensitization and analgesic efficacy.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences for Mac version 26 (IBM Corporation, Armonk, NY, USA). Data were tested for normality using visual inspection, and if unclear, the Shapiro–Wilk normality test was used. Student's t-test or Mann–Whitney U-test was used to compare continuous variables between groups. For statistical comparison of the effects of placebo vs. morphine on the CPT, HPT, and PPT, data were analyzed using Student's t-test, as these assessments were compared using the threshold change. Itch intensity (mean/peak/area under the curve [AUC]) and FLPI (mean/peak) were analyzed using two-way analysis of variance with repeated

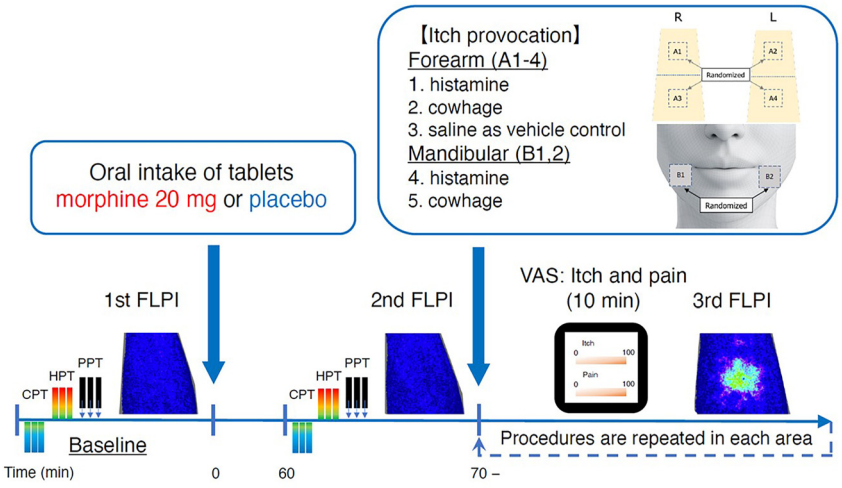

Figure 2: Flowchart of study procedures. Tablets containing either morphine or placebo were administered to the participants in a blinded random order. Two itch provocations and saline (control) were applied on the forearm, and two itch provocations were applied in the mandibular area in a randomized order. One area of the forearm was not used. CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; FLPI, full-field laser perfusion; VAS, visual analog scale.

measures with the following factors: treatment (morphine or placebo) and provocation (histamine or cowhage). Sidak post-hoc tests were conducted for subsequent multiple comparisons. Intergroup analyses were performed using Pearson or Spearman correlations. A subgroup analysis of the participants who experienced side effects was conducted using correlation analysis. Demographic data are presented as means±standard deviations, whereas other values as means±standard errors. A $p<0.05$ was considered statistically significant. Please refer to the Supplementary Files regarding the intervention, randomization, blinding, and sample size (Appendix S2).

Results

A total of 24 healthy volunteers were recruited (men: 16, women: 8, age: 28.0±5.0 years). The participants completed all procedures without experiencing any severe adverse effects; no withdrawals occurred in either group (Table 1).

Table 1: Demographic data and profiles of the study participants.

Variable	Morphine (n=12)	Placebo (n=12)
Age, years	27 ± 4	29 ± 6
Sex, n, %		
Male	7 (58)	9 (75)
Female	5 (42)	3 (25)
BMI, kg/m^2	24.5 ± 4.8	23.8 ± 4.2
Last meal, min	150 ± 81	211 ± 232
Participants with adverse effects, n	6[a]	0

Parametric data are presented as mean±SD. BMI, body mass index; SD, standard deviation. [a]Two participants experienced mild drowsiness, two felt light dizziness, one felt a heavy head, and one reported dry mouth. All participants completed all procedures without experiencing severe adverse effects, and no withdrawals occurred in either group.

Pain thresholds

Figure 3 shows the ratio of the threshold change from baseline (before tablet intake) to 60 min after tablet intake between the morphine and placebo groups. Morphine exhibited a hypoalgesic effect by significantly decreasing CPT ($p=0.044$, 95 % confidence interval [CI]: −15.89 to −0.23) and increasing PPT ($p=0.007$, 95 % CI: 3.56 to 19.50), while it tended to increase the HPT ($p=0.057$, 95 % CI: −0.25 to 14.60) (Figure 3). Additionally, ΔCPT (before and after tablet intake) tended to correlate with ΔPPT (before and after tablet intake) ($R=0.6$, $p=0.053$).

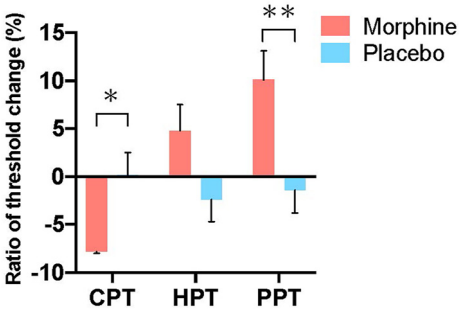

Figure 3: Ratio of threshold change between before and after tablet intake as analgesic effects to each stimulation (cold, heat, and pressure). Morphine decreases cold and increases pressure pain thresholds. In contrast, no significant difference was found between the effects of the placebo and morphine on heat pain stimulation. *$p<0.05$, **$p<0.01$. CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold.

Itch and pain sensitivity

None of the participants reported spontaneous itching after oral administration of morphine at the doses used. Temporal profiles of itch intensity following histamine and cowhage application in the forearm and mandible are presented in Figure S1A–D. In the forearm, histamine and cowhage showed similar itch intensity profiles in both groups (Figure S1A and B). No significant differences were observed in the itch intensity in any area between the groups (Figure S1A–D). Moreover, no difference was found in pain intensity following itch provocation in any areas (Figure S1E–H).

Neurogenic vasodilation

Significant differences were observed in the superficial blood perfusion at baseline at the mandibular site. Changes in the mean and peak superficial blood perfusion values were analyzed by subtracting the baseline value from the value after provocation (Figure 4A–D). Following histamine provocation in the forearm, the change in mean/peak superficial perfusion showed a significant treatment × provocation interaction (mean: $F_{1.1,\ 12.2}$=6.4, p=0.024/peak: $F_{2,22}$=6.6, p=0.006), and post hoc comparisons showed that the morphine group presented significantly higher mean values than those of the placebo group (mean: p=0.023, 95 % CI: 2). In contrast, the mean and peak values after cowhage showed a significant difference only in the mandibular peak value (p=0.025, 95 % CI: 29.6–356.6).

Correlation analysis

There was no correlation between itch intensity and analgesic efficacy in the morphine group. Exploratory subgroup analysis on the six participants who experienced side effects showed a significant correlation between ΔPPT (subtraction of the PPT value before morphine administration) and itch intensity containing the mean, peak, and AUC following histamine and cowhage provocations in the forearm area (histamine: R=0.95, p=0.003; R=0.96, p=0.002; and R=0.95, p=0.003, cowhage: R=0.85, p=0.032; R=0.84, p=0.038; and R=0.85, p=0.031). Regarding the demographic data of the six participants who experienced morphine-induced side effects, three were males, and three were females, with an average age of 28.2±1.4. The details of the side effects were as follows: two participants experienced mild drowsiness, two experienced light dizziness, one experienced a heavy head, and one reported dry mouth.

Discussion

This human volunteer study presented four novel findings: (1) morphine did not increase or decrease experimentally provoked histaminergic and non-histaminergic itch intensities; (2) morphine significantly increased histamine-evoked superficial blood perfusion (neurogenic inflammation); (3) morphine effectively, as expected, alleviated pain sensations to cold and pressure stimulation; and (4) provoked itch intensity did not correlate with analgesic efficacy in the morphine group, but an explorative subgroup analysis revealed a significant correlation between histamine- and cowhage-provoked itch intensity and analgesic efficacy.

Itch and pain intensities

Previous reports revealed that morphine can promote itch sensitivity, particularly in the mandibular area [4, 22]. The facial area, innervated by the trigeminal nerve, contains a high density of opioid receptors and has the highest incidence of opioid-induced itching, as seen in the clinic [4, 22]. However, the present results showed no changes in the provoked itch intensities after morphine intake following histaminergic or non-histaminergic provocation in the forearm and mandibular areas. The oral dose of morphine was 20 mg; hence, it could not be determined whether a higher dose or another route of administration would have an effect. However, the occurrence of side effects increases at higher doses [23]. None of the participants reported spontaneous itching after taking morphine tablets, possibly because of the dose or route of administration. Prospective studies have shown that chronic itch is observed in 2–10 % of patients receiving oral morphine for cancer pain [24], and morphine-induced pruritus has been reported to occur in approximately 55 % of intravenous [25] and 85 % of intrathecal patients [26]. Since the administration of oral morphine is unlikely to produce spontaneous pruritus, the present study focused on enhancing the effect of itch-evoking substances.

Histamine and cowhage induce mild pain sensations in addition to itch sensations [18], and although morphine modulates cold and pressure pain thresholds, it does not affect pain intensity by itch provocation. Our results revealed that oral morphine could alleviate mechanical and thermal nociceptive pain, as expected based on previous studies [27]. However, it did not affect the experimentally induced itch and pain sensations provoked by histamine or proteases. In the present study, opioids were found to be less effective than cold pain and pressure in treating heat pain.

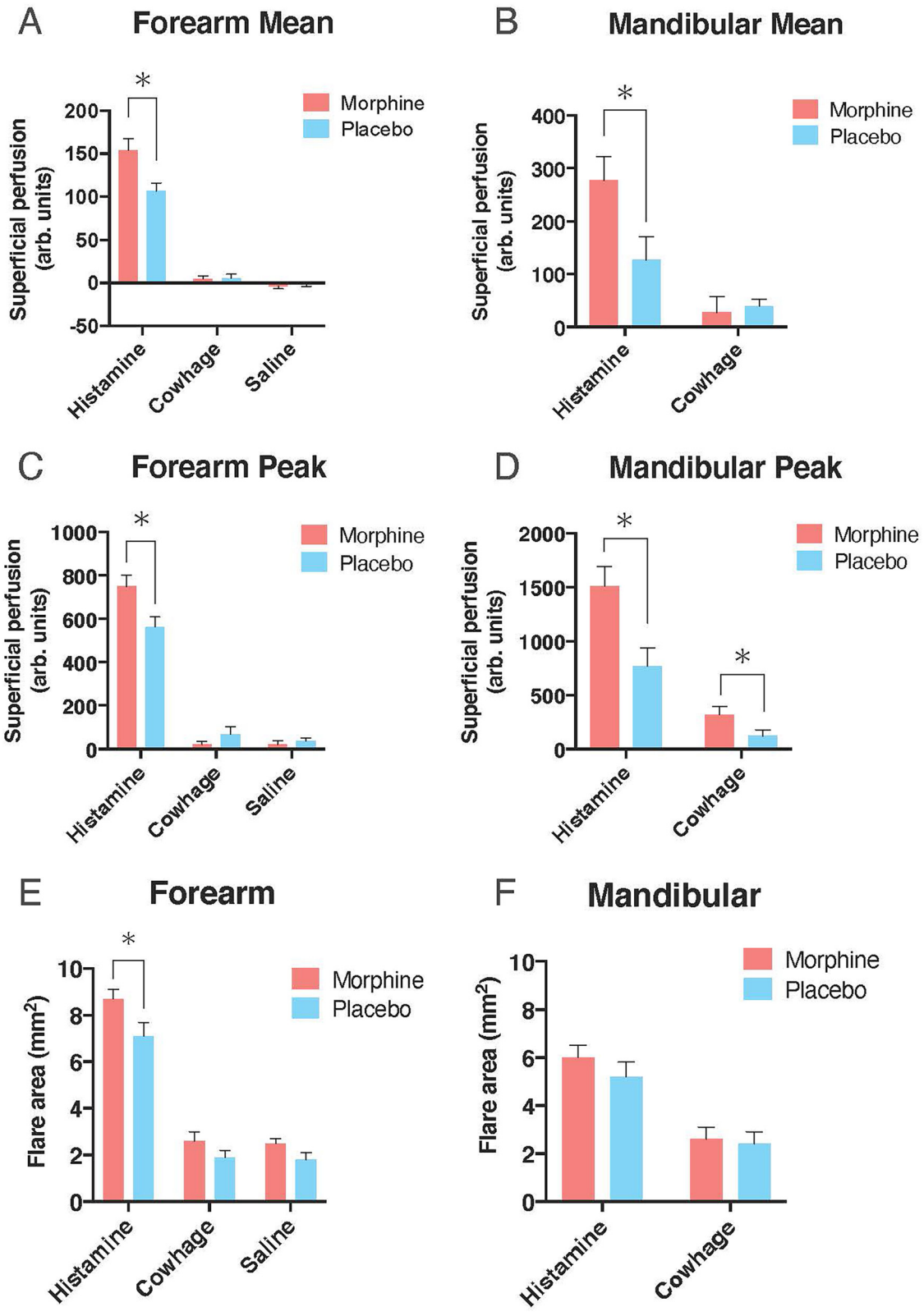

Figure 4: Comparison of change in the superficial blood perfusion and flare area following each itch provocation between morphine and placebo groups. The morphine group exhibited increased superficial blood perfusion and flare area following histamine provocation in the forearm and mandibular regions compared with the placebo group. *p<0.05.

The effect of opioids on heat pain has been examined using various stimuli, but the results are controversial [28, 29]. However, the nociceptive component via A-δ fibers shows increasing dominance at high heat intensity [30], and it has been shown that for heat stimulation, pricking pain via A-δ fibers was felt at the end of the stimulation at high intensities [31]. It was speculated that A-δ fibers were likely to be less activated until the noxious range. The effect of attenuating the A-δ-mediated nociceptive component could be limited, and as a result, morphine was less effective [27].

Neurogenic inflammation

It has been reported that both agonists and antagonists of opioid receptors induce wheal and flare responses by mast cell degranulation in human skin [32, 33]. Furthermore, morphine leads to the non-immunological release of histamine [34], which stimulates the histamine receptor type 1 via itch-specific C-fibers in humans [35]. High concentrations of certain locally administered opioids induce mast cell degranulation and subsequent itch [14–16]. This phenomenon was not caused by non-histaminergic itch but only by histamine and did not affect the provoked itch sensation. Therefore, the present results support the peripheral hypothesis that oral administration of morphine further increases superficial blood perfusion via a mast cell-destabilizing effect. The flare area results are consistent with this phenomenon. Further investigations using other routes of morphine administration, such as transdermal or intrathecal, are required to clarify the role of peripheral and central responses.

Pain thresholds

Consistent with other studies [27], the present results validate the hypoalgesic effect of morphine, which was included in the present study as a control for opioid action. Pressure pain stimulation has been reported to be most sensitive to morphine analgesia [27], as indicated in the present study, in which the pressure pain threshold was the modality most affected by morphine.

Correlation between itch sensitivity and analgesic efficacy

A significant correlation between histamine- and cowhage-induced itch intensities in the forearm region and analgesic efficacy was observed in participants who experienced side effects during the study. According to the clinical data of oral morphine immediate-release formulation 20 mg in healthy individuals, the plasma morphine concentration after 1–3 h of oral administration was stable at 10–20 ng/L [36]. However, opioid sensitivity varies widely among individuals and is modulated by both genetic and environmental factors [37]. It has been reported that people strongly affected by morphine show higher plasma concentrations of morphine and its metabolites than people who respond less, and central side effects are associated with high metabolite concentrations [38]. Analgesic efficacy is proportional to pruriceptive sensitivity in the presence of sufficient opioid effect. This could lead to central modifications, such as spinal disinhibition, in opioid-hypersensitive individuals or when sufficient opioids reach the central opioid receptors.

Clinical significance

Although morphine intake effectively alleviated pain sensation, it did not modulate itch sensation. This indicates that the opioid effects on histaminergic- and non-histaminergic-evoked itching are independent of the opioid effects on thermal and mechanical pain pathways. It has been reported that opioid receptor antagonists could dose-dependently attenuate the scratching behavior induced by spinal morphine administration in primates, whereas antihistamines did not [39]. Hence, opioid-induced itch may not be caused by histaminergic receptors but via μ-opioid receptors [40]. Morphine causes histamine release due to mast cell degranulation, but this can also be caused by direct stimulation of the G-proteins of mast cells [14]. Although oral morphine further increased peripheral superficial blood perfusion and flare size following histamine provocation, the intensity of provoked itch did not differ between the morphine and placebo groups; therefore, the peripheral vasomotor response does not directly correlate with the intensity of opioid-induced itch in humans. This interpretation is consistent with the fact that antihistamines can alleviate peripheral vasomotor responses but are not effective in relieving opioid-induced itching [41, 42].

Our results revealed that the analgesic efficacy in opioid-sensitive individuals was significantly correlated with pruriceptive intensity. A mouse experiment suggested that H1 histamine receptors are closely related to μ-opioid receptors [43]. Hence, opioids may affect central pruriceptive processes in individuals who receive sufficient doses of opioids. The central contribution of pruriceptive modulation may be greater than that of itching caused by the peripheral vasomotor response.

Limitations

A limitation of this study is that the amount of morphine used may not have been sufficient for all participants. However, oral morphine (30 mg) frequently exhibits adverse clinical effects [27]. Therefore, we administered oral morphine (20 mg). A different administration route, such as intrathecal administration, may be more appropriate because it causes more consistent itch responses. Regarding the correlation analysis, the results are speculative, and the statistical power was insufficient in the explorative subgroup because the number of participants who experienced adverse effects was small. However, it is unrealistic to conduct this study only on individuals who would experience side effects. Further investigations using high doses and different types of opioids are required to validate this phenomenon in humans. Sex and hormonal influences (e.g., menstrual cycle) may affect itching and pain measurements. Additionally, the participants may have experienced the effects of habituation and sensitization, which could have affected the results depending on the experimental order. Since most of the participants were young people in the present study, we could not evaluate a factor of age-dependency as a factor. It has long been reported that age is an important determinant of oral opioid tolerance, and older adults are less likely to require dose escalation [44]. Thus, older participants may experience stronger side effects and be more pruritic than younger participants. Although no sex differences were found for each parameter in this study, it is possible that the sample size was insufficient to evaluate sex differences.

Conclusions

Oral administration of 20 mg morphine did not attenuate experimental histaminergic- and non-histaminergic-provoked itch intensities in healthy volunteers but selectively increased superficial blood perfusion to histamine provocation. This suggests that different opioid mechanisms in histaminergic and non-histaminergic evoke neurogenic inflammation.

Acknowledgments: We gratefully acknowledge the work of the past and present members of our laboratory. We are grateful to Hjalte H. Andersen for helping us make the original idea a reality and to Ann-Marie Wegeberg and Isabelle Myriam Larsen for their assistance with the present study.

Research ethics: The regional ethics committee approved the study (N-20190049), and was registered at ClinicalTrials.gov (NCT04115462) before the enrollment of the first participant.
Informed consent: All participants provided written and verbal informed consent before the start of the study.
Author contributions: Study design: HO, AMD, LAN; Participants recruitment: HO, SLV; Study assistance: NA; Data collection: HO; Data analysis: HO, SLV; Approval of final version of the manuscript: HO, SLV, NA, AMD, LAN.
Competing interests: The authors declare that they have no conflicts of interest.
Research funding: The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121).
Data availability: The data that support the findings of this study are available from the corresponding author, Silvia Lo Vecchio, upon reasonable request.

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Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/sjpain-2023-0034).