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Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin

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Abstract **The effect of menthol and alcohol as its vehicle on thermal sensations, pain, experimental itch and irritation were studied in 18 subjects, using a computerized thermal sensory analyzer, laser Doppler flowmetry and an evaporimeter for transepidermal water loss (TEWL). Menthol had a subjective cooling effect lasting up to 70 min in 12/18 subjects; however, it did not affect cold and heat threshold, nor did it affect cold and heat pain threshold. Alcohol produced an immediate cold sensation lasting up to 5 min in 4/18 subjects and lowered the sensitivity of cold sensation threshold ($P < 0.05$). Histamine injection did not change thermal and pain thresholds. Menthol did not alleviate histamine-induced itch magnitude, nor its duration. Following histamine injection, cold sensation median threshold decreased by 1.2° C from (29.9° C to 28.7° C) on the site treated with menthol ($P < 0.01$) with similar changes in thresholds at the alcohol-treated site ($P < 0.05$). Warm sensation and pain threshold in subjects receiving histamine injections, measured after menthol and alcohol application, did not differ from their baseline values with histamine alone. TEWL at the site treated with menthol was significantly higher ($P < 0.05$) than at the alcohol-treated and the control site ($P < 0.01$), suggesting that menthol has a higher skin irritating effect, or at least alters the stratum corneum water permeability. Our results suggest that menthol fulfills the definition of a counterirritant, but does not affect histamine-induced itch, nor does it affect pain sensation.**

Key words Thermal thresholds · Itch sensation · Transepidermal water loss · Laser Doppler flowmetry

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Introduction

Menthol, an old remedy in Chinese medicine extracted from plants of the genus *Mentha*, is widely used as both a cooling agent and a counterirritant for relieving pain especially in the muscles, viscera or remote areas [1–3], as well as for the treatment of pruritus. However, there are no controlled studies evaluating the effect of menthol as a topical agent for the treatment of pain and pruritus using a quantitative sensory testing device. Moreover, menthol is known to be an irritant, based on clinical observations rather than experimental data.

This study assessed the following:

1. the effect of topically applied menthol on thermal sensation, especially its cooling effect;
2. the effect of menthol on thermal pain threshold;
3. the effect of menthol on experimentally induced itch;
4. the effect of menthol on skin microcirculation;
5. the irritating effect of menthol as reflected by transepidermal water loss.

Subjects and methods

A group of 18 volunteers (9 males and 9 females) with an average age of 47 ± 5 years participated in the studies of thermal and pain thresholds, skin microcirculation and transepidermal water loss, and 16 of these volunteers participated in the itch study. All subjects provided written informed consent.

Menthol

L-Menthol (99.9%; Sigma, St Louis, Mo.) 10% in 80% ethanol and 10% deionized H_2O was employed. Ethanol was used as a solvent. The stimuli were applied in a standardized amount of 100 mg in 1 ml over a 16-cm^2 area onto which a peltier probe was placed in the flexor aspect of the upper forearm. The effect of menthol was compared with that of the vehicle of 80% ethanol and 20% deionized H_2O. Only one compound was tested at a time, as previous studies have shown that it is difficult to distinguish between sensations arising from different areas. The subjects were unaware as to the side on which the active agent was applied.

Quantitative thermal testing

All thermal tests were performed with a computerized quantitative thermal sensory device (TSA 2001; Medoc, Ramat Yishai, Israel) with a 5×2.5 cm peltier probe. The probe was placed on the volar aspect of the upper forearm. The method of limits was used [4] in which the threshold was determined as the average of four successive stimuli for cold and warm sensations and three stimuli for cold pain and heat pain thresholds. Rates for temperature change were 1°C/s for warm and cold sensation and 2°C/s for cold and heat pain.

Laser Doppler flowmetry

Skin blood flow was measured using laser Doppler flowmetry (LDF) (MBF3D; Aca Derm, Menlo Park, CA, USA) operating in the wavelength range 780–820 nm. Both arms were simultaneously monitored. Two unheated probes in standard round plastic probe holders were placed on the ventral surface of both forearms, 6 cm from the anticubital fossa and held in position with adhesive tape (3M, Medical Suppliers, St. Paul, MN, USA). Skin blood flow values were averaged over 1 min.

Transepidermal water loss

Transepidermal water loss (TEWL) was measured with an evaporimeter (Tewameter, TM 210; Courage & Khazaka, Aca Derm, Menlo Park, CA, USA). The probe, a small hollow cylinder (10 mm diameter, 20 mm height), was held on the skin surface of the forearm until a stable TEWL was established (approximately 1 min). The results are expressed as g/m^2 per h. Previously established guidelines for the measurement of TEWL were applied [5].

Experimental procedure

All subjects were studied in a controlled room at a constant temperature (18°C) and a relative humidity of 40–50%. The subjects were rested for an acclimatization period of 30 min before study.

Cold and warm sensations and thermal pain

The baseline thermal thresholds of cold sensation, warm sensation, cold pain and heat pain were measured with the thermal sensory testing device. Menthol was then applied to the volar aspect of one forearm and the peltier probe was placed on the same area. The control vehicle was applied to the contralateral forearm. Thermal thresholds were then measured for the above-mentioned sensations.

Histamine-induced itch

Itch was experimentally induced in both forearms by the intracutaneous injection of 100 μg histamine dihydrochloride (Sigma, St Louis, Mo.) dissolved in 1ml normal saline. Thermal thresholds for cold, warm, cold pain and heat pain were evaluated while subjects noted the duration of itch and itch magnitude using a visual analog scale of 100 mm. Itch magnitude was evaluated for the first 10 min. After the application of menthol and vehicle to the forearms, the subjects received an additional similar histamine injection and the same measurements were repeated as before.

Skin blood flow

Skin blood flow was measured on both forearms before, and 5 min after, the application of menthol and the control vehicle.

Transepidermal water loss

Baseline TEWL was measured in both forearms before, and 5 min after, the application of menthol and the control vehicle.

Statistical evaluation

Differences between baseline thermal and pain thresholds following menthol and alcohol treatments were tested using nonparametric Kruskal Wallis analysis of variance and the Neuman Kulis test. A two-tailed matched *t*-test was used to compare the effects of menthol and alcohol on TEWL, skin blood flow, itch duration and itch magnitude in relation to baseline measurements. The results are expressed as medians ± SD.

Results

Cold and warm sensations and thermal pain

Menthol was perceived as causing a cold sensation in 12 of the 18 subjects (7 males and 5 females). The duration ranged between 5 and 70 min (average 32 min). Further, 8 subjects complained of a burning sensation which lasted up to 40 min, and 7 of these had perceived a cold sensation. Alcohol had an immediate cold sensation effect in 4 of 18 subjects which lasted up to 5 min. The results of the experiments on thermal sensation and thermal pain before and after menthol and alcohol treatment are shown in Table 1. Menthol did not affect cold sensation thresholds or warm sensation thresholds, nor did it affect cold or heat pain thresholds. Alcohol did increase cold sensation thresholds but had no affect on warm and thermal pain thresholds.

Histamine-induced itch

Histamine induced itch in 14 of the 16 subjects (8 females and 6 males). Histamine injection did not change the thermal and pain thresholds. Menthol did not alleviate histamine-induced itch magnitude (33.3 ± 3.7 mm vs 29.2 ± 3 mm baseline), nor did it affect itch duration (12 ± 5.3 min vs 11.5 ± 15 min). Following histamine injection, cold sensation threshold was lower by 1°C on the menthol-treated side (28.7 ± 0.8°C vs 29.9 ± 0.5°C baseline with histamine; $P < 0.01$), with similar changes in thresholds at

Table 1 Thermal thresholds and cold and heat pain thresholds in the forearm of volunteers ($n = 18$) before and after application of menthol and alcohol (all values are in degrees centigrade)

	Baseline ($n = 18$)	Menthol ($n = 18$)	Baseline ($n = 18$)	Alcohol ($n = 18$)
Cold sensation	30.2 ± 0.4	29.2 ± 0.9	29.4 ± 0.4	26.7 ± 1*
Warm sensation	33.6 ± 0.2	33.7 ± 0.4	33.9 ± 0.2	33.7 ± 0.9
Cold pain	18.3 ± 1.1	21.5 ± 2.2	24.3 ± 1.1	19.6 ± 1.9
Warm pain	40.9 ± 1.2	41.87 ± 1	40.8 ± 0.8	40.2 ± 1.1

*$P < 0.05$, baseline vs alcohol

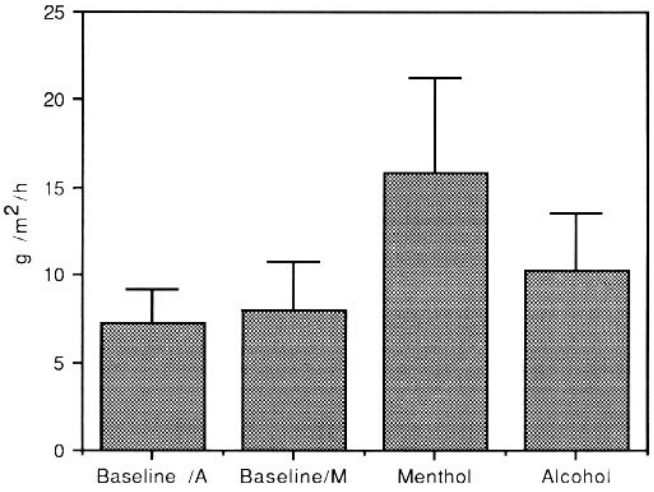

Fig. 1 The effect of menthol and alcohol on TEWL in comparison with baseline values. TEWL after menthol application was significantly higher than after alcohol application ($P < 0.05$) and higher than baseline values ($P < 0.01$) (the bars represent median values ± SD)

the site of alcohol application (27.3 ± 1.1° C vs 29.4 ± 0.4° C baseline with histamine; $P < 0.05$). Warm sensation and pain thresholds in patients receiving histamine injections measured during menthol and alcohol application did not differ significantly from their baseline values with histamine alone.

Laser Doppler flowmetry

Results obtained 5 min after menthol or alcohol application did not differ from baseline skin blood flow measurements (data now shown).

Transepidermal water loss

TEWL from the menthol- and alcohol-treated sites (5 min after application) was significantly higher than baseline. The median values were 15.8 ± 5.5 g/m^2 per h for menthol and 10.2 ± 3.2 g/m^2 per h for alcohol, and the baseline value was 7.5 ± 2.3 g/m^2 per h (Fig. 1). TEWL after menthol treatment was significantly higher than after alcohol treatment ($P < 0.05$), suggesting that menthol has a higher skin irritating effect, or at least alters stratum corneum permeability to water.

Discussion

Menthol had a subjective cooling effect in most subjects without changing the cold sensation threshold, in contrast to the effect of alcohol which lowered the cold sensation threshold. However, during histamine-induced itch, menthol significantly reduced the cold sensation threshold, suggesting that menthol has some effect on terminals of nerve fibers transmitting cold. Hence, the cooling effect of menthol in inflammation may be an effect on nerve fibers. Interestingly, although the vehicle (alcohol) had an effect on the cold sensation threshold, the subjective perception of cold was transient and minimal.

Menthol, widely used in sport medicine for relief of pain due to muscle strains and local inflammations [2], in concentrations above 2% has a local anesthetic action when applied to the human tongue or to animal skin [6, 7]. However, we failed to demonstrate an analgesic effect of menthol against heat-induced pain. Our results coincide with those of Green [8, 9] who did not find an effect of menthol at similar concentrations on heat and cold pain thresholds. Future studies might assess the effect of menthol on mechanically induced pain.

Menthol sensitizes cold thermoreceptors and increases electrical discharge from cold receptors [7, 10]. We therefore expected that menthol would enhance the sensation of cold and that the cold sensation threshold would be at an elevated temperature. Menthol had no effect on cold threshold and it increased the cold sensation threshold after histamine-induced itch. These findings do not support our initial hypotheses, and do not coincide with those of Green [8, 9] who found that menthol at the same concentrations raised the perception of cooling and attenuated the perception of moderate warming. A possible explanation for this discrepancy is that the two studies assessed the effect of menthol on sensation differently. Green used noncomputerized thermal testing in which the subject stated at different given temperatures the intensity of his or her sensation of heat but did not assess temperature and pain thresholds. We, on the other hand, used a computerized quantitative thermal sensory testing device, enabling us to provide an accurate numerical thermal perception, but did not check sensation intensity. The importance of using this instrument is well documented [11, 12]. It has been recently used to characterize the function of small nerve fibers and their associated free nerve endings which mediate thermal and pain sensations [11, 12].

Our results concerning the effects of alcohol on cold sensation add to the understanding of alcohol's effect as an irritant. These findings disagree from those of Green who stated that alcohol is an inactive nociceptive compound, and our discussion above is also relevant to this discrepancy [8].

Long considered as an effective topical antipruritic agent, the cooling effect of menthol gives logical support to its possible antipruritic effect [1]. However, few controlled studies have been yet performed to evaluate its antipruritic effect. Recently Bromm et al. [13] have demonstrated that a 1% menthol solution has a significant antipruritogenic effect. The current study utilized a high menthol concentration (10%) which failed to alleviate histamine-induced itch. Melton and Shelly reported that the application of menthol at the lower concentration of 1% did not alleviate itch [14]. Future studies may assess the antipruritic activity of different concentrations of menthol using the technique presented here.

The irritant effect of alcohol to the skin is well documented [15]. In the current study, menthol dissolved in an alcohol solution had a significantly higher irritant effect than alcohol alone, as expressed by TEWL. After both applications, TEWL was significantly higher than baseline ($P < 0.01$). However, there was no visible erythema after these applications. It is noteworthy that the effect of menthol was assessed after a short period of time, that is 5 min after application. Support for these findings comes from the work of Hong and Shellock [2] who found that Euclyptamint, containing eucalyptus oil, lanolin and 15% natural menthol, significantly increases skin blood flow over the area of application within 5 min. The irritant effect of menthol causes local vasodilation [1, 2]. However, the values of skin blood flow in our study did not differ from the baseline values 5 min after application of menthol. A possible explanation for the elevated TEWL is that menthol did not completely evaporate from the skin within 5 min, although it is known to be a volatile compound. The transient increase in TEWL suggests a possible use as a percutaneous penetration enhancer. Further studies may assess the effect of different concentrations of menthol on TEWL.

In conclusion, local application of menthol to the forearm skin did not alter the thermal sensation thresholds in noninflammatory states. High concentrations of menthol did not alleviate itch nor did they have an analgesic effect for heat and cold pain. However, menthol fulfills the definition of a counterirritant since it irritated the skin and caused a sensation of coolness on the skin. Taken together, these experiments provide some insight into menthol's mechanism of action in itch.

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