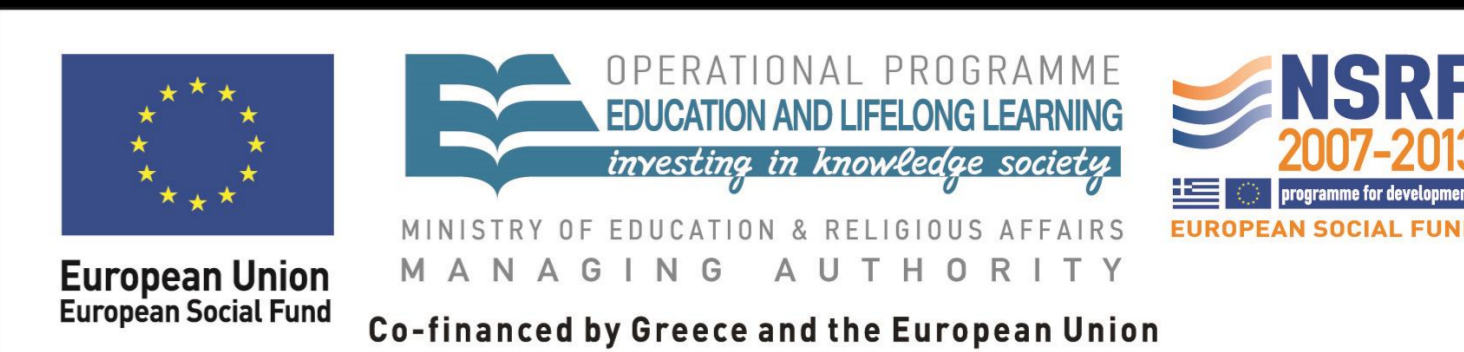


ACUTE EFFECT OF DIETARY AND SKIN TRPM8 ION CHANNEL STIMULATION ON HUMAN THERMOREGULATION AND METABOLISM

Angela Valente^{1,2}, Athanasios Z. Jamurtas², Yiannis Koutedakis^{2,3}, and Andreas D. Flouris¹

¹FAME Laboratory, Centre for Research and Technology Hellas, Trikala, Greece; ²Department of Exercise Sciences, University of Thessaly, Trikala, Greece; ³School of Sport, Performing Arts and Leisure, University of Wolverhampton, UK.



SUMMARY

Transient receptor potential melastatin 8 (TRPM8) is the receptor for cold sensation and is located on the cell membrane of brown adipocytes and sensory neurons on the skin, and can be activated by both cold and L-menthol. Indeed, both skin and dietary L-menthol treatments increase brown adipose tissue (BAT) activity and metabolism in mice, leading to reduced body weight. However, the effects of these treatments in humans remain incompletely understood. The aim of this study was to examine the effect of dietary versus skin TRPM8 stimulation on metabolism and thermoregulation in humans. Nine healthy male volunteers were randomly distributed into either L-menthol skin and dietary treatment groups. Participants in both groups were treated with 10 mg/kg L-menthol and placebo. Fasted participants remained seated in a 24-25°C and 40-50% relative humidity environment. Core temperature, heat storage, metabolic rate, and mean skin temperature were measured at baseline, immediately following each treatment, and every hour thereafter for 7 hours. Each assessment lasted 15 min. TRPM8 stimulation via L-menthol skin and dietary treatments result in cutaneous vasoconstriction and increased metabolic heat production. Moreover, the effects produced by skin treatment appear to be stronger, as compared to those of dietary treatment.

INTRODUCTION

BAT in mammals functions to generate heat and maintain body temperature in cold environments via a process known as non-shivering thermogenesis. BAT activity has been positively correlated with resting metabolic rate, which suggests that it plays an important role in metabolism. TRPM8 is the receptor for cold sensation and is located on the cell membrane of both brown adipocytes and sensory neurons on the skin. TRPM8 can be activated by both cold and exogenous chemical agonists, such as L-menthol. Indeed, both skin and diet L-menthol treatments evoke cold sensation and increase BAT activity. Moreover, frequent TRPM8 activation leads to a decrease in body weight gain which suggests that TRPM8 is involved in behavioral heat-gain responses and metabolism. The activation of TRPM8 by L-menthol skin and diet treatments in animal models appear promising, but their efficacy in humans remains to be established. The aim of the present study was to examine, for the first time, the effect of dietary versus skin TRPM8 stimulation on metabolism and thermoregulation in adult male participants.

METHODOLOGY

Nine healthy male volunteers were randomly assigned into either the L-menthol skin (ST; n=4) or the dietary (DT; n=5) treatment groups. Participants in both groups were treated with 10 mg/kg L-menthol [ST: gel; DT: capsule (Figure 1)] and placebo (ST: water; DT: lactose capsule) in a random order on two different days. The L-menthol or water gel was applied on the SKIN group participants' neck, left arm and leg.

Participant preparation days:

- record their diet using a log and their physical activity using a pedometer (Tanita PD-637, Tokyo, Japan);
- avoid excessive stressors, alcohol, coffee, and passive smoke 24 hours prior to each assessment.

Assessment days:

- 12-hour fasted participants wearing the same clothing on both assessment days;
- laboratory environment 24-25°C and 40-50% relative humidity;
- no food consumption during data collection.

Measurements:

Core temperature (T_c), body heat storage (S), metabolic rate (M), and mean skin temperature (T_{sk}) were measured at baseline, immediately following each treatment, and every hour thereafter for 7 hours. Each assessment lasted 15 min.

Instruments:

- Rectal Temperature: was measured using a thin and flexible core temperature thermistor (Mon-A-Therm Core, Mallinkrodt Medical, St Louis, USA).
- Body Heat Storage and Skin Temperature: body heat storage was measured non-invasively using partitioned calorimetric techniques using probes placed on the forehead, abdomen, forearm, hand, quadriceps, shin and foot surfaces (Biomnic Ltd., Trikala, Greece).
- Indirect Calorimetry: participants were asked to breathe through a low resistance one-way valve attached to a face mask. Exhaled gases were used to assess oxygen uptake and the respiratory quotient using a portable gas analyser (Oxycon Mobile, CareFusion, San Diego, USA).

RESULTS

The placebo condition data were subtracted from the L-menthol condition data to eliminate the effect of diurnal variation. Kruskal-Wallis one-way ANOVA was used to assess the effect of each treatment on all variables showing a change across time for both ST and DT (Figure 2; p<0.05). Post hoc Mann-Whitney U tests showed that ST reduced T_{sk} within 2 hours and increased S, M, and T_c within 4 hours (p<0.05). A similar, albeit weaker, effect was observed following DT (p<0.05). Between-treatments comparisons showed that ST produced a strong vasoconstriction [evident by a greater reduction in T_{sk} (p<0.05)] that resulted in a greater increase in S, M, and T_c (p<0.05).

DISCUSSION

The present study examined the effect of DT versus ST TRPM8 stimulation on metabolism and thermoregulation in humans. We found that TRPM8 activation via L-menthol ST and DT result in cutaneous vasoconstriction and increased metabolic heat production. Moreover, the effects produced by ST appear to be stronger, as compared to those of DT.

ACKNOWLEDGEMENTS

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Figure 1. L-menthol crystals used to produce gel creams and capsules.

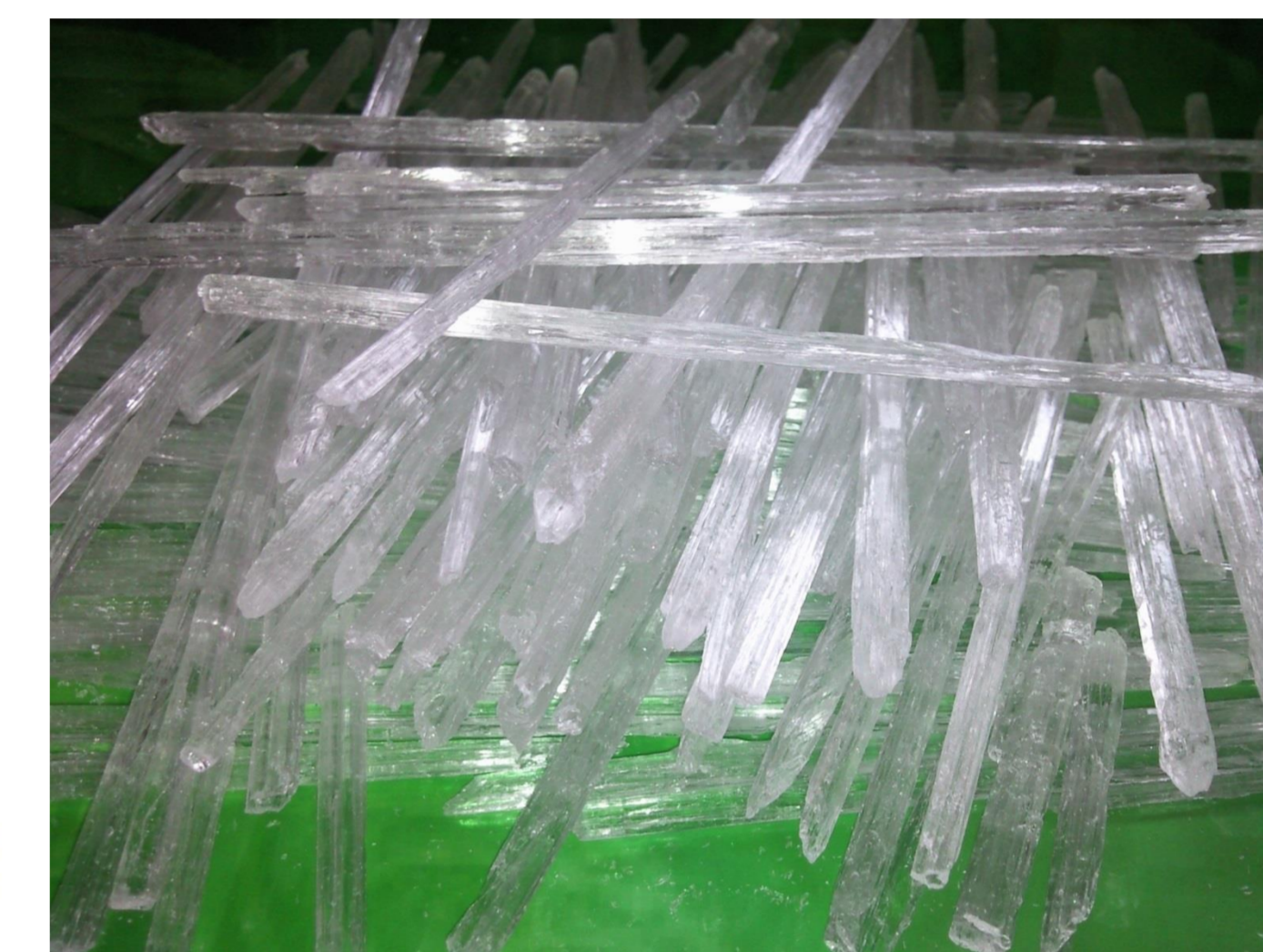
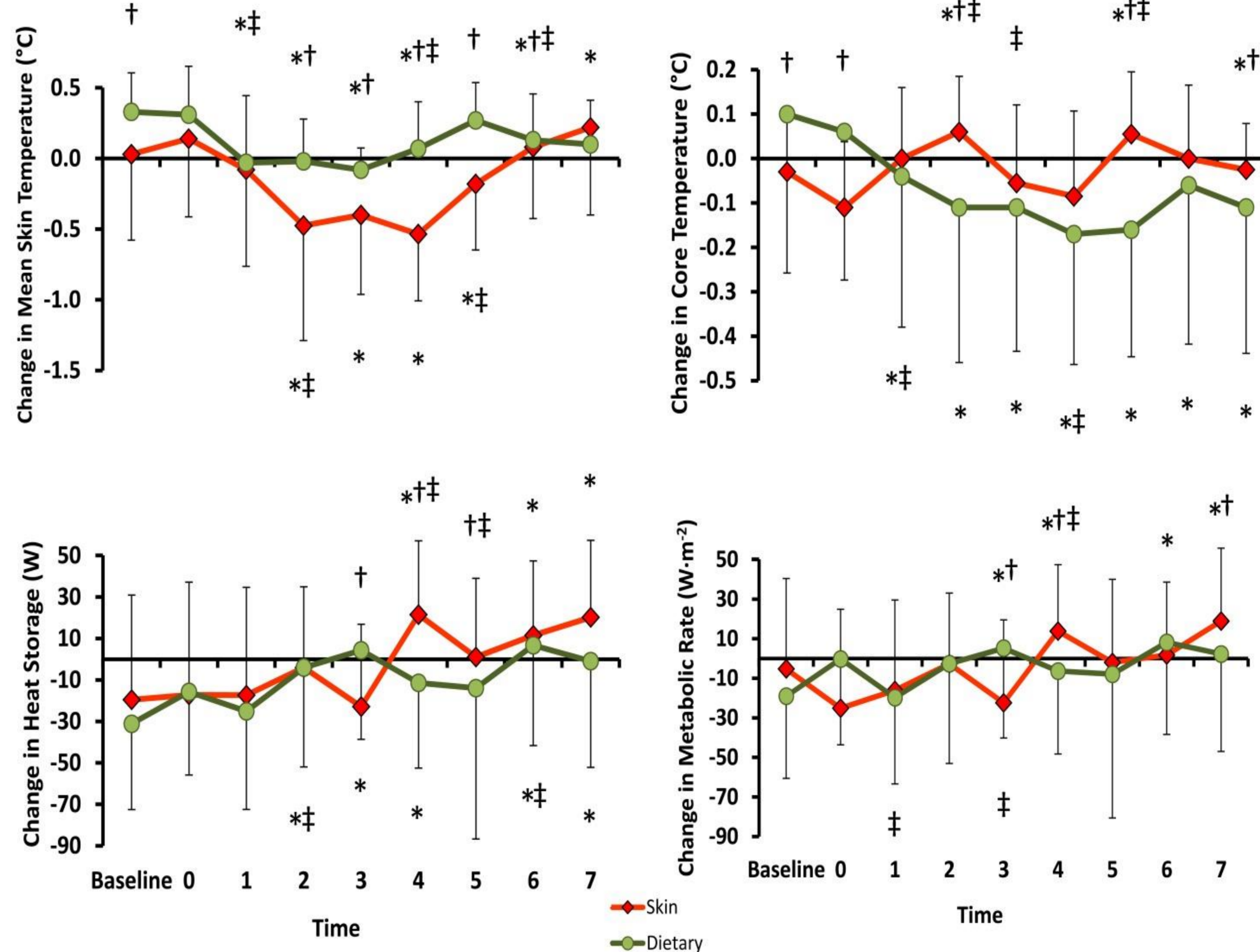


Figure 2. Median±SD change (L-menthol condition minus placebo condition) in mean skin temperature, core temperature, body heat storage, and metabolic rate in the skin and dietary treatment groups. Symbols are placed at the respective end of the SD bars: * = difference from baseline for the same treatment; ‡ = difference from the previous time-point for the same treatment; † = difference between treatments for the same time-point.



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