Study Protocol and Statistical Analysis Plan

Title: The Influence of Topical Capsaicin on Thermoregulatory and Perceptual Outcomes During Exercise Within the Heat

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Abstract

The purpose of this study is to examine the human thermoregulatory impact of applying a commercially available capsaicin cream to the skin prior to moderate intensity walking under heated conditions. Eligible participants will be aged 19-45 years, have no previously known adverse reactions to capsaicin (active ingredient) based upon a self-report, no adverse reactions to capsaicin as determined through application to a small forearm area, and cleared for physical activity via the 2022 Physical Activity Readiness Questionnaire (PARQ). There will be a total of 3 experimental visits to the laboratory. Visit 1 will test for adverse capsaicin reaction by applying a small amount of cream to the forearm (~2 x 2 in). Anthropometric and body composition data will also be collected at this time. Visits 2 and 3 will consist of 30 min of treadmill walking at a moderate pace (3.5 mph, 5% grade) under hot conditions (38°C, 60%RH). Visits 2 and 3 will be randomized and counterbalanced for capsaicin or a hypoallergenic cream (control) application. Creams will be applied to areas commonly exposed during outdoor activity in warm conditions (shoulder to wrist, mid-thigh to ankle). Accordingly, participants will wear shorts and a tank top shirt during exercise. Core temperature, skin temperature, galvanic skin response, laser doppler blood flow, and heart rate will be continuously recorded throughout the exercise bout via an integrated analog to digital converter. Sweat will be collected during exercise using commercially available absorbent patches. Thermal sensation will be assessed throughout exercise via the ASHRAE thermal sensation Likert scale (cold to hot). Lastly, nude body weight will be recorded pre and post exercise for sweat rate determination. The capsaicin and control trials will be separated by a 7-14 day washout period. There will be no follow up visits.

Purpose and Rationale

The purpose of this study is to examine the impact of applying a capsaicin-based cream to the skin on human thermoregulation and thermal perception during exercise in the heat. The capsaicin chemical compound is found in many hot sauces, making it strongly associated with feelings of heat and pain. Topical capsaicin receptors can invoke a tingling sensation that can be perceived as heat. The capsaicin receptor is a part of a family of membrane proteins called transient receptor potential (TRP) channels [1]. TRPs allow for the perception of environmental stimuli and act as sensory mediators. The capsaicin receptor in our body, also known as vanilloid receptor one, is a TRPV1 channel. Besides activation of the TRPV1 channel by capsaicin, it is also activated by ambient noxious heat [1,3]. Capsaicin activated TRPV1 receptors lead to vasodilation of the skin [1]. This vasodilation is vital to the cooling of the body, as it gets rid of excess heat, aiding in thermoregulation. This can be contradictory to the perceived heat since it aids in cooling. It was first discovered that TRPV1 plays a role in thermoregulation when it was found that capsaicin has hypothermic action that can lower core temperature significantly in multiple species, including humans [2]. This evidence supported that TRPV1 has profound effects on maintaining homeostasis of internal body temperature.

If topical capsaicin provokes vasodilation, then the question remains as to why it is not more commonly used by humans in hot environments. This could be because of the previously referenced negative feelings of capsaicin. Currently, topical capsaicin creams are marketed as an analgesic, commonly aimed at those experiencing arthritic pains; yet this is not their full physiological potential. There is a physiological conflict between the perceived hot sensation of capsaicin compared to the observed physiological effects. It is currently unknown if over-the-counter capsaicin creams can aid in performance during exercise in the heat, or if the perceived burning sensation would hinder

performance. This requires further investigation into the effects that topical capsaicin may have on exercise performance in the heat.

Participants

12-15 subjects, aged 19 to 45, will be needed to complete the study. Keeping the age range of 19-45 ensures that the participants will be of consenting age and cleared for physical activity participation.

Research Plan

Three experimental visits to the laboratory will be conducted. All visits will take place at the University of Nebraska at Omaha, Exercise Physiology Laboratory. Visit 1 will consist of the physical activity readiness questionnaire (PARQ), adverse reaction to Rugby Capsaicin Cream (0.025%), and body composition (hydrostatic weigh, bioelectrical impedance). Visits 2 and 3 will be separated by 7-14 days, randomized, and counterbalanced for experimental (capsaicin) and control (hypoallergenic cream) trials. Both the experimental and control visits will follow the same protocol.

Participants will arrive following an overnight fast state while also refraining from strenuous activity, alcohol consumption, tobacco use, and recreational drugs for the previous 24 hour period. During these visit researchers will apply Rugby capsaicin cream using a gloved hand from shoulder to wrist and mid-thigh to ankle (areas outside of the clothing). A hypoallergenic cream (Remedy Essentials Unscented Moisturizing Body Lotion, Medline Industries inc.) will be applied during the control visit.
Exercise will consist of 30 min of moderate intensity treadmill walking (3.5 mph at 5% grade) within a heated temperature/humidity-controlled chamber (38°C, 60% relative humidity).
Participants will be weighed before, and after completion of the exercise calculate sweat rate. Prior to the exercise session, participants will sit for 5 min in an ambient room temperature environment as a baseline. During baseline and during the exercise core temperature, skin temperature, laser doppler blood flow, galvanic skin response, and heart rate will be collected continuously. Sweat patches will be adhered to the forehead during exercise at minute 10 for collection of sweat composition over the next 10-20 minutes.
Thermal perception using the ASHRAE scale (cold to hot) will be assessed pre and during exercise.

EXPERIMENTAL VISIT 1

Visit 1 will take approximately 1 hour. Participants will then complete the physical activity readiness questionnaire (PARQ) to be cleared for physical activity. Participants will have a small amount of the capsaicin cream and control cream applied to a small area of the forearm (~2 x 2 in) to test for any adverse reaction over a period of 15 minutes. Those without a reaction will have height, weight, and body fat composition measured. Then, resting blood pressure and heart rate will be taken. Those without a reaction, and a resting blood pressure lower than 140/90, will have height, weight, and body fat composition measured. Height and weight will be measured using a medical scale and stadiometer, respectively. Body fat will be assessed with hydrostatic weighing using an electronic load cell-based system (Exertech, Dresbach, MN) correcting for residual lung volume or via a bio- electrical impedance analyzer (InBodyUSA, Cerritos, CA).

EXPERIMENTAL VISITS 2 AND 3

Visits 2 and 3 will take approximately 2 hours each. Upon arrival at the lab, a nude body weight will be collected with the subject in a private room. While still in the room, subjects will self-insert a rectal

thermistor 12-15 cm beyond the anal sphincter and don a chest strap heart rate monitor. After dressing in their exercise clothing, subjects will exit the private room so that chest, forearm, and calf thermistors can be adhered to the skin with tape.
Laser doppler flow (forearm and or/finger) will be adhered with tape and galvanic skin response (fingers) will be adhered using Velcro straps to the skin. Measuring instruments will be recorded using an integrated digital to analog converter (ADInstruments, Colorado Springs, CO).

Following instrumentation, subjects will sit for 5 minutes as a baseline for all recordings in a temperate environment. Immediately after, a researcher with gloved hands will topically apply capsaicin or the control hypoallergenic cream from the shoulder to wrist and mid-thigh to ankle. Subjects will then enter the heat chamber (38°C, 60% relative humidity) and immediately begin a 30-minute walk on a treadmill (3.5 mph, 5% grade). Subjects will be intermittently asked to hold their arm steady for laser doppler flow collection (10, 20, 30 minutes). Subjects will also briefly pause at minute 10 in order to adhere an absorbent patch to their forehead for sweat collection over the following 10-20 minutes. Thermal perception using the ASHRAE scale (cold to hot) will be assessed pre and during exercise. After 30 minutes of walking, subjects will exit the chamber for removal of all skin and finger sensors. Subjects will then re-enter the private room, remove their own rectal thermistor with gloved hands, and then a final nude body weight will be recorded after toweling off.

The rectal thermistor will measure core temperature. The heart rate monitor will measure the beats of the heart. Skin thermistors will measure the temperature of the skin surfaces. Laser doppler flow measure the relative units of blood flow velocity. Galvanic skin response measures skin conductivity changes as individuals begin to sweat. Sweat is collected for assessment of sweat composition. Thermal perception is assessed for individual perception surrounding the temperature of the ambient environment. Nude body weight is measured to calculate sweat rate.

Statistical Analysis

Recruitment

Previous exercise research suggests that the difference in response of matched pairs is normally distributed with a standard deviation of 0.86. If the true difference of the mean response of matched pairs is 0.75, we will need to complete 12 experimental trials for each condition to be able to reject the null hypothesis that this response difference is zero with a power of 0.8. The Type I error probability associated with this test of the null hypothesis is 0.05.

Interventions

A repeated measures two-way ANOVA (Time x condition) will be used for the dependent variables. If the F-ratio values are found to be significant, a Fisher's Least Significant Difference post hoc analysis will be conducted. A type I error probability of < 5% will be considered significant ($p < 0.05$). All data will be analyzed using a combination of Microsoft Excel and the Statistical Package for the Social Sciences (SPSS).