Do common over-the-counter antihistamine medications modify thermoregulatory responses during passive heat stress?

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Abbreviations

Allergic rhinitis (AR)

Heat-related illness/injury (HRI)

Over-the-counter (OTC)

World Health Organization (WHO)

Occupational Safety and Health Administration (OSHA)

National Institute for Occupational Safety and Health (NIOSH)

American College of Sports Medicine (ACSM)

National Athletic Trainers Association (NATA)

Journal of the American Medical Association (JAMA)

Change in body temperature from baseline (ΔT_{body})

Placebo (PLA)

Diphenhydramine (DPH)

Loratadine (LOR)

Desloratadine (DES)

Urine Specific Gravity (USG)

Abstract

Over the coming decade, climate change is expected to increase the duration and intensity of pollen season and contribute to higher atmospheric concentrations of inhaled allergens (Corden & Millington, 2001; D'Amato et al, 2015). This is likely to increase the number of individuals who suffer from respiratory conditions such as allergic rhinitis (AR), worsen their symptoms, and stress healthcare infrastructure (Beggs, 2004; Kim et al, 2018; Ziska & Caulfield, 2000; Ziska et al, 2019). Currently, guidance suggests all antihistamines may increase an individuals' risk of heat-related illness/injury (HRI) during heat stress by suppressing human thermoeffector responses (Casa et al, 2015; Coco et al, 2016; OSHA, 2011; O'Connor & DeGroot, 2024; Roberts et al, 2023; WHO, 2011). However, whether over-the-counter (OTC) antihistamines for allergy, taken as recommended, alter sudomotor and/or cardiovascular responses during heat stress has not been critically analyzed in humans. This thesis sought to determine whether the oral ingestion of three common OTC antihistamines (diphenhydramine, loratadine & desloratadine) would alter sudomotor, cardiovascular, or perceptual responses to heat stress when compared to a placebo pill (sugar). A total of 10 young healthy participants (5M, 5F, 22.6 ± 1.8 yrs, 174 ± 10 cm, 73.6 ± 10.8 kg) completed our double-blind randomized crossover procedure where they consumed either i) 50 mg diphenhydramine ii) 10 mg loratadine iii) 5 mg desloratadine or iv) a sugar pill before being passively heated to a mean body temperature 1.5℃ above baseline. Preliminary data suggests that OTC antihistamines do not alter local sweat rate of the forearm [$Mg/cm^2/min^1$ (Placebo (PLA): 0.411, diphenhydramine (DPH): 0.436, loratadine (LOR): 0.368, desloratadine (DES): 0.432)], skin blood flow [%max (DPH: 25.71, LOR: 21.81, DES: 21.10, PLA: 21.27)], heart rate [BPM (DPH: 72.25, LOR: 78.34, DES: 74.86, PLA: 74.94)], mean arterial pressure [Mm/Hg (DPH: 81.95, LOR: 82.09,

DES: 82.20, PLA: 80.98)], or rate-pressure product [Mm/Hg (DPH: 8604, LOR: 9051, DES: 9126, PLA: 8851)] during passive heating, suggesting they may continue to be a safe option to allergic symptom management during periods of heat exposure. Further research aimed at examining different OTC antihistamines and/or doses, in other heat-vulnerable groups and types of heat stress is required to wholly conclude the HRI risk posed by OTC antihistamines.

Introduction

Respiratory conditions such as allergic rhinitis (AR) currently affect approximately 20-25% of Canadians and up to 50% of individuals in certain high-income countries (Bousquet et al, 2020; Keith et al, 2012). Further, individuals working in professional sectors where airborne allergen exposure is common (ie. Carpenters frequently exposed to wood dust) are up to 78% more likely to develop symptoms of occupational AR (Shao & Bernstein, 2019). The World Allergy Organization predicts that respiratory conditions such as AR and asthma will become increasingly prevalent over the next decade due to rising global ambient temperatures extending and amplifying the pollen season, thereby increasing pollen's overall allergenicity (D'Amato et al, 2015). Similarly, more frequent extreme weather events such as heavy rainfall and flooding will exacerbate the spread of fungal spores further increasing the potential for individuals to experience AR symptoms (Corden & Millington, 2001). Individuals who experience mild AR symptoms are less likely to seek medical attention, contributing to the belief that the condition is generally underdiagnosed. A Danish study reported undiagnosed AR cases in 32% of their 571 adult participants (Nolte et al, 2006). Furthermore, up to 80% of asthmatics are comorbid with AR, which increases both symptom severity and the risk of misdiagnosis (Bousquet et al, 2008).

Independently, AR can have detrimental effects on social life, work productivity, and academic performance. A Swedish occupational study estimated the nationwide financial burden

associated with AR and the common cold comprises €2.7 billion in yearly losses due to absenteeism and decreased productivity (Hellgren et al, 2009). To alleviate symptoms of AR individuals often self-medicate with low-cost antihistamine medications available over-the-counter (OTC) (Simon & Simons, 2008). Among American adults, OTC antihistamines are the most popular medication for alleviating symptoms of AR (Ajmani et al, 2017).

In Canada, allergy season spans from April to September and generally peaks mid-summer (July to August) (Dayal & Sinha, 2020). Coincidentally, this timeframe superimposes on the hottest periods of the year where extreme heat events are more common, and heat-related illness/injuries (HRI) are prevalent among Canadians (Adam-Poupart et al, 2014).

To protect from HRI, humans employ physiological thermoeffector actions (Sweating and cutaneous vasodilation) to dissipate excess body heat (Flouris, 2019). By redistributing blood flow peripherally to cutaneous vascular beds, body heat is more readily lost to the environment through radiative, convective and conductive means (Kenny & Flouris, 2014). Similarly, the excretion and subsequent evaporation of water molecules in sweat releases heat from the skin surface and represents the body's largest modifiable physiological response to heat stress (Kenny & Flouris, 2014).

The physiological mechanisms behind sweating and cutaneous vasodilation are dictated by a negative feedback loop in the autonomic nervous system (Ravanelli et al, 2021). Upon stimulus, afferent thermoreceptors send information for central integration in the hypothalamus, before an efferent stimulus is transmitted to effector organs (cutaneous vascular beds and sweat glands). When the signal arrives, sympathetic axons release neurotransmitters that bind to muscarinic receptors on endothelial tissue or sweat glands which leads to cutaneous vasodilation and sweating (Shibasaki et al, 2006). Theoretically, any condition, medication, or environment

interrupting these processes could impair cutaneous vasodilation and/or sweating during heat stress, reduce body heat dissipation, and cause dangerous elevations in core temperature (Shibasaki & Crandall, 2010).

Currently, several public health authorities suggest the anticholinergic/antimuscarinic properties of antihistamine medications to impair sweating during heat stress thereby decreasing heat dissipation and increasing HRI susceptibility. The World Health Organization's (WHO) public heat-health advice currently instructs individuals to refrain from using all antihistamines during hot weather (WHO, 2011). The Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) list antihistamine medications under factors that increase workers' risk of heat intolerance and increase the risk for HRI (OSHA, 2011). Current NIOSH guidelines require all workers to report antihistamine use during medical evaluations (Coco et al, 2016). In addition, the American College of Sports Medicine (ACSM) and the National Athletic Trainers Association (NATA) advise athletes that self-administering antihistamine medication might predispose them to exertional heat illness and heat stroke (Casa et al, 2015; Roberts et al, 2023). A review published in the Journal of the American Medical Association (JAMA) included antihistamines under medications that may be risk factors for exertional heat illness among athletes (O'Connor & DeGroot, 2024).

More recently, a systematic review and meta-analysis by Hospers et al (2024) suggested more research is required to determine if drugs with anticholinergic effects including OTC antihistamines are associated with higher core temperature(s) during heat stress from sweating impairment. Additionally, Williams (2021) discussed from a diagnostic perspective how climate change will increase the importance of identifying HRI-susceptible groups in coming years, and

suggests individuals taking medications with anticholinergic properties (ie. Antihistamines) may fall under this classification.

However, without empirical evidence and systematic evaluation, the relationship between OTC antihistamines and sweating remains unclear. Thus, the purpose of the present study is to assess whether three commonly used OTC antihistamines diphenhydramine (Benadryl®), loratadine (Claritin®), and desloratadine (Aerius®) alter thermoregulatory control during heat stress.

Review of Literature

This review of literature will provide a comprehensive overview of human thermoregulation as it relates to heat stress, heat-related injury/illness (HRI), and the potential effect of OTC antihistamine use. The initial portion of the review will detail the basics of human thermoregulation and heat exchange. Following this will be a brief review of typical cardiovascular and thermoregulatory responses to heat stress. After, a review of the prevalence and symptomatology of HRI and allergic rhinitis (AR). Following will be a brief review of muscarinic and histamine receptors, accompanied by an overview of known medications that affect thermoregulation. Lastly, an overview of over-the-counter (OTC) antihistamines diphenhydramine, desloratadine, loratadine, and a brief discourse concerning their potential effects on thermoregulatory responses to heat stress.

Human Thermoregulation

Human beings are constantly exchanging heat with their ambient environment through a combination of four heat transfer avenues: Radiation, convection, conduction, and evaporation (Kenny & Flouris, 2014). Radiative heat transfer occurs via electromagnetic energy absorbed by

or emitted from the body. Convective heat transfer is heat energy transferred to or from air that is passing over an object. Conductive heat transfer occurs between two objects that are in contact. Lastly, evaporative heat transfer refers to heat that is dissipated from the body from the evaporation of water or sweat (Kenny & Flouris, 2014). At comfortable temperatures, small changes in behaviour, such as changing clothing or environment often suffice in maintaining thermal equilibrium. When behavioural responses are insufficient, the thermoregulatory system engages physiological mechanisms to help mitigate large perturbations in core temperature.

When cold-stressed, the thermoregulatory system must decrease heat dissipation and increase heat storage to sustain a body temperature compatible with life. Acute exposure to cold stress elicits shivering, where repetitive isometric muscle contractions increase metabolic heat production. Additionally, blood is redistributed centrally away from the periphery to sustain vital organ function and lessen dry heat exchange (Pozos & Danzl, 2001).

When heat stressed, human physiology is tasked with balancing internal heat production and external heat dissipation, regardless of environmental factors. Body heat that is released to one's surrounding environment from radiation, convection and/or conduction is termed "dry heat loss", and heat loss caused by the evaporation of water from skin (ie. Sweat) is called "active" or "evaporative heat loss" (Kenny & Flouris, 2014).

Upon entering a hot environment, behaviors such as removing clothing can manipulate dry heat exchange to satisfy the amount of heat dissipation required for thermal equilibrium. Left to progress, initial body heat storage acts as the stimulus for thermoeffector responses (sweating & cutaneous vasodilation) (Crandall & Wilson, 2015). The drive for thermoeffector responses are centrally mediated, but amenable to peripheral modulation, as alterations in local skin temperature are also known to influence sweat output (Stolwijk et al, 1971). The sympathetic

drive for thermoeffector responses are governed by negative feedback loops in the autonomic nervous system that function to adapt rates of bodily heat transfer to balance heat storage (Ravanelli et al, 2021). Abiding by the energy conservation law, to remain in thermal equilibrium, the rate at which the body stores heat must always equal the rate at which the body dissipates heat regardless of environmental factors (Cramer & Jay, 2016). When heat loss mechanisms are insufficient to match the combined endogenous and exogenous heat load, it can cause the body to store excess heat leading to potentially dangerous elevations in core temperature.

Thermoregulatory Responses to Heat Stress

Humans readily manipulate heat exchange variables through thermoreceptor-mediated alterations in physiology and/or behaviour called thermoeffector responses. Behaviourally, heat-stressed people may respond by seeking a cooler environment or modifying clothing. Physiologically, changes in metabolism, blood redistribution, and sweat excretion modulate heat transfer by increasing body heat dissipation from the skin surface (Flouris, 2019). Thermoeffector responses are governed by a negative feedback loop in the autonomic nervous system consisting of afferent sensation, central integration, efferent signaling & end-organ output (Ravanelli et al, 2021).

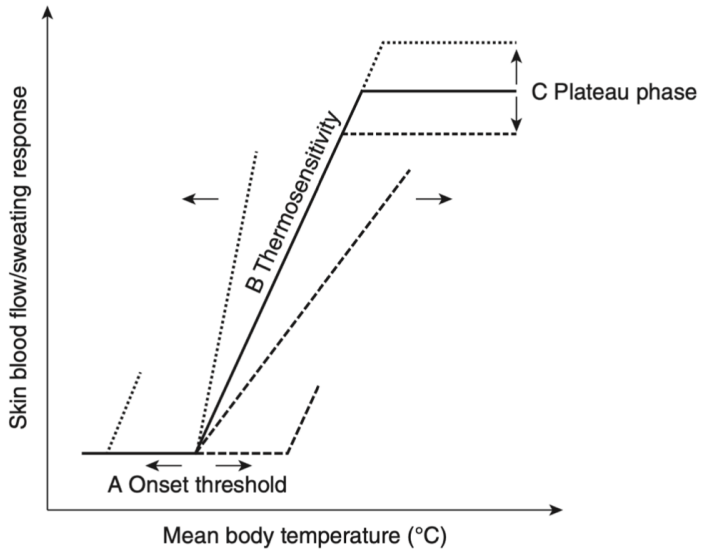
Thermoeffector onset threshold refers to the point following heat stress that sweating or cutaneous vasodilation begins to rise from baseline. After onset, thermosensitivity refers to the relationship between mean body temperature and thermoeffector output. During compensable heat stress, the plateau phase of the thermoeffector response curve will occur, signifying heat balance has likely been achieved (Ravanelli et al, 2020). Abiding by the model presented by Ravanelli et al (2017, 2021), during uncompensable heat stress, the plateau phase is indicative of

one's maximum physiological thermoeffector output rate (Cramer et al, 2022; Ravanelli et al, 2017; Ravanelli et al, 2021).

Thermoeffector onset threshold, thermosensitivity, and the plateau phase of thermoeffector output (see Figure 1) collectively determine the net heat storage an individual experiences during heat stress (Kenny & Flouris, 2014). An attenuation in thermoeffector onset, thermosensitivity, and/or a reduced maximum output may result in greater body heat storage during heat stress.

Figure 1

The relationship between thermoeffector response variables and mean body temperature during heat stress



Note. Taken from Kenny & Flouris (2014).

The imbalance between heat generation and heat loss mechanisms during initial heat exposure causes a sufficient rise in body temperature before exceeding thermeffector onset thresholds. Increasing time elapsed between initial heat gain and sweat onset will have a proportional impact on thermal strain (Périard & Racinais, 2019). Similarly, inter-individual

variations in thermosensitivity can modulate overall heat storage. Ambroziak et al (2024) recently suggested improvements in thermosensitivity post-acclimation are attributable to warm sensitization of the peripheral thermoafferent pathway in mice; hinting that in general, humans with greater thermosensitivity require less thermoafferent stimulation to elicit the same degree of thermoeffector response (Ambroziak et al, 2024). This promotes heat tolerance by allowing for maximal heat dissipation processes to occur earlier during heat stress, attenuating overall body heat storage (Ambroziak et al, 2024; Stolwijk et al, 1971). Factors such as age and acclimatization are known to influence thermosensitivity (Barry et al, 2020; Van Someren, 2011). Similar to thermoeffector onset and thermosensitivity, maximum steady-state sweat rates have large inter-individual and regional variability. Maximum steady-state sweat rates are also influenced by various factors such as age, acclimatization/acclimation, and medications (Barry et al, 2020; Cheshire & Feasley, 2008; Van Someren, 2011). Beyond physiological factors, heat stress compensability is ultimately determined by the ambient conditions (temperature, humidity, wind/air flow) in which heat exchange occurs (Cottle et al, 2022; Jay et al, 2015). Hot, humid conditions decrease temperature and vapor pressure gradients between ambient air and skin, thereby limiting sweat evaporation (Kerslake, 1972). Hyperthermia, an abnormally high body temperature, will ensue if an individual cannot achieve the rate of heat dissipation required to remain in thermal equilibrium (Spector et al, 2019).

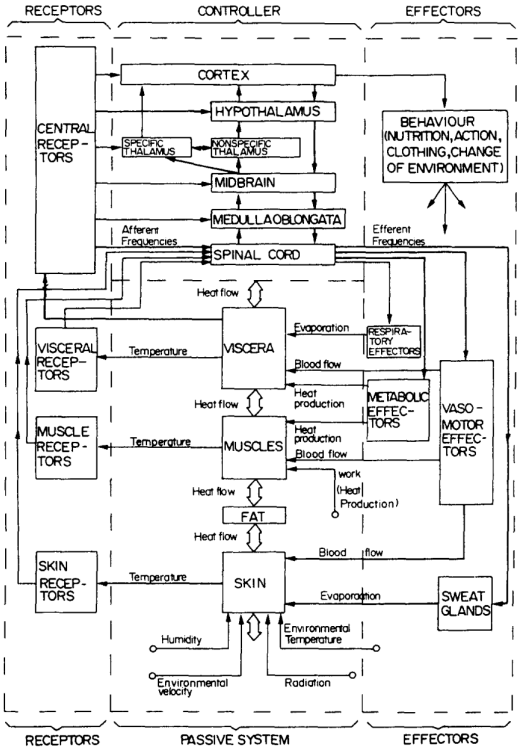
Neural and Peripheral Control of Thermoeffectors

Evaporative heat loss enabled by sweat secretion onto the skin surface represents the human body's largest modifiable thermoeffector response to heat stress (Kenny & Flouris, 2014). The central sympathetic drive for sweating is described as being initiated centrally (neurally) and modulated peripherally (Stolwijk et al, 1971).

Neural control. Collectively, the autonomic nervous system can mitigate rises in body temperature through a negative feedback loop consisting of afferent sensation, central integration, efferent signaling & end-organ output (Ravanelli et al, 2021). Although the exact neurological pathway responsible for the sweating response is not fully understood, human studies measuring skin sympathetic nerve activity have identified specific neural signals for cutaneous vasodilation and sweating (Shibasaki et al, 2006). Elevations in body heat storage, sensed by thermoreceptors throughout the body and in skin, act as a stimulus for the sweating response (Stolwijk et al, 1971). Stimulated thermoreceptors transduce thermoafferent information along the autonomic nervous system. Information ascends through the parabrachial nucleus and spinal cord before arriving at the preoptic area of the hypothalamus for central integration (Ravanelli et al, 2021). Here, thermal information is processed to derive an appropriate physiological/behavioural response.

Figure 2

The negative thermoregulatory feedback loop within the autonomic nervous system



Note. Taken from Werner (1980).

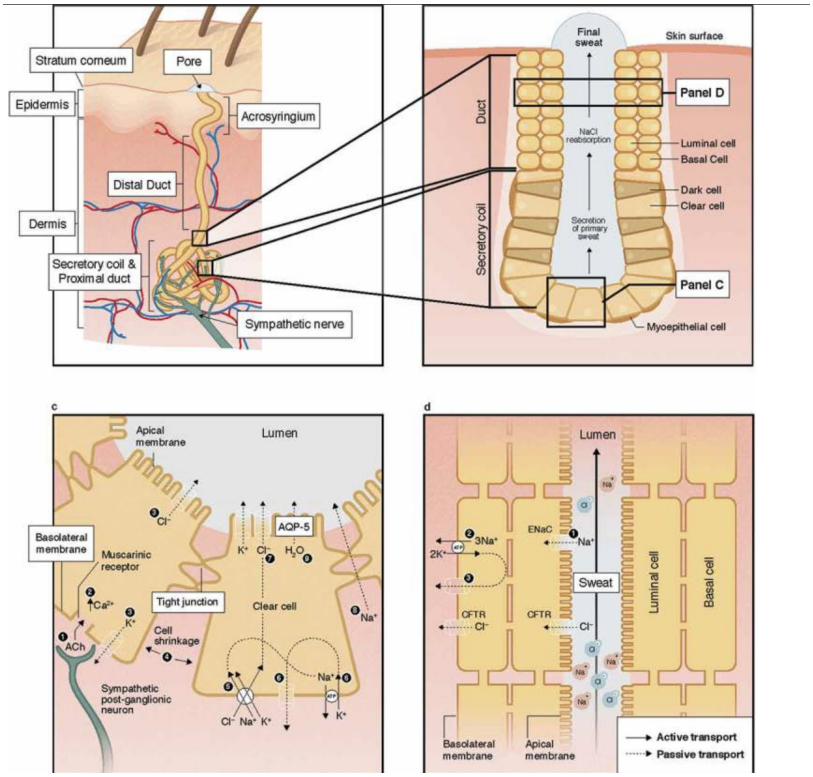
Thermoefferent signaling refers to descending information traveling through the autonomic nervous system to eventually synapse with thermoeffector organs. Here, alterations in skin region, temperature and certain other physiological factors can modulate the onset and intensity of the sweating response peripherally (Ravanelli et al, 2021).

Peripheral Control. The neurotransmitter involved with peripheral thermoefferent transduction is acetylcholine. Stimulated presynaptic neurons release acetylcholine into the synaptic cleft to bind with muscarinic-3 (M3) receptors on the basolateral membrane of eccrine (sweat) glands. Although synaptic concentrations of acetylcholine share a relationship with sweat rate, it is ultimately the amount of acetylcholine binding to eccrine muscarinic receptors that dictates the sympathetic drive for sweat expulsion (Shibasaki et al, 2006). The enzyme

acetylcholinesterase breaks down junctional acetylcholine and thus plays a role in maintaining consistent steady-state sweat rates (Baker, 2019).

Figure 3

Eccrine sweat gland anatomy and mechanism of sweat secretion



Note. Taken from Baker (2019).

The binding of acetylcholine to eccrine muscarinic receptors causes intracellular calcium ion concentrations to rise, increasing the permeability of potassium and chloride ion channels. The rapid efflux of sodium, potassium and chloride from secretory cells creates an osmotic gradient allowing for an isotonic precursor fluid (water) to permeate cellular membranes into the lumen of secretory coils (Baker, 2019). As the isotonic precursor fluid is contracted through secretory ducts, sodium, potassium, and chloride ions are continually reabsorbed, maintaining osmotic gradients across cell membranes and leaving sweat on the skin's surface hypotonic relative to the secretory ducts (Baker, 2019; Shibasaki et al, 2006). From here, expelled sweat

can be evaporated, shaken, absorbed, or otherwise shed from the skin, dissipating varying amounts of thermal energy from the body.

Role of Muscarinic Receptors in Sweating

Muscarinic acetylcholine receptors are G protein-coupled receptors found in the cell membranes of neurons throughout the body (Fryer et al, 2012). There exist five subtypes of muscarinic receptors (M1-M5), and each plays a role in neurotransmission for various bodily processes. Almost all muscarinic receptors can be found in the parasympathetic nervous system. In fact, only M3 muscarinic receptors involved in the human sweat response receive sympathetic stimulation (Fryer et al, 2012). These receptors exist in the basolateral membrane of eccrine glands.

Afferent thermosensation is mediated by six families and 28 separate types of transient receptor potential (TRP) ion channels that operate over specific temperature ranges. During heat stress, superficial and deep TRPV3/4 warmth receptors embedded in the terminals of afferent nerve fibers encode subtle increases in core and skin temperature (Schepers & Ringkamp, 2010). Local thermoafferent information is transduced along warm C fibers to centrally integrate in the hypothalamus, where a proportional thermoeffector response is then transmitted along efferent nerve fibers. When the efferent signal arrives at junctions between sympathetic sudorific axons and eccrine secretory cells, the neurotransmitter acetylcholine is released into the synaptic cleft. Acetylcholine is then received by postjunctional M3 receptors on eccrine secretory cells and ion-gated sodium, potassium, and chloride channels activate (see Figure 3) (Murota et al, 2015). The directional flow of ions increases water content in secretory cells by osmosis, which swell with water. The osmotic gradient persists as water diffuses into the lumen of secretory coils, which then contract, expelling fluid onto the skin's surface to spur evaporative heat transfer. As the

amount of acetylcholine binding to eccrine muscarinic receptors dictates the sympathetic drive for sweat expulsion, any anticholinergic agent or molecule with affinity for muscarinic receptors could block acetylcholine from binding with M3 receptors, reduce sympathetic drive to eccrine glands, and suppressing the sweat response peripherally (Shibasaki et al, 2006).

Cardiovascular Responses to Heat Stress

Human physiology must balance cardiac output and vascular tone with external stressors to maintain arterial pressure within an appropriate range and deliver oxygen to tissues in need. Unchecked, wide fluctuations in arterial pressure can compromise systemic circulation and have catastrophic consequences such as syncope, ischemia, or in severe cases, death.

The body has neural and peripheral mechanisms that interact in their influence over vascular tone. Arterial baroreceptors are mechanoreceptors embedded in endothelium that are sensitive to “stretching” forces from circulating blood pushing outward against vessel walls (Armstrong et al, 2023). These receptors signal information about blood pressure and volume afferently to the brain for central integration. Neural feedback from baroreceptors allows for the vascular system to be dynamic in response to orthostatic stress by mitigating regional fluctuations in blood pressure through controlling local vascular tone(s) (Armstrong et al, 2023). This system cooperates with renal function to manage blood pressure and avoid hyper/hypovolemia. Under nonthermal conditions, endothelial baroreceptor input is the primary neural mediator of vascular tone (Kenny et al, 2010). Under increasing hyperthermia, the influence of baroreceptors over vascular tone gradually reduces in place of adrenergic and cholinergic mechanisms (Kenny et al, 2010). Moreover, shear/friction force from blood flow over endothelial walls can stimulate nitrous oxide production directly within blood vessels,

providing endothelial cells overriding peripheral control over local vascular tone, to an extent (Li et al, 2005).

During heat stress, cutaneous vasodilation refers to the redistribution of blood flow from the core to the periphery to increase body heat dissipation from skin through dry avenues (radiation, conduction, convection). Of note, cutaneous blood flow has been observed to increase from 0.2-0.5L/min during regular conditions up to as much as 7-8 L/min during heat stress (Vassallo & Delaney, 1989). This increase in skin blood flow caused by the vasodilation of cutaneous vascular beds is neurally mediated by two branches of the sympathetic nervous system. At the onset of heat stress, an initial, small rise in skin blood flow is attributable to the withdrawal of the adrenergic vasoconstrictor branch (Kellogg, 2006). After this initial rise, the remaining increase in skin blood flow is mediated by the active cholinergic vasodilatory branch, which is the primary sympathetic driver behind cutaneous vasodilation during advanced heat stress (Kellogg, 2006).

The decrease in peripheral resistance caused by cutaneous vasodilation must be compensated for elsewhere in the cardiovascular system to avoid cerebral hypoxia. To limit the increased cardiac demand brought on by thermal strain, the body responds by vasoconstricting deep non-vital vascular beds and reducing central organ blood flow (Crandall & Wilson, 2015). Additionally, the heart responds to decreased venous return (preload) with inotropy, a shift in the contractile property of the heart to maintain stroke volume whilst increasing heart rate (Crandall & Wilson, 2015).

Heat Injury/Illness

HRI is a blanket term describing any adverse condition caused by dangerously high, unmitigated body temperatures (Spector et al, 2019). Examples range from milder conditions

such as heat exhaustion, to more severe, potentially life-threatening conditions such as heat stroke. Symptoms of heat exhaustion include extreme fatigue, cramps, and dizziness. Clinically, heat stroke is characterized by a core temperature exceeding 40°C with symptoms including confusion, slurred speech, erratic behaviour, seizure, and coma (Spector et al, 2019). Without proper treatment, instances of heat stroke can be fatal, cause organ damage, and/or long-term neurological deficits. Between 2008 and 2014, the Occupational Safety and Health Administration (OSHA) reported 109 heat-related deaths in the US (Arbury et al, 2014). Between 2009-2017, a time period that largely coincides with preparatory construction efforts for the 2022 International Federation of Association Football (FIFA) World Cup, the average annual death rate for Nepalese migrants working in Qatar was 150 deaths per 100,000 workers. During this time period, up to 200 of the 571 observed cardiac-related deaths were attributable to unmitigated heat exposure (Pradhan et al, 2019). Further, high case numbers of HRI during heat waves can place stress on vital local emergency services. Between 2001 and 2004, HRIs accounted for an estimated 20,775 hospitalizations in American emergency departments (Sanchez et al, 2010).

The lasting complications of heat injuries often have considerable negative effects on the quality of life of the affected individual. The primary risk factors for HRI are exposure to high-temperature, high-humidity environments, and strenuous physical activity (Spector et al, 2019). Certain other factors, such as age, body composition, fitness, hydration status, plasma osmolality, acclimation/acclimatization, and certain medications can each independently modulate risk (Barry et al, 2020; Cheshire & Feasley, 2008; Shibasaki & Crandall, 2010; Van Someren, 2011).

Heat waves may pose the most significant global threat of the 21st century. Researchers suggest that climate change is increasing the duration and intensity of heat waves (Lee et al,

2021; Meehl & Tebaldi, 2004; Vogel et al, 2019). The increased thermal load brought upon by extreme periods of heat is accompanied by an increased risk of HRI (Lee et al, 2021). In 2003, a heat wave in France resulted in approximately 14,800 deaths (Kovats & Hajat, 2008). American and European mortality rates from HRI surpass earthquakes, tornadoes, floods, and hurricanes combined (Levy et al, 2015). A retrospective study examining the prevalence of occupational heat illness among South Australian workers during extreme weather events found that, between 2001 and 2010, employees were 4-7 times as likely to develop heat illness during heat waves versus regular conditions (Xiang et al, 2015). Despite known risk factors and ample effective cooling protocols, HRI remains a fundamental concern for athletes, military, occupational sectors, and individuals residing in heat-prone areas.

Allergic Rhinitis

AR is one of the most prevalent respiratory conditions in the world, affecting up to 50% of individuals in certain high-income countries (Bousquet et al, 2020). According to the Canadian Allergy, Asthma, and Immunology Foundation, 20-25% of Canadians suffer from symptoms of AR (Keith et al, 2012). Often comorbid with asthma and/or conjunctivitis, the disease carries a substantial burden on the quality of life of affected individuals who may experience congestion, rhinorrhea, difficulty breathing, fatigue, and general discomfort (Bousquet et al, 2020). The symptoms are caused by immunoglobulin E-mediated reactions to airborne allergens such as pollen, fungal spores, or dust. In other words, AR is a consequence of an individual with precipitating genetic factors becoming exposed to specific environmental triggers (Bousquet et al, 2020).

D'Amato et al (2015) predict that over the following decade increases in atmospheric carbon dioxide associated with anthropometric climate change will increase pollen's

allergenicity by magnifying the duration and intensity of the pollen season (D'Amato et al, 2015). Similarly, researchers believe extreme weather events such as heavy rainfall and flooding will increase the atmospheric concentration of fungal spores, another common inhaled allergen (Corden & Millington, 2001). Predictably, an increase in the overall atmospheric concentration of inhaled allergens will increase the prevalence and intensity of AR symptoms over the following decades (Beggs, 2004; Kim et al, 2018; Ziska & Caulfield, 2000; Ziska et al, 2019). Symptoms of AR are caused by overreaction of the human body's immune response. When a perceived allergen enters the body, the lymphatic system, and specifically mast cells, produce histamine and other compounds that aid in ridding the irritant (Naclerio, 1990). Consequently, the proceeding immune response causes mucosal inflammation and classic symptoms of AR. Thus, histamine plays a central role in the pathogenesis of AR (Thangam et al, 2018).

Histamine

Histamine is a naturally produced organic compound that plays an important role in the human immune response as well as various other physiological functions in the intestines, central nervous system, and female reproductive system (Patel & Mohuiddin, 2020). Histamine is produced primarily by mast cells. Once stimulated by a specific antigen, such as inhaled pollen, mast cells release histamine into circulation to eventually bind with one of four types of G protein-coupled histamine receptors (H_1-H_4) around the body (Patel & Mohuiddin, 2020). During allergic reactions, stimulated H_1 receptors in the nasal cavity, paranasal sinuses, and bronchi cause mucosal inflammation, a characteristic symptom of AR (Patel & Mohuiddin, 2020). Similarly, stimulated H_1 receptors in endothelium cause vasodilation and can reduce mean arterial pressure (Patel & Mohuiddin, 2020).

Concerning human thermoregulation, counterintuitively, histamine independently suppresses the sweat response by blocking a specific enzyme involved with sweat secretion (Murota et al, 2015). To this end, antihistamines have been suggested as a potential treatment avenue to improve sweating in patients with pure idiopathic sudomotor failure (Suma et al, 2014). However, the independent effect of histamine on sweat output is minute in relation to the effect of direct cholinergic stimulation to eccrine glands (Murota et al, 2015).

Over-the-Counter H_1 Antihistamines

H_1 receptor antagonists, also known as H_1 antihistamines, are the choice treatment method for AR among American adults (Ajmani et al, 2017). Commonly sold OTC in pill form, first-generation H_1 antihistamines such as diphenhydramine (Benadryl®) and second/third-generation H_1 antihistamines such as loratadine (Claritin®, Alavert®) and desloratadine (Aerius®, Clarinex®) are all regarded as acceptable treatments for AR (Simon & Simons, 2008). Both first and second/third-generation H_1 antihistamines elicit their primary effects by blocking histamine from the binding sites of H_1 receptors. However, because histamine and muscarinic receptors share similar molecular composition, some H_1 receptor antagonists also have a tendency to block muscarinic receptors, including human M3 receptors that line the basolateral membrane of sweat glands (Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005).

Diphenhydramine (Benadryl®) is sold OTC at a regular dose of 25 mg, or an extra-strength dose of 50 mg. Taken in pill form, the drug is quickly metabolized with an oral bioavailability recorded between 40% and 60%. It has been recorded to reach peak plasma concentration about 2-3 hours after administration and is fully eliminated from the body approximately ∽9 hrs post oral ingestion (Paton & Webster, 1985; Simon & Simons, 2008). As a first-generation H_1 antihistamine, it crosses the blood-brain barrier and exerts a sedative effect,

impairing cognitive and motor function. To this end, diphenhydramine is often used as an off-label sleep aid (Zhang et al, 2010). Unwanted sedation and alarming reports of accidental overdose are two reasons physicians now primarily recommend second/third-generation antihistamines for AR symptoms. Newer compounds such as loratadine and desloratadine are less likely to cross the blood-brain barrier and cause sedation or toxicity (Paton & Webster, 1985). Diphenhydramine is a potent H_1 receptor antagonist referring to its tendency to bind to H_1 receptors and block the action of histamine in the human nervous system. The drug was suggested to also have a high affinity for human/non-human muscarinic receptors (Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). Physiologically, histamine and muscarinic receptors mediate a variety of functions in endothelial tissue, the respiratory tract, and the heart. Resultantly, large doses of oral diphenhydramine have been reported to block vasodilation, relax bronchospasm, and even cause changes in atrioventricular rhythm (Church & Church, 2013). Despite clear safer alternatives, diphenhydramine remains a popular choice for alleviating symptoms of AR due to factors including product longevity, brand recognition, OTC availability, and low costs (Walker et al, 2007).

Loratadine (Claritin®, Alavert®) and desloratadine (Aerius®, Clarinex®) are also H_1 receptor antagonists commonly sold OTC in pill form at doses of 10 mg and 5 mg respectively. Loratadine is a second-generation H_1 antihistamine and the parent compound of third-generation H_1 antihistamine desloratadine (Although some sources still consider desloratadine to be second-generation). Loratadine is metabolized to desloratadine in the liver, before being converted again to their common active metabolite 3-hydroxydesloratadine. Both desloratadine and loratadine take ~2 hrs to reach peak plasma concentrations in blood and reach terminal elimination ~27 and ~24 hrs after oral ingestion, respectively (Barenholtz & McLeod, 1989; Simon & Simons, 2008).

As second and third-generation H_1 antihistamines, neither molecule can independently cross the blood-brain barrier. As a result, the drugs are non-sedative and non-impairing when taken as recommended, providing a safer alternative to diphenhydramine whilst maintaining decongestive effects (Simon & Simons, 2008).

Orzechowski and colleagues (2005) quantified differences in cholinergic antagonism between fexofenadine, diphenhydramine, desloratadine, loratadine, and several other H_1 antihistamines. Using *in vivo* rats and *in vitro* guinea pigs injected with acetylcholine, researchers monitored changes in mean arterial pressure and trachealis muscle contractions across 10 antihistamines and utilized bioassay models to rank the drugs based on the extent of observed vaso/bronchodilatory blockade. Out of the four drugs, both models ranked diphenhydramine highest in terms of cholinergic antagonism. Further, both desloratadine and loratadine had statistically significant inhibitory effects on acetylcholine binding, while cetirizine (REACTINE®) and fexofenadine (Allegra®) had none (Orzechowski et al, 2005).

Gillard et al (2003) utilized functional assay methods comprising extracted/cloned human histamine and muscarinic receptors expressed through guinea pig heart tissue. Their results suggested second/third-generation OTC antihistamines cetirizine, fexofenadine, loratadine and desloratadine all have high affinity for human H_1 receptors. However, loratadine and desloratadine differ from cetirizine and fexofenadine in their tendency to bind with muscarinic receptors, and specifically human M3 receptors that play a role in sweating. Out of all the second/third-generation OTC antihistamines tested by Gillard et al (2003), desloratadine exhibited the greatest affinity for H_1 receptors yet the lowest selectivity for H_1 receptors over M3 receptors. For this reason, Gillard et al, (2003) suggested desloratadine would be the likeliest

second/third-generation OTC antihistamine to cause unwanted muscarinic (or antimuscarinic by blocking binding sites) side-effects in humans.

Liu & Farley (2005) investigated the antimuscarinic effects of first and second-generation OTC antihistamines diphenhydramine, loratadine, desloratadine, hydroxyzine, cetirizine and fexofenadine using mucus gland cells isolated from the respiratory tract of pigs and cultured in lab. Their method of indexing antimuscarinic action involved flooding mucus cell cultures with acetylcholine and monitoring fluctuations in mucus production and acetylcholine concentration before and after adding an antihistamine. From this, a concentration-response relationship was calculated for each of the six drugs, and antimuscarinic potency was estimated by comparing values to muscarinic receptor activation using the dose-ratio method of Schild (Colquhoun, 2007). The drugs were then ranked on antimuscarinic potency against M3 receptors as: Diphenhydramine = desloratadine > hydroxyzine. Interestingly, loratadine, fexofenadine and cetirizine had no effect on cholinergic activity at the even the highest drug concentration (100 μM) tested by Liu & Farley (2005).

Medication & Heat Stress

Pharmacological agents can impair physiological and behavioural thermoregulatory responses. For example, selective serotonin reuptake inhibitors (SSRI), an antidepressant medication, have been suggested to alter the brain's hypothalamic set point during central integration and suppress the sweating response, a condition known as hypohidrosis. Alternatively, amitriptyline, another antidepressant medication, stimulates peripheral adrenergic receptors and causes excessive sweating, or hyperhidrosis (Cheshire & Feasley, 2008).

Concerning HRI, drug mechanisms that decrease heat dissipation and/or increase heat storage are particularly dangerous. Antiplatelets such as aspirin and clopidogrel have been

observed to reduce cutaneous blood flow during heat stress, decreasing dry heat loss and increasing thermal load (Wee et al, 2023). Diuretics and angiotensin-converting enzyme (ACE) inhibitors pose slightly different, yet significant risks to elderly cardiovascular patients by inducing renal absorption, increasing the risk of dehydration and thereby HRI (Wee et al, 2023). Amphetamines and other sympathomimetic agents such as cocaine can increase HRI risk by increasing body heat storage, altering thermal perception, and impairing heat dissipation (Crandall et al, 2002; Levine et al, 2012). General anesthetics such as the opioid propofol downregulate autonomic nervous system activity and significantly increase thresholds for thermoeffector responses, drastically increasing the potential for HRI when heat-stressed (Kurz, 2008). The common OTC non-steroidal anti-inflammatory drug (NSAID) acetaminophen (Tylenol®) has previously been suggested to reduce perceptual thermal strain during athletic performance in heat, although thermoregulatory control remains unaffected (Burtscher et al, 2013; Coombs et al, 2015; Mauger et al, 2014).

The effects of neuropsychiatric medications on thermoregulatory measures are well researched as conditions affecting the autonomic nervous system have the potential to cause sweating dysfunction (Aminoff & Wilcox, 1971; Appenzeller & Goss, 1971). Of note, levodopa, a dopamine replacement medication, has been observed to ameliorate sweating dysfunction in patients with Parkinson's by restoring dopaminergic concentration levels in thermoregulatory areas of the brain (Wee et al, 2023). Alternatively, atropine, a potent antimuscarinic medication used to suppress tremors in patients with Parkinson's disease, has been observed to reduce sweating by competitively binding to M3 receptors lining sweat glands (Wee et al, 2023).

Antihistamines and Physiological Responses to Heat Stress

The relationship between sweating and antihistamines is unclear. First, second and third-generation H_1 antihistamines such as diphenhydramine, loratadine, and desloratadine are theorized to reduce sweating from limited evidence corroborating their affinity for M3 muscarinic receptors that play a role in sweating (Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). The common OTC antihistamine diphenhydramine (Benadryl®) has been reported to suppress the sweat response in patients with Parkinson's disease/Parkinsonism at supramaximal doses (≥200 mg oral, 50-400 mg parenteral) (Litman, 1952; McGeer et al, 1961). Although, these findings are unclear as sweating dysfunction is a common comorbidity of Parkinson's disease/Parkinsonism (Appenzeller & Goss, 1971). Another study noted oral ingestion of 75 mg diphenhydramine taken orally reduced galvanic skin conductance by 25% in their sample of fifteen healthy male participants. However, skin conductance is a measure of cutaneous moisture and sympathetic activity, not a direct measure of local blood flow or thermoregulatory sweating (Braithwaite et al, 2013; Hou et al, 2006; Montagu & Coles, 1966). One case report observed diphenhydramine to attenuate sweating in the affected region of a man with abnormal gustatory sweating, however also reported no changes in thermal sweating during a bout of passive heat stress (Tankel, 1951). Mortality reports released by the U.S. Centers for Disease Control and Prevention (CDC) have described antihistamines as "co-occurring" but not causal to previous work-related hyperthermia deaths (Karasick, 2020). Recently Williams, (2021) discussed how climate change may disproportionately affect individuals who take medications with anticholinergic effects including OTC antihistamines as they impair sweating and heat dissipation. Additionally, a recent meta-analysis by Hospers et al (2024) suggested there is no link between OTC antihistamines and increased core temperature during heat stress but

only incorporated results from a single study utilizing 540 mg fexofenadine (Allegra®), an antihistamine with reportedly no antimuscarinic properties (Gillard et al, 2003; Liu & Farley, 2005; McCord et al, 2008; Orzechowski et al, 2005). The article called for additional research to determine whether OTC antihistamines impair heat dissipation during heat stress (Hospers et al, 2024). Counterintuitively, diphenhydramine has been suggested as a potential treatment avenue to improve sweating in patients with pure idiopathic sudomotor failure (Suma et al, 2014). Possibly due to H_1 receptor antagonism reducing acetylcholine signal and blocking histamine-induced sweat inhibition upstream of the synaptic junction (Murota et al, 2015). Similarly, desloratadine and loratadine have been successful in treating cholinergic and idiopathic urticaria without sudomotor (sweating) dysfunction (Potter et al, 2009; Prasetyo & Prakoeswa, 2010). In a double-blind crossover trial on six firefighters, King (2023) reported oral ingestion of desloratadine (10 mg) prior to an exhaustive bout of work-specific heat stress did not elicit any changes in hematological markers of thermal strain compared to a placebo. However, researchers did not report specific thermoregulatory response variables (ex. Local/whole-body sweating, core temperature, etc.) and this data has not yet been published or peer reviewed. Other studies have reported 50 mg diphenhydramine and 540 mg fexofenadine taken orally do not alter core temperature during exercise, but do not report specific sweating variables (Local/whole-body sweating, etc.) (McCord et al, 2008; Montgomery & Duester, 1992). Recently, we demonstrated that oral ingestion of 50 mg of diphenhydramine hydrochloride has no effect on sweating, cardiovascular, or perceptual responses to 60 minutes of treadmill exercise in a warm environment (30°C, 30%RH) (Newhouse et al, 2024). Empirical evidence supporting any relationship between manufacturer-recommended dose OTC antihistamines and sweating dysfunction is scarce.

The effects of OTC antihistamines on cardiovascular responses during heat stress are similarly unclear. Certain findings suggest antihistamines could decrease skin blood flow during heat stress by influencing cutaneous vasodilation. Contrarily, a placebo-controlled study on emotional blushing confirmed loratadine (10 mg) augments facial cutaneous blood flow in healthy individuals instructed to sing children's nursery rhymes (Drummond & Lester, 2018). However, emotional blushing and thermal cutaneous vasodilation differ in mechanism. The findings of Lockwood and colleagues (2005) and McCord and Halliwill (2006) provide evidence that H_1 receptor antagonism is responsible for blunting postexercise hypotension. Researchers believe the blunting effect is caused by the blockade of H_1 and H_2 receptors responsible for initiating the production of nitrous oxide and other prostaglandins involved with systemic vasodilation after exercise. However, both studies utilized a high dose (540mg) of orally ingested fexofenadine, a potent second-generation antihistamine (Lockwood et al, 2005; McCord & Halliwill 2006). For context, this dose is ~3x greater than the highest manufacturer-recommended dose offered OTC. Moreover, fexofenadine, diphenhydramine, desloratadine and loratadine vary considerably in H_1 receptor and M3 receptor binding affinity (Bosma et al, 2018; Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). Although previous research has confirmed that H_1 receptor blockade causes reductions in cutaneous blood flow during heat stress, both Lockwood et al, (2005) and McCord & Halliwill (2006) reported 540 mg of fexofenadine elicited no measurable changes in cutaneous vascular conductance (forearm & thigh) between drug and placebo conditions (Wong et al, 2004). Bosma and colleagues (2018) suggested in their investigative review of antihistamine binding affinity that fexofenadine has significantly less H_1 receptor binding affinity compared to diphenhydramine. These findings suggest it is more likely for diphenhydramine, loratadine and desloratadine to impact vascular

tone than fexofenadine, at similar doses. We recently reported a slight reduction in blood pressure at rest and during exercise following oral consumption of diphenhydramine at the recommended single dose (Newhouse et al, 2024), whether this effect is observed during passive heat stress with different antihistamines remains largely unknown.

Certain studies suggest myocardial M3 and/or M2 receptor blockade could potentially decrease parasympathetic stimulation of the heart and increase heart rate. Conversely, Montgomery & Duester (1992) reported in their double-blind placebo crossover trial that oral ingestion of either 50mg of diphenhydramine or 60mg of a nonsedative counterpart terfenadine did not alter heart rate during an exhaustive bout of active heat stress. Although testing was completed in a thermoneutral environment (~23°C), we did not observe an effect during exercise in ~30°C (Newhouse et al, 2024). It remains unknown whether these observations will remain under even greater uncompensable heat stress. Further, diphenhydramine, desloratadine, and loratadine have variable binding affinities to H_1 and M3 receptors which may result in different responses to heat stress between antihistamines (Bosma et al, 2018; Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). No conclusive empirical data is currently available documenting the effects of OTC-dosage diphenhydramine, desloratadine, or loratadine on cardiovascular responses during passive heat stress. However, Table 1 summarizes all the current available evidence documenting the effects of antihistamines on human thermoregulatory responses to heat stress.

Table 1

Existing evidence on antihistamines & human thermoregulation during heat stress

Study	Heat Stress	Antihistamine (Dose, route)	Noteworthy Findings	Delimitations / Limitations
Mackmull, 1948	None	Diphenhydramine (≥100 mg, oral)	Increased diastolic & systolic blood pressure at rest	- Utilized dose 2x higher than what is available OTC - Did not incorporate heat stress protocol
Tankel, 1951	Passive	Diphenhydramine (50 mg, subcutaneous)	Impaired gustatory sweating	- Reported no changes to thermal sweating in response to heat stress - Case study (n=1)
Litman et al, 1952	Passive	Diphenhydramine (50 mg, intravenous & 200-250 mg, oral)	Caused visible anhidrosis	- Demographic (Parkinson's patients) comorbid with sweating dysfunction - Measured anhidrosis visually
McGeer et al, 1962	None	Diphenhydramine (150 mg, oral)	Treated hyperhidrosis after dopa	- Single case report (n=1) - No control - No direct measurement of sweating
Kobza, 1968	Passive (Post)	Clemizole (20 mg, oral)	Blunted postexercise hypotension	- Reductions were after, not during heat stress - Clemizole (Allercur®, Histacur®) no longer available OTC
Montgomery & Duester, 1992	Active	Diphenhydramine (50 mg, oral)	Did not alter rectal temperature or heart rate	- Little thermoregulatory challenge (Tested in a thermoneutral environment) - Did not directly measure sweating
Scavone et al, 1998	Active	Diphenhydramine (25 mg, oral)	Did not alter heart rate	- Utilized a dose 25 mg lower than what is available OTC (Extra-strength Benadryl®) - Little thermoregulatory challenge (Tested in a thermoneutral environment)
Wong et al, 2004	Passive	Pyrilamine maleate (200 mg, subcutaneous)	Reduced skin blood flow	- Subcutaneous pyrilamine maleate not indicated for AR or available OTC - Effects may be directly attributable to antihistamine action
Lockwood et al, 2005	Active (Post)	Fexofenadine (540 mg, oral)	Blunted postexercise hypotension	- Utilized a dose ~3x greater than highest available OTC dose - Blunting effect observed after, not during, active heat stress
McCord & Halliwill, 2005	Active (Post)	Fexofenadine (540 mg, oral)	Blunted postexercise hypotension	- Utilized a dose ~3x greater than highest available OTC dose - Blunting effect observed after, not during, active heat stress
Hou et al, 2006	None	Diphenhydramine (75 mg, oral)	Reduced skin conductance	- Utilized a dose 25 mg greater than the highest available OTC dose (Extra-strength Benadryl®) - Did not incorporate heat stress protocol
McCord et al, 2008	Active (Post)	Fexofenadine (540 mg, oral)	Did not alter core temperature	- Did not measure sweating directly - Fexofenadine has no documented affinity for muscarinic receptors
King, 2023	Active	Desloratadine (10 mg, oral)	Did not alter hematological markers for thermal strain	- Incomplete dataset - Data is from an academic source but is not yet peer-reviewed

Newhouse et al, 2024	Active	Diphenhydramine (50 mg, oral)	Slightly reduced mean arterial pressure, otherwise no effect on thermoregulation	- Results cannot be extended to advanced heat stress (Passive heating) - Results cannot be extended to other OTC antihistamines

Note. All studies utilized human participants.

Indeed, supramaximal doses of some OTC antihistamines may suppress thermoeffector responses in clinical populations - although this is not a typical use case (Litman, 1952; McGeer et al, 1961). There currently exists sparse empirical evidence confirming or refuting that orally ingested OTC antihistamines alter any thermoregulatory or cardiovascular response during heat stress in healthy young adults at their manufacturer-recommended dose. Despite this paucity of data, public health authorities such as the World Health Organization (WHO), Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), American College of Sports Medicine (ACSM), National Athletic Trainers Association (NATA) and a recent scientific article published in the Journal of the American Medical Association (JAMA) suggest antihistamines may increase HRI risk during heat stress citing the drugs' antimuscarinic, anticholinergic properties (Casa et al, 2015; Coco et al, 2016; OSHA, 2011; O'Connor & DeGroot, 2024; Roberts et al, 2023; WHO, 2011).

Summary

AR can significantly impact an individual's quality of life by compromising sleep, productivity, and social interactions. Nearly a quarter of Canadians are affected by AR, and OTC antihistamines are low-cost, widely available, and relatively safe methods to relieve symptoms (Keith et al, 2012; Walker et al, 2007). Any medication affecting human thermoregulatory control during heat stress could place an individual at an increased risk of HRI if they are unable to produce an appropriate thermoeffector response to adequately mitigate heat storage. To this end, public health authorities such as the WHO, OSHA, NIOSH, ACSM, NATA and academic

journals such as JAMA have suggested antihistamine medications impair sweating and predispose individuals to HRI during heat stress (Casa et al, 2015; Coco et al, 2016; OSHA, 2011; O'Connor & DeGroot, 2024; Roberts et al, 2023; WHO, 2011). This advisory stems from data confirming antihistamines have affinity for muscarinic receptors in non-human subjects and from limited data in clinical populations (Gillard et al, 2003; Litman et al, 1952; Liu & Farley, 2005; McGeer et al, 1961; Orzechowski et al, 2005). If antihistamine mechanisms were to block acetylcholine from binding to postjunctional M3 receptors, it could suppress sympathetic innervation to eccrine glands, thus sweat output. However, to our knowledge, no empirical evidence exists to confirm that OTC antihistamines, taken orally at manufacturer-recommended doses, can impair thermoregulatory control and increase the risk of HRI during heat stress.

Concerning public health, advising against antihistamine use during hot weather may be a conservative primary-prevention measure for HRI. However, the idea that OTC antihistamine medications pose a legitimate HRI risk during heat stress is currently unsubstantiated. Physiological mechanisms by which OTC antihistamines could theoretically suppress human sweating and/or reduce skin blood flow during thermal stress have been somewhat corroborated in studies using non-human samples, clinical populations, and supramaximal doses (Gillard et al, 2003; Hou et al, 2006; Liu & Farley, 2005; Litman et al, 1952; Lockwood et al, 2005; McCord & Halliwill, 2006; McGeer et al, 1961; Orzechowski et al, 2005; Wong et al, 2004). However, this notion lacks reliable outcome data utilizing realistic doses in healthy human subjects, thus the true risk remains unclear. Taken further, some studies currently suggest first-generation antihistamines as a possible treatment avenue for sweating dysfunction (Suma et al, 2014). Regardless, currently no data exists to confirm or deny any relationship between OTC antihistamines and sudomotor and/or cardiovascular responses to heat stress.

If OTC antihistamines do not increase HRI risk, the advice of public health authorities' may be needlessly conservative, could negatively impact AR sufferers' quality of life, and may unnecessarily burden healthcare systems with patients that could otherwise treat AR at home. It is for this reason our primary research question is aimed at understanding whether OTC antihistamines alter human thermoregulation during heat stress, as it is necessary information to wholly inform evidence-based public safety guidelines.

Research Questions

(1) Does oral ingestion of a first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine alter sudomotor responses during passive heating compared to a placebo?

(2) Does oral ingestion of a first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine alter cardiovascular responses during passive heating compared to a placebo?

(3) Does oral ingestion of a first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine alter perceptual responses during passive heating compared to a placebo?

Hypotheses

(1) No first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine will elicit a significant alteration in sudomotor responses to passive heat stress versus a placebo pill.

(2) No first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine will elicit a significant alteration in cardiovascular responses to passive heat stress versus a placebo pill.

(3) No first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamine will elicit a significant alteration in perceptual responses to passive heat stress versus a placebo pill.

Methodology

The present thesis meets the criteria of a clinical trial as the methodology incorporates the prophylactic administration of a medication to healthy participants and modifies its delivery. To this end, researchers sought approval from Health Canada (ID: AH-PHS-2023), the Thunder Bay Regional Health Sciences Centre Research Ethics Board (#100241), and registration with ClinicalTrials.gov (NCT06217367). All data collection was completed in Lakehead University's Environmental Physiology laboratory located in Thunder Bay, Ontario, Canada. This section will cover procedures for participant sampling, data collection, equipment, calculations, statistical analyses, and provide a comprehensive overview of the proposed study's experimental design.

Participant Sampling

To determine an adequate sample size *a priori*, we first had to define a "meaningful" difference in sweating. Considering sweating impairment, previous research has defined a "meaningful" difference as anything beyond the typical day-to-day intra-individual variation in a sweating variable (ie. Local sweat rate of the forearm) (Kenefick et al, 2012; Rutherford et al, 2021). Utilizing this definition, studies such as Kenefick et al (2012) and Rutherford et al (2021) have reported large cohen's *d* effect sizes (~1.13) for measuring local sweat rate of the forearm

within-subjects using the ventilated sweat capsule method and advanced heat stress. From this, a G*power sample size calculation determined we would be adequately powered at n=8 to detect meaningful differences in local sweating within-subjects using the ventilated sweat capsule (Kenefick et al, 2012; Rutherford et al, 2021). Thus, to account for expectedly high dropout rates, we aimed to recruit a minimum of 24 participants.

All participants were between the ages of 18 and 39 years and did not take any form of medication including sedatives or central nervous system depressants, with exception given to oral contraceptives. Four out of five female participants were prescribed a continuous-cycle contraceptive or intrauterine device. None of the studied participants had a history of cardiovascular disease, cancer, type 1 or 2 diabetes, chronic obstructive pulmonary disorder, or cystic fibrosis. Similarly, no participant reported a hypersensitivity to diphenhydramine, loratadine, desloratadine, or pill additives prior to their participation. All participants reported that they did not smoke tobacco products within 12 months of their participation start date, as this has been linked to impaired cutaneous blood flow during heat stress (Moyen et al, 2015). No participant had a body mass index over 30 kg/m^2 or was pregnant/breastfeeding. Lastly, participants did not take antihistamine medications within 48 hours of test dates. Participant recruitment procedures involved convenience sampling, sharing of the study poster wherever authorized around the Lakehead University campus, and on social media.

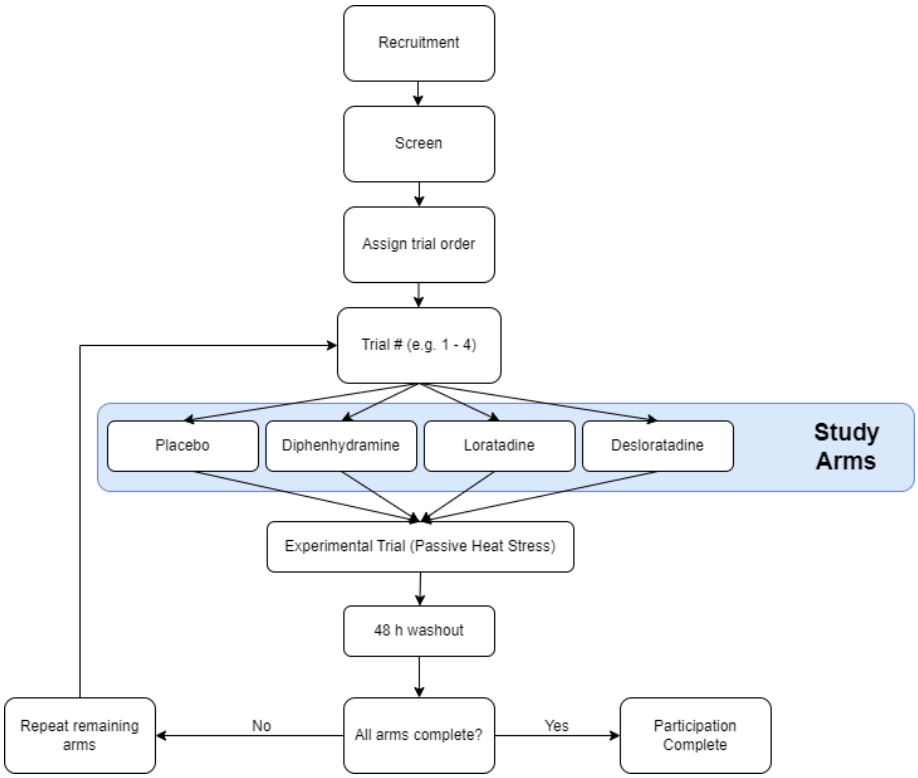
Experimental Trials

Figure 4 illustrates the double-blind crossover design of the randomized controlled clinical trial. Participants were recruited, screened and assigned a trial order. All trials were scheduled more than 48 hours apart to ensure terminal elimination of any OTC antihistamine and lessen any residual effects of acute acclimation from passive heating (Barenholtz & McLeod,

1989; Simon & Simons, 2008; Weller et al, 2007). Lastly, participants were tested at the same time of day (within ∽2hrs) to avoid any influence of diurnal or circadian rhythm.

Figure 4

Illustration of study design



Note. Trial order was randomly assigned.

Upon arrival at the testing facility, participants were asked to provide a urine sample to assess their hydration level. On three occasions participants were given 500ml of water before commencement to avoid effects of dehydration (Urine-specific gravity (USG) exceeding/approximating 1.0250). Participants were then asked to provide self-assessments of subjective thermal sensation using a 6-point visual analog scale where an assessment of -3 represents cold and 3 represents hot. Similarly, self-assessments of subjective thermal comfort were taken using a 4-point visual analog scale where reporting a 0 represents comfortable and

reporting a 3 represents very uncomfortable. Self-assessments of sleepiness utilizing the Stanford Sleepiness Scale were taken as confirmatory data to subjectively evaluate whether any of the treatments caused sedation.

Experimental protocol. To begin, participants were asked to ingest either i) 50mg of Benadryl® (diphenhydramine), ii) 10 mg Claritin® (loratadine), iii) 5 mg Aerius® (desloratadine), or iv) placebo (sugar pill) in a random predetermined order (See Figure 4). Then, participants' weight was measured using an electronic scale (GBK-333Ha, Adams Equipment) and a pediatric grade temperature probe (DeRoyal) was inserted through participants' nasal cavities into the esophagus to a depth of 40 cm. After, four thermocouple wires (T-type thermocouple wire, Omega Engineering) were affixed to the participant with surgical tape at four sites (arm, chest, thigh, and calf) to measure skin temperature. Next, two ventilated sweat capsules were affixed to participants' chest and forearm. These capsules measure local sweat rate by circulating dried air over skin at a controlled rate using a glass flowmeter (FL3905G, Omega Engineering) to collect evaporated water from sweat. The humidity of effluent air was then measured using a temperature and humidity probe (HMT330, Vaisala). After, a four-lead electrocardiogram (BioAmp, AD instruments) to measure heart rate and an automated brachial blood pressure cuff (Tango M2, SunTech) was affixed to the participant. Additionally, a laser doppler skin blood flow probe (Perimed 457, Periflux 5000) capable of measuring cutaneous vascular conductance, an index of microvascular perfusion, was affixed to participants' left forearm with surgical tape. The location of the laser doppler skin blood flow probe was kept consistent for all trials using anatomical landmarks. Finally, participants donned a water perfusion garment (COOLTube suit, MedEng) attached to a circulating hot water bath (TC-102, Brookfield) over top of the aforementioned measurement equipment. Similar experimental set-

ups have been utilized in previous inquiries on human thermoregulation such as Crandall et al, (2002) and Barry et al, (2020).

The passive heating protocol commenced ∽2 hrs post pill ingestion to approximate peak plasma concentration levels for diphenhydramine, loratadine & desloratadine (Barenholtz & McLeod, 1989; Paton & Webster, 1985; Simon & Simons, 2008). Pre-trial measures of sleepiness were taken at this time. All continuous data acquisition was sampled at 1000hz (PowerLab 16/35, AD instruments) using Labchart 8 Software. To achieve baseline values, participants laid supine whilst 32°C water was circulated throughout the water perfusion garment. After ten minutes of baseline data including esophageal temperature, skin temperature, local sweat rate(s), skin blood flow, brachial blood pressure, heart rate, thermal comfort, and thermal sensation, the circulating water temperature was raised to 49°C marking the beginning of the heating period. Additionally, two adult-sized sleeping bags were additionally placed on top of participants. For the experimental data, assessments of thermal sensation, thermal comfort, and brachial blood pressure were taken every ten minutes during heating. The heating period would end when the participant's esophageal temperature (T_{eso}) reached a 1.5°C increase from baseline, taking an average of 83 minutes (M=83.08, SD=16.88). This level of heat stress/extent of esophageal temperature increase was chosen to provide an adequate number of ΔT_{body} observations without endangering participants. Passive heating was terminated immediately if participants' esophageal temperature exceeded 39.5°C (Clinical hyperthermia = T_{core} >40°C) or participants reported that the heat stress had become intolerable (Spector et al, 2019).

After the passive heating protocol, participants were cooled by circulating 20°C water throughout the perfusion suit. Here, while still affixed to the participant, the laser-doppler skin blood flow probe was heated to 44°C to induce a maximal thermal vasodilatory response in

participants' cutaneous vascular beds (Rowell, 1977). Raw values (arb. unit) from this post-trial measurement of cutaneous perfusion were referenced against values taken during the heating period to index skin blood blow as a percentage of one's maximum vasodilatory response. After, a subsequent measure of body mass was taken once all measurement equipment was removed. Lastly, a final sleepiness assessment was administered before allowing participants to depart the testing facility.

Calculations. To calculate local sweat rate ($mg/cm^2/min^{-1}$), the absolute humidity of effluent air leaving the ventilated capsule was multiplied by flow rate (1.7 L/min). Then, this value was divided by the skin surface area ($2.89cm^2$) covered by the capsule. Sweating onset was determined as the ΔT_{body} at which local sweat rate of the arm begins increasing from baseline. Thermosensitivity was calculated using local sweat rate of the arm functioned against ΔT_{body} as the slope of a line created between sweating onset and the beginning of steady-state sweating. Whole body sweat rate (g/min) was calculated by taking the difference between participants' mass taken before and after heating protocols and dividing by total heating time. Skin blood flow (%max) was recorded using arbitrary units but expressed as a percentage of the maximum skin blood flow observed during the local heating of the laser-doppler probe. Mean skin temperature (°C) was calculated using the weighted average of four sites: Arm: 30%, chest: 30%, thigh: 20% & calf: 20% (Ramanathan, 1964). Mean body temperature was calculated using a weighted average of mean skin temperature (20%) and esophageal temperature (80%) (Ravanelli et al, 2021).

Statistical Analysis

Using a 4x7 two-way repeated-measures analysis of variance (rmANOVA), local sweat rate of the forearm, local sweat rate of the chest, skin blood flow, heart rate, mean arterial

pressure, rate-pressure product, thermal sensation, thermal comfort, esophageal temperature, and skin temperature were assessed between four levels of treatment (Placebo (PLA), diphenhydramine (DPH), loratadine (LOR), desloratadine (DES)), and seven levels of ΔT_{body} (0°C, Δ0.25°C, Δ0.5°C, Δ0.75°C, Δ1.0°C, Δ1.25°C, Δ1.5°C). Supplementary analyses of local sweat rate of the forearm and local sweat rate of the chest were conducted independently using two-way 2x7 rmANOVAs set to the same seven levels of ΔT_{body} but exclusive to PLA & DPH treatment legs. Additionally, two analyses of participants' sleepiness were conducted: One using a two-way 4x3 rmANOVA with four levels of treatment (PLA, DPH, LOR, DES) and three levels of trial phase (Arrival, pre-heat stress & post-heat stress) and another using a one-tailed 2x3 two-way ANOVA conducted with the same three levels of trial phase but exclusive to PLA & DPH treatment legs.

The dependent variables sweat onset, thermosensitivity, whole-body sweat rate, hydration, and mean ΔT_{body} were compared between treatment (Four levels: PLA, DPH, LOR, DES) utilizing a 1x4 two-way rmANOVA. Additionally, sweat onset, thermosensitivity, and whole-body sweat rate were assessed using separate paired samples T-tests ran solely between placebo and antihistamine treatments (PLA-DPH, PLA-LOR, & PLA-DES).

To investigate similarities in our participants' response to passive heating, local sweat rate of the forearm, local sweat rate of the chest, skin blood flow, heart rate, mean arterial pressure, and rate-pressure product were functioned against ΔT_{body} (Seven levels: 0°C, Δ0.25°C, Δ0.5°C, Δ0.75°C, Δ1.0°C, Δ1.25°C, Δ1.5°C) and investigated using Pearson correlation tests ran independently between placebo and antihistamine treatments (PLA-DPH, PLA-LOR, & PLA-DES).

All statistical analyses were conducted using GraphPad Prism (Version 9) software. Descriptive statistics of participants' sweating onset, thermosensitivity, and whole-body sweat rate for each treatment leg were reported as the mean and standard deviation. Treatment effects between OTC antihistamine and placebo treatment legs were reported alongside 95% confidence intervals and P-values calculated from independent paired samples T-tests. Sphericity was not assumed in our dataset but was evaluated using Greenhouse-Geisser's epsilon and corrected for using the Greenhouse-Geisser's correction. Statistical significance was accepted at $p<0.05$, and significant main effects of treatment detected by rmANOVA with four levels of treatment (PLA, DPH, LOR, & DES) were investigated post-hoc using Tukey's Honest Significant Difference (HSD) multiple comparisons test. No post-hoc correction was deemed necessary as Tukey HSD controls family-wise error rate at the desired significance level (0.05). The method adjusts individual confidence levels for each pairwise comparison so that the multiple comparisons test's comprehensive rate of committing one instance of type 1 error always remains equal to 5%. Significant main effects detected by rmANOVA with two levels of treatment (PLA & DPH) were investigated post-hoc using an uncorrected Fisher's Least Significant Difference (LSD) test. When significant interaction effects were detected, simple main effects analyses were ignored, and the interaction was investigated with a corresponding post-hoc test (Tukey HSD or Fisher's LSD). Then, to interpret strength, the effects were graphed on an interaction plot.

As a preliminary study, equal groups of male and female participants were recruited. However, until the relationship between OTC antihistamines and thermoeffector suppression can be described using scientifically supported sex-independent effect sizes, we cannot be certain our sample is statistically powered to make sex-segregated observations.

Results

The present study sought to determine whether three common OTC antihistamines (diphenhydramine, loratadine, and desloratadine) alter human thermoeffector responses during passive heat stress when compared to a placebo pill. The following section will detail our participant sample and cover the sudomotor, cardiovascular, perceptual and confirmatory results of our double-blind randomized crossover trial.

Participants

A total of 26 participants were recruited, however 16 participants were deemed ineligible per our inclusion criteria or withdrew before completing all four experimental trials. A total of 10 participants (5M, 5F, Age: 22.6 ± 1.8yrs, Height:174.0 ± 9cm, Weight: 73.6 ± 10.8kg) completed all four experimental trials. There were negligible differences in participants' hydration status (USG, $F_{(2.493, 22.43)}$=1.580, p=0.226) and mean increase in body temperature from baseline (ΔT_{body}(°C), $F_{(1.932, 17.38)}$=1.403, p=0.272) across the four treatment conditions (Placebo (PLA), diphenhydramine (DPH), loratadine (LOR), desloratadine (DES)).

Sudomotor Response Variables

Table 2 features descriptive statistics for sweat onset, thermosensitivity and whole-body sweat rates, three key characteristics of human's thermoregulatory control over sweating.

Table 2

Descriptive statistics for sweat onset, thermosensitivity and whole-body sweat rate across three OTC antihistamine treatment legs and a placebo

	Treatment Leg			
Sweating Characteristic	**PLA**	**DPH**	**LOR**	**DES**
Sweat Onset (ΔT_b, °C)	0.85 (0.28)	0.73 (0.34)	0.81 (0.18)	0.74 (0.21)
Thermosensitivity (mg/cm^2/min/°C)	1.82 (1.16)	1.81 (1.20)	1.65 (0.80)	1.54 (0.90)
Whole-body Sweat Rate (g/min)	13.32 (8.15)	12.10 (7.57)	12.26 (7.12)	13.73 (7.42)

Note. Participants were passively heated to a 1.5°C increase in body temperature (ΔT_{body}). Whole-body sweat rate was indexed from weight measurement taken pre/post heat stress. Values for sweat onset and thermosensitivity were calculated from measurements of local sweat rate of the forearm taken using a ventilated sweat capsule and capacitance hygrometry. [PLA: placebo, DPH: diphenhydramine, LOR: loratadine, DES: desloratadine].

Table 3 features treatment effects in sweat onset, thermosensitivity and whole-body sweat rate displayed between placebo and OTC antihistamine treatment legs. Under identical circumstances, reducing thermosensitivity, suppressing whole-body sweat rate, and/or delaying sweat onset will increase the internal heat gain an individual experiences during heat stress (Kenny & Flouris, 2014).

Table 3

Mean differences in sweating characteristics between a placebo and three OTC antihistamines

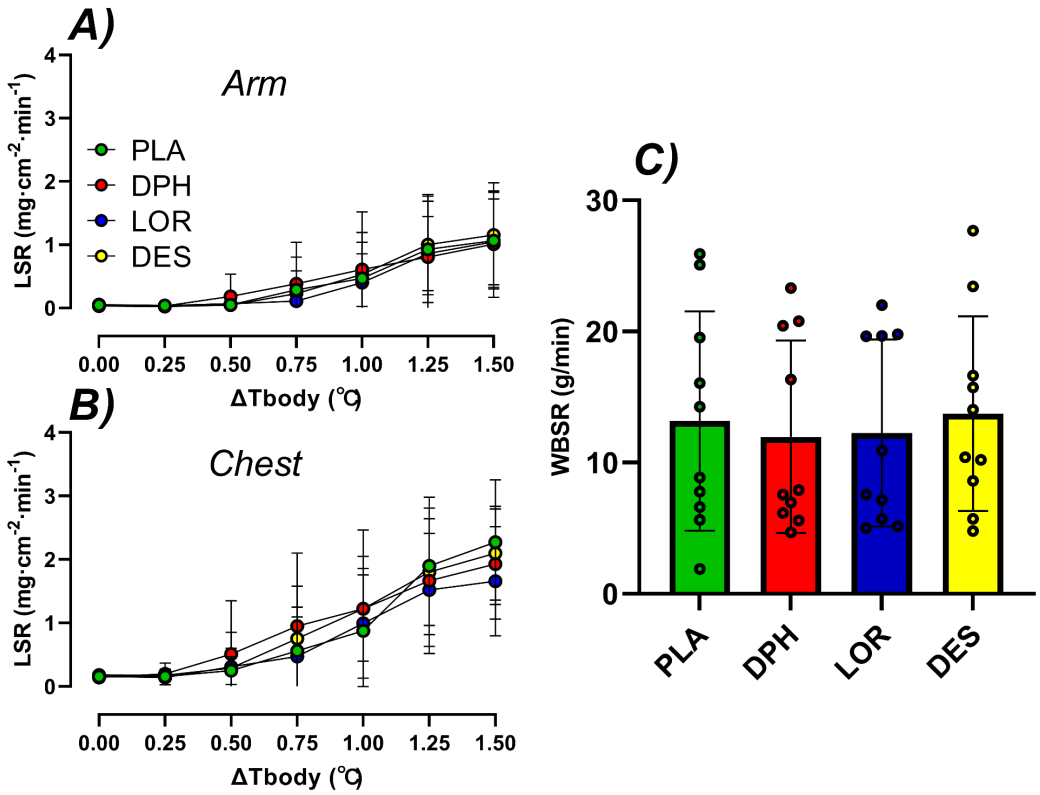
	DPH - PLA		LOR - PLA		DES - PLA	
Sweating Characteristic	**Diff (95%CI)**	**P-value**	**Diff (95%CI)**	**P-value**	**Diff (95%CI)**	**P-value**
Sweat Onset (ΔT_{body}, °C)	-1.7 (-13.9 to 10.5)	0.79	0.9 (-13.3 to 15.1)	0.90	-5.9 (-3.6 to 15.4)	0.25
Thermosensitivity (mg/cm^2/min/°C)	-0.11 (-0.29 to 0.07)	0.22	-0.07 (-0.25 to 0.12)	0.65	-0.13 (-0.32 to 0.06)	0.26
Whole-body Sweat Rate (g/min)	0.02 (-0.49 to 0.53)	0.98	-0.15 (-0.66 to 0.36)	0.52	-0.26 (-0.87 to 0.35)	0.37

Note. Participants were passively heated to a 1.5°C increase in body temperature (ΔT_{body}). Whole-body sweat rate was indexed from weight measurement taken pre/post heat stress. Values for sweat onset and thermosensitivity were calculated from measurements of local sweat rate of the forearm taken using a ventilated sweat capsule. [PLA: placebo, DPH: diphenhydramine, LOR: loratadine, DES: desloratadine].

Figure 5 incorporates whole-body and local measurements of the human sweat response. Panels A & B display forearm and chest measurements of local sweat rate (LSR), taken utilizing the ventilated sweat capsule method and plotted as a function of rise in body temperature during passive heat stress. Panel C is a bar graph illustrating whole-body sweat rate (WBSR) organized by treatment, calculated from the difference in body weight measurements taken before/after passive heating divided by heating time.

Figure 5

Local sweat rate (LSR) of the forearm and chest as functions of rise in body temperature (ΔT_{body}) and whole-body sweat rate (WBSR) between treatments



Note. Effects of three OTC antihistamines and a placebo on whole-body and local sweating during passive heat stress. Panels A & B depict local sweat rate (LSR) data measured at the arm and chest respectively. LSR is graphed along the Y-axis while ΔT_{body} is plotted on the X-axis. All LSR data is reported as mean and standard deviation. Panel C contains mean whole-body sweat rate (WBSR) organized by treatment. Dots represent individual data and error bars denote standard deviation. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

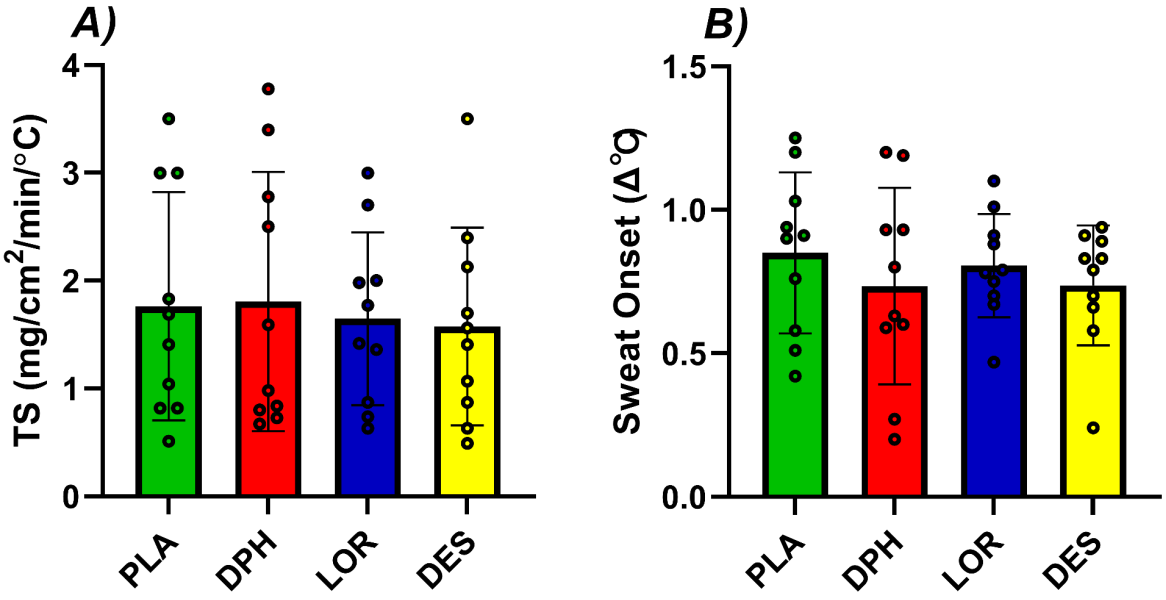
There was no main effect of treatment on participants' whole-body sweat rate ($F_{(2.075, 18.68)}$=1.077, p=0.363). Further, no interaction was detectable between the effects of treatment and ΔT_{body} on local sweat rate of the forearm ($F_{(2.497, 22.47)}$=0.913, p=0.435) or chest ($F_{(4.885, 43.96)}$=1.509, p=0.208). A main effect of ΔT_{body} was observed for both local sweat rate of the arm ($F_{(1.587, 14.28)}$=15.94, p=0.001) and chest ($F_{(2.091, 18.82)}$=30.48, p<0.001). However, no main effect of treatment was observed at either site (Arm: $F_{(1.436, 12.93)}$=0.189, p=0.758, Chest: $F_{(2.300, 20.70)}$=0.794, p=0.481). A Pearson correlation analysis found that placebo values for local sweat rate of the forearm and chest were nearly perfectly correlated with values from diphenhydramine (Arm: $r_{(6)}$: 0.98, p<0.001, Chest: $r_{(6)}$: 0.96, p<0.001), loratadine (Arm: $r_{(6)}$: 0.99, p<0.001 Chest: $r_{(6)}$: 0.98, p<0.001), and desloratadine (Arm: $r_{(6)}$: 1.00, p<0.001 Chest: $r_{(6)}$: 0.98, p<0.001) treatment legs.

Additional analyses excluding loratadine and desloratadine data were completed to provide an isolated comparison between diphenhydramine and placebo treatment legs. Firstly, a paired T-test showed that diphenhydramine (M=12.10, SD=7.564) & placebo (M=13.31, SD=8.155) did not differ in terms of whole-body sweat rate ($t_{(9)}$=1.445, p=0.183). Secondly, two separate two-way 2x7 rmANOVAs conducted between treatment (Two levels: PLA & DPH), and ΔT_{body} (Seven levels: 0°C, Δ0.25°C, Δ0.5°C, Δ0.75°C, Δ1.0°C, Δ1.25°C, Δ1.5°C) were conducted on local sweat rate of the forearm and chest. The results showed that the effects of treatment and ΔT_{body} did not interact on local sweat rate of the forearm ($F_{(1.78, 16.00)}$=1.065, p=0.360) or chest ($F_{(2.33, 21.00)}$=2.378, p=0.110). Main effects of ΔT_{body} were detected on local sweat rate of the forearm ($F_{(1.47, 13.25)}$=10.43, p=0.003) and chest ($F_{(2.19, 19.74)}$=22.76, p<0.001). However, no main effects of treatment were detected on local sweat rate of the forearm ($F_{(1, 9)}$=0.115, p=0.743) or chest ($F_{(1, 9)}$=0.151, p=0.706).

Figure 6 contains Panels A & B which depict the results between treatments for thermosensitivity (TS) and sweat onset respectively. Sweat onset and thermosensitivity (TS) are measures that quantify the initial human sudomotor response to acute heat stress. Both were calculated using local sweat rate of the forearm and functioned against ΔT_{body} on a scale increasing by 0.1°C. Sweat onset was interpreted as the point of ΔT_{body} at which sweating was initially detected. Thermosensitivity (TS) was interpreted as the slope of a line created between sweat onset and the beginning of steady-state sweating.

Figure 6

Between-treatments differences in thermosensitivity (TS) and sweat onset



Note. The effects of three OTC antihistamines and a placebo on thermosensitivity (TS) and sweat onset during a passive heating protocol. Panel A contains TS and Panel B contains sweat onset. Individual bars represent treatment means and error bars indicate standard deviation. Dots represent individual data. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

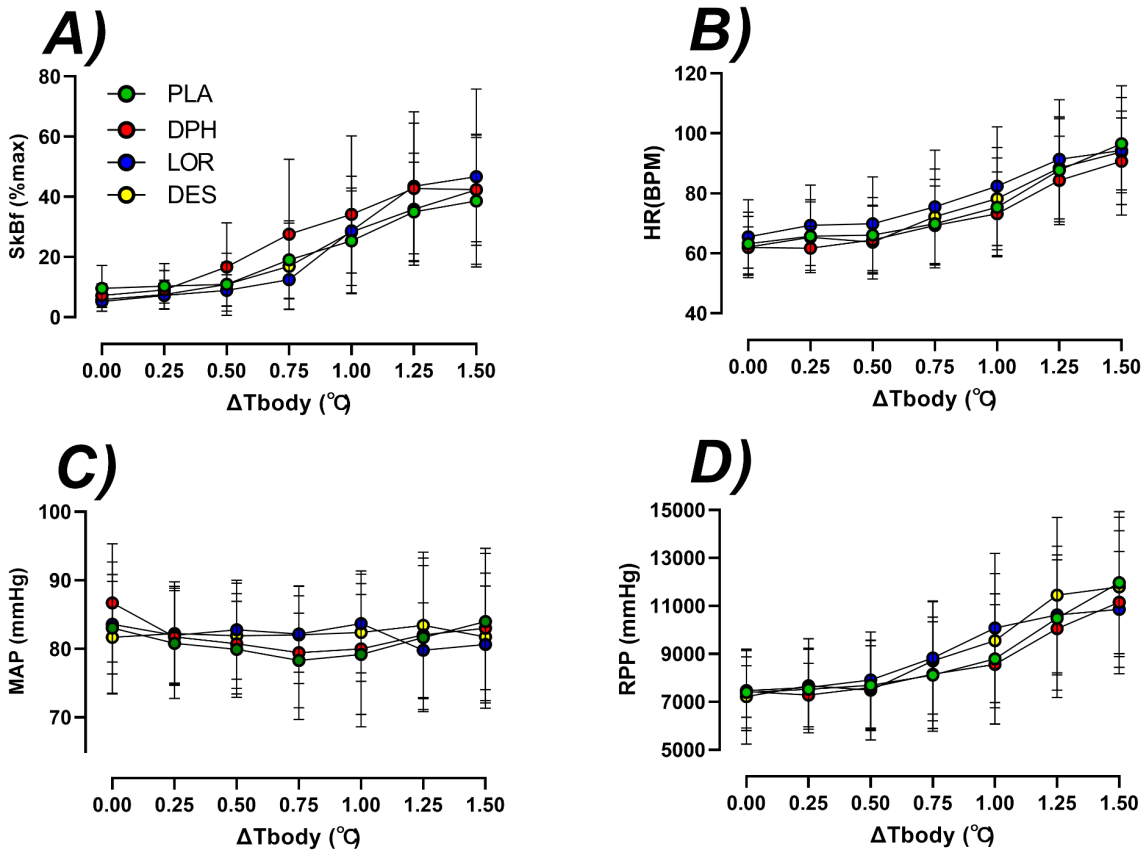
There was no main effect of treatment on participants' sweat onset ($F_{(2.171, 19.54)}$=0.708, p=0.516) or thermosensitivity ($F_{(1.303, 11.73)}$=1.705, p=0.222). Two additional analyses excluding loratadine and desloratadine treatment legs were completed to compare diphenhydramine and placebo treatment legs in isolation. A paired T-test showed that diphenhydramine (M=0.790, SD=0.354) & placebo (M=0.860, SD=0.259) did not differ in terms of sweat onset ($t_{(9)}$=0.920, p=0.382). Additionally, a two-sample Wilcoxon test showed that diphenhydramine (M=1.216, SD=0.810) & placebo (M=2.066, SD=1.983) did not differ in terms of thermosensitivity (W=-33.0, p=0.055). Our results suggest neither first (diphenhydramine, 50mg), second (loratadine, 10mg) or third (desloratadine, 5mg) -generation OTC antihistamines caused a discernible effect on the human sweating response during passive heat stress when compared to a placebo.

Cardiovascular Response Variables

Figure 7 displays four variables associated with the human cardiovascular response to heat stress, plotted as functions of participants' rise in body temperature from baseline (ΔT_{body}) during passive heating. Panels A & B display skin blood flow (SkBf) and heart rate (HR) respectively, which increase in tandem shortly after the onset of passive heating. Panels C & D depict mean arterial pressure (MAP) and rate-pressure product (RPP) during passive heating, variables utilized to index oxygen demand to the heart and stress being placed on the cardiovascular system.

Figure 7

Human cardiovascular responses as functions of rise in body temperature (ΔT_{body})



Note. All variables are displayed as functions of rise in body temperature (ΔT_{body}) during passive heating. Panel A displays skin blood flow (SkBf) as a percentage of maximum vasodilatory response. Panel B displays heart rate (HR) in beats per minute. Panel C & D displays mean arterial pressure (MAP) and rate-pressure product (RPP) respectively in millimeters of mercury (mmHg). Plotted data represents the treatment mean and error bars represent standard deviation. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

The effects of treatment and ΔT_{body} on skin blood flow during heat stress did not interact ($F_{(3.425, 30.83)}$=0.907, p=0.460). Further, simple main effects analysis concluded ΔT_{body} ($F_{(2.301, 20.71)}$=47.55, p<0.001) but not treatment ($F_{(1.768, 15.91)}$=0.424, p=0.628) had an independent main effect on skin blood flow during passive heating. A Pearson correlational analysis determined placebo values for skin blood flow were strongly correlated with diphenhydramine ($r_{(6)}$:0.96, p<0.001), and nearly perfectly correlated with loratadine ($r_{(6)}$: 0.99, p<0.001) and desloratadine ($r_{(6)}$: 0.99, p<0.001).

No interaction effect was observed between the effects of ΔT_{body} and treatment on heart rate ($F_{(4.851, 43.66)}$=1.076, p=0.386). Also, an independent main effect of ΔT_{body} ($F_{(2.329, 20.96)}$=81.76, p<0.001) but not treatment ($F_{(1.904, 17.13)}$=1.277, p=0.303) was detected on heart rate during simple main effects analysis. Also, a Pearson correlational analysis determined placebo values for heart rate were nearly perfectly correlated with diphenhydramine ($r_{(6)}$: 0.99, p<0.001), loratadine ($r_{(6)}$: 0.98, p<0.001), and desloratadine ($r_{(6)}$: 0.99, p<0.001).

No interaction effect between treatment and ΔT_{body} on mean arterial pressure during heat stress was detected ($F_{(4.852, 43.66)}$=1.337, p=0.267). Simple main effects analysis suggests neither ΔT_{body} ($F_{(2.147, 19.33)}$=1.582, p=0.231) or treatment ($F_{(2.706, 24.35)}$=0.185, p=0.889) independently affected mean arterial pressure during heat stress. A Pearson correlational analysis determined placebo values for mean arterial pressure were correlated strongly with diphenhydramine ($r_{(6)}$: 0.82, p=0.023), moderately with loratadine ($r_{(6)}$: -0.36, p=0.422), and weakly desloratadine ($r_{(6)}$: -0.175, p=0.708).

No interaction effect was observed between treatment and ΔT_{body} on rate-pressure product throughout heat stress ($F_{(3.966, 35.69)}$=2.051, p=0.109). Simple main effects analysis suggests ΔT_{body} ($F_{(1.806, 16.25)}$=41.65, p<0.001) but not treatment ($F_{(2.062, 18.56)}$=0.690, p=0.518) had

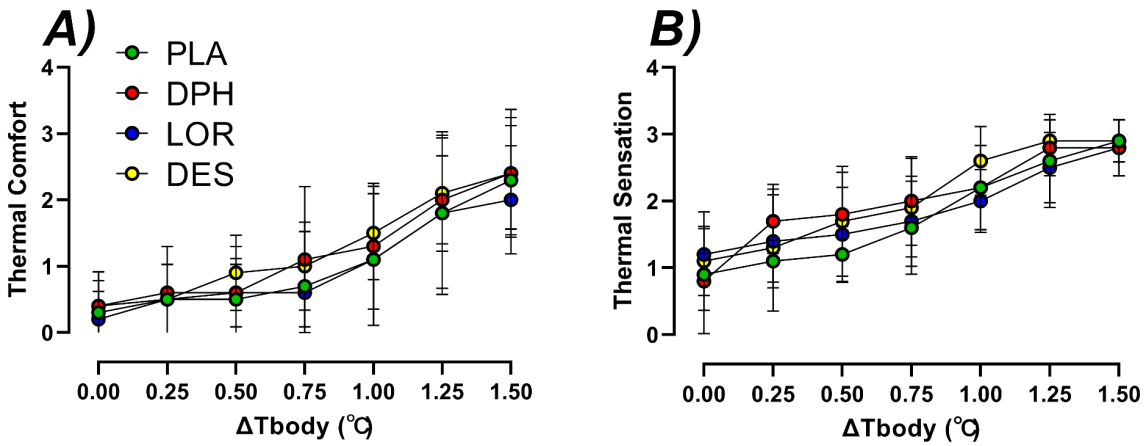
an effect on rate-pressure product during heating. A Pearson correlational analysis determined placebo values for rate-pressure product were correlated near perfectly with diphenhydramine ($r_{(6)}$: 1.00, p<0.001), and strongly with loratadine ($r_{(6)}$: 0.91, p=0.004) and desloratadine ($r_{(6)}$: 0.97, p<0.001).

Thermal Perception Variables

Figure 8 displays data on participants' perceived thermal stress during passive heating. Panel A features thermal comfort and Panel B depicts thermal sensation. Both measures are functioned against ΔT_{body} during passive heating.

Figure 8

Participants' thermal comfort and sensation as functions of rise in body temperature (ΔT_{body})



Note. Effects of three OTC antihistamines and a placebo on participants' self-reports of thermal comfort and thermal sensation during heat stress. Panel A displays perceived thermal comfort and Panel B shows perceived thermal sensation. Data is plotted as treatment mean and error bars represent standard deviation. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

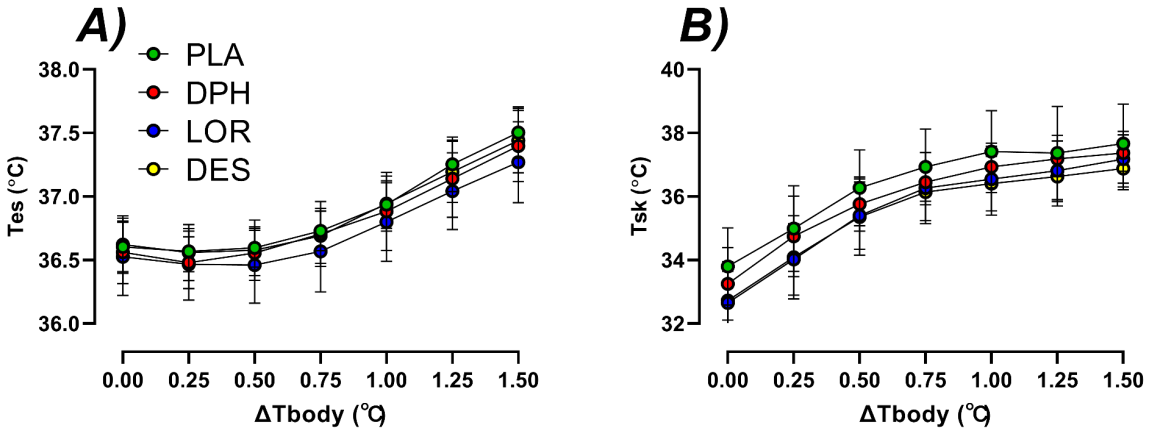
No interaction effects were observed between ΔT_{body} and treatment on participants' thermal comfort ($F_{(4.687, 42.18)}$=0.707, p=0.613) or sensation ($F_{(5.829, 52.46)}$=1.750, p=0.130) during heating. Further, ΔT_{body} had a main effect on both thermal comfort ($F_{(1.659, 14.93)}$=54.36, p<0.001) and thermal sensation ($F_{(2.251, 20.26)}$=78.99, p<0.001) during heating. However, no independent main effect of treatment was detected for either aspect of thermal perception (Thermal comfort: $F_{(2.408, 21.67)}$=1.437, p=0.260, thermal sensation: ($F_{(2.020, 18.18)}$=0.959, p=0.403).

Thermometry and Sleepiness Data

Figure 9 displays thermometry data indicative of deep (esophageal) and superficial (skin) tissue temperatures plotted against ΔT_{body}. Panel A shows a delayed positive inflection in esophageal temperature (T_{es}) at the onset of passive heating. Panel B depicts a sudden increase in skin temperature (T_{sk}) at the onset of passive heating that gradually tapers after as temperature/vapor pressure gradients between skin and the immediate environment decrease. The curvature of either graph is shaped by heat that is transferred to peripheral tissues like skin at the onset of heating before penetrating to deeper tissues such as the inner esophagus.

Figure 9

Esophageal temperature (T_{es}) and skin temperature (T_{sk}) as functions of rise in body temperature (ΔT_{body})



Note. The effects of three antihistamines and a placebo on participants' esophageal (T_{es}) and skin temperature (T_{sk}) functioned against rise in core temperature (ΔT_{body}) during passive heating. Panel A shows esophageal temperature (T_{es}) and Panel B shows skin temperature (T_{sk}). Data is plotted as treatment mean and error bars represent standard deviation. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

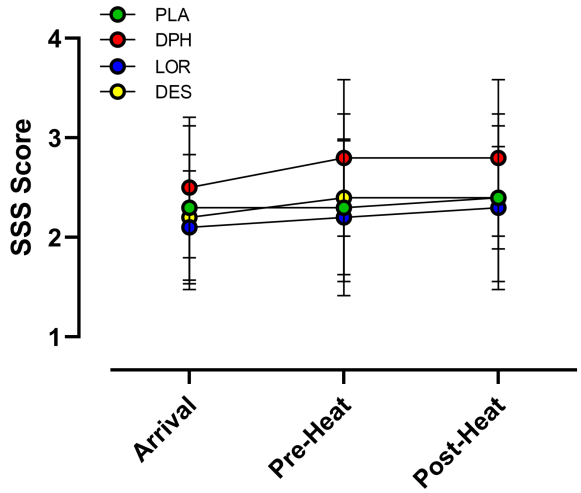
No interaction effects were detected between treatment and ΔT_{body} on esophageal ($F_{(3.334, 30.00)}$=0.944, p=0.440) or skin ($F_{(3.514, 31.62)}$=0.817, p=0.511) temperature responses during heating.

However, ΔT_{body} had a detectable main effect on both esophageal ($F_{(2.238, 20.15)}$=334.5, p<0.001) and skin ($F_{(2.336, 21.03)}$=383.6, p<0.001) temperature. Lastly, no main effects of treatment were detected on esophageal ($F_{(2.297, 20.67)}$=1.403, p=0.270) or skin ($F_{(2.138, 19.24)}$=2.373, p=0.117) temperature responses during heat stress.

Figure 10 displays sleepiness measured at three points throughout experimental trials: Arrival (Before pill ingestion), pre-heat stress (~2hrs post pill ingestion), and post-heat stress (~4hrs post pill ingestion).

Figure 10

Participants' self-reported Stanford Sleepiness Scale (SSS) score across three time phases of the experimental protocol



Note. Effects of three OTC antihistamines and a placebo on participants' subjective reports of sleepiness upon arriving at the testing facility, before heat stress, and after heat stress. Values measured as score on the Stanford Sleepiness Scale (SSS) and displayed as treatment leg mean and standard deviation. Colours indicate treatment leg [PLA: placebo (green), DPH: diphenhydramine (red), LOR: loratadine (blue), DES: desloratadine (yellow)].

No interaction effect between treatment and trial phase on participants' self-reported sleepiness was observed ($F_{(3.091, 27.81)}$=0.135, p=0.942). Further, simple main effects analysis showed that trial phase did not affect participants' sleepiness ($F_{(1.385, 12.46)}$=0.594, p=0.508). Contrarily, treatment leg impacted participant's sleepiness in a way that approaches statistical significance ($F_{(2.624, 23.62)}$=2.972, p=0.058).

Thus, a separate one-tailed two-way 2x3 rmANOVA was conducted between treatment (Two levels: PLA & DPH) and trial phase (Three levels: Arrival, Pre-Heat, & Post-Heat) to further analyze whether diphenhydramine positively affected participants' ratings of sleepiness. It was determined that the effects of trial phase and treatment on participants' sleepiness did not interact ($F_{(1.687, 15.19)}$=0.296, p=0.356). Simple main effects analysis did not detect any main effect of trial phase on participants' sleepiness ($F_{(1.674, 15.07)}$=0.302, p=0.353). However, treatment was observed to have a statistically significant main effect on participants' sleepiness ($F_{(1.000, 9.000)}$=4.373, p=0.033). On further post-hoc investigation using an uncorrected Fisher's LSD test, no significant differences between diphenhydramine and placebo treatment legs were detected at arrival ($t_{(9)}$=1.000, p=0.343), pre-heat stress ($t_{(9)}$=1.816, p=0.096), or post-heat stress ($t_{(9)}$=1.078, p=0.309).

Discussion

The purpose of the present thesis was to assess whether three common OTC antihistamines (diphenhydramine, loratadine, and desloratadine) alter human thermoeffector responses during heat stress. Our results provide the first empirical evidence that human thermoeffector (sudomotor and cardiovascular) responses to heat stress remain largely unaffected by first (diphenhydramine, 50mg) second (loratadine, 10mg) or third (desloratadine, 5mg) - generation OTC antihistamines. Our lack of significant findings contrasts the advice of several public health agencies by suggesting that OTC antihistamines may be safe to use during periods of heat stress (Casa et al, 2015; Coco et al, 2016; OSHA, 2011; Roberts et al, 2023; WHO, 2011). However, our findings are preliminary and must be corroborated with additional research utilizing broader demographics and *in situ* heat event protocols before informing public health policy or practice.

Sudomotor Findings

Liu & Farley (2005), Orzechowski et al (2005) and Gillard et al (2003) provided evidence that diphenhydramine, loratadine and desloratadine, to varying degrees, have affinity for M3 receptors and can elicit measurable antimuscarinic effects in some human/non-human samples using receptor assay models. Extending these findings to humans provides a logical mechanism by which OTC antihistamines could impair sweating during heat stress; by blocking M3 receptors on the basolateral membrane of secretory cells.

Contrarily, none of the OTC antihistamines utilized in our study (50mg diphenhydramine, 10mg loratadine, 5mg desloratadine) altered sweat onset, thermosensitivity, whole-body sweat rate, or local sweat rate during passive heating compared to a placebo pill. Our findings deviate from early inquiries such as McGeer et al (1961) and Litman et al (1952) who reported that supramaximal doses (≥150mg oral, 50mg intravenously) of diphenhydramine caused visible anhidrosis in their sample of Parkinson's disease/Parkinsonism patients. Albeit, autonomic conditions such as Parkinson's disease are often comorbid with sweating dysfunction, which could have confounded their results (Bae et al, 2009). Additionally, the dose of antihistamine/route(s) of administration utilized by Litman et al (1952) and McGeer et al (1961) are not available OTC or indicated for AR, thus not representative of typical use.

Our results also contrast the findings of Hou et al (2006) who reported that oral ingestion of 75 mg diphenhydramine reduces galvanic skin conductance, a common index of sympathetic activity, by up to 25% at rest (Braithwaite et al, 2013; Hou et al, 2006; Montagu & Coles, 1966). However, skin conductance, also known as galvanic skin response, is not a direct measurement of sweating, but rather an indirect measure of sweat gland activity which may include sudorific and non-sudorific pathways (Montagu & Coles, 1966; Braithwaite et al, 2013). Also, Hou et al

(2006) did not incorporate any form of heat stress, and measured skin conductance on glabrous skin at the fingertips (A common procedure in psychology to index mental excitation) rather than non-glabrous skin that contributes to thermoregulatory sweating (Montagu & Coles, 1966).

The only other human study supporting antihistamines' suppressing sweating is a case study by Tankel (1951) that found deep subcutaneous injection of diphenhydramine (50mg) to reduce gustatory sweating on the affected side of a man with severe facial trauma. However, gustatory sweating mechanisms differ from thermal sweating, and Tankel (1951) reported that his subject's sweating response remained unaffected during heat stress after the same dose of diphenhydramine.

Recently, evidence from our lab demonstrated that oral ingestion of 50mg of diphenhydramine does not alter the human sweat response during 60 minutes of active heat stress, offering additional support for OTC antihistamines not impacting sweating (Newhouse et al, 2024). The absence of sweating impairment observed in both our active and passive heating inquiries aligns with evidence from King (2023) who recently demonstrated that ingesting 10 mg of desloratadine does not alter hematological markers of thermal strain in firefighters subject to work-specific heat stress. Although, the data presented by King (2023) is limited as it is not from a peer-reviewed scholarly journal. Additionally, our results align with earlier results from Montgomery & Duester (1992) and McCord (2008) suggesting that neither 50 mg diphenhydramine or 540 mg fexofenadine alter core temperature post-exercise.

Studies on non-human samples/subjects suggest loratadine, desloratadine, and diphenhydramine can be graded from least muscarinic affinity to most muscarinic affinity as follows: Loratadine, desloratadine, diphenhydramine (Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). From this, one might expect the first-generation H_1 antihistamine

diphenhydramine, with the highest reported affinity for M3 receptors, to be more likely to alter sweating than later generations (loratadine & desloratadine). Contrarily, statistical comparisons excluding loratadine and desloratadine data showed that sweat onset, thermosensitivity, whole-body sweat rate and local sweat rate of the forearm and chest were not different across diphenhydramine and placebo treatment legs in isolation.

Speculatively, the reason none of our OTC antihistamines had an effect on sweating, is due to a lack of competitive antagonism against M3 receptors. Abiding by the model presented utilized by Ravanelli et al (2017, 2021), during uncompensable passive heat stress, thermoeffector responses (skin blood flow and sweating) increase with body temperature until plateauing at a maximum output value (Cramer et al, 2022; Ravanelli et al, 2017; Ravanelli et al, 2021). Considering the present dataset, values for maximum local sweat of the forearm were achieved in 93% of experimental trials, did not differ between treatments ($F_{(1.428, 12.85)}$=0.311, p=0.666), and are consistent with values from published data using similar measurement procedures and high heat strain (Rutherford et al, 2021). Skin blood flow, another physiological marker of heat stress, plateaued in 95% of trials. These markers are evidence that our passive heating protocol elicited consistent near-maximum thermoeffector response values and thus the adequate conditions to gauge sweating impairment during advanced heat stress. Regardless, our lack of effects on other key characteristics of the sweating response such as sweat onset and thermosensitivity indicate sweating was wholly unaffected by OTC antihistamines. The likeliest explanation for this lack of effect is that no OTC antihistamine blocked the amount of M3 receptors required to elicit reductions in sweating at the specific dose that we prescribed (DPH: 50mg, LOR: 10mg DES: 5mg). Results may differ across different OTC antihistamines such as cetirizine (Zyrtec®, REACTINE®) and fexofenadine (Allegra®). However, studies such as Liu

& Farley (2005), Orzechowski et al (2005) and Gillard et al (2003) suggest cetirizine and fexofenadine have a significantly lower tendency to bind to muscarinic receptors compared to diphenhydramine, loratadine and desloratadine. From this, it is unlikely that recommended doses of cetirizine or fexofenadine would alter our results. Albeit, the muscarinic binding affinities of diphenhydramine, loratadine, desloratadine, cetirizine and fexofenadine have yet to be directly assessed in living human subjects, thus more research is required to confirm this. No data relating to thermoregulatory responses is currently available for other OTC antihistamines marketed as AR medication such as first-generation H_1 antihistamine chlorpheniramine (Chlor-Trimeton®) and second-generation levocetirizine (Xyzal®).

From evidence proving diphenhydramine, loratadine, and desloratadine have selectivity for M3 receptors over H_1 receptors in samples of extracted human/non-human receptors (Albeit, not *in-vivo*), it is likely that elevating the dose of these drugs and/or using routes of administration with higher bioavailability would eventually impact sweating (Gillard et al, 2003; Liu & Farley, 2005; Orzechowski et al, 2005). However, more research is required to assess the specific drug potencies at which diphenhydramine, loratadine and desloratadine begin to suppress sweating and contribute to HRI risk.

Sample size G*power calculations conducted *a priori* suggested we would be adequately powered at n=8 to detect meaningful differences in local sweating using the ventilated sweat capsule at high heat stress (Rutherford et al, 2021). Thus, it is likely our sample (n=10) was sufficiently powered to detect differences in thermal sweating characteristics across OTC antihistamine and placebo treatment legs. However, there remains a chance that our lack of results is secondary to unforeseen circumstances such as high inter-individual variability in the way individuals' respond to OTC antihistamines during heat stress (Rutherford et al, 2021).

Given our current mean differences with the sample tested, it is unlikely that increasing our sample size would shift treatment effects for local and whole-body sweat rate outside the boundaries of a clinically meaningful sweating impairment.

Cardiovascular Findings

Thermal strain acts as a stimulus for thermoregulatory responses such as cutaneous vasodilation and sweating. The subsequent rise in skin blood flow causes a reduction in total peripheral resistance, and the cardiovascular system responds by increasing cardiac output to maintain systemic blood pressure (Rowell et al, 1969). Considering typical cardiovascular responses to heat stress, potential alterations from OTC antihistamines would likely be via two known physiological/pharmacological pathways:

(1) Endothelial H_1 / muscarinic receptor blockade could potentially increase arterial pressure by withdrawing vasodilation.

(2) Myocardial M3 and/or M2 receptor antagonism could potentially increase heart rate by decreasing parasympathetic tone.

Either mechanism could increase blood pressure and/or alter cardiovascular functioning during heat stress and potentially increase HRI risk.

The present study demonstrated that OTC-strength diphenhydramine, loratadine, and/or desloratadine does not impact heart rate during passive heat stress. Our results align with that of Montgomery & Duester (1992) who reported similar findings in their sample of twelve participants, suggesting that oral ingestion of 50mg of diphenhydramine does not alter heart rate responses during a thermoneutral (~23°C), exhaustive bout of exercise. Similarly, Scavone et al, (1998) reported in their randomized crossover trial that 25mg of orally administered diphenhydramine did not have any effect on heart rate versus a placebo. Albeit, the methodology

carried out by both Montgomery & Duester (1992) and Scavone et al, (1998) did not incorporate a standardized heat stress protocol. However, adding to the findings of Montgomery & Duester (1992) and Scavone et al, (1998), our lab previously demonstrated that 50 mg diphenhydramine does not alter heart rate during 60 minutes of active heat stress (Newhouse et al, 2024). Taken with the results of the present study, there is clear evidence in healthy subjects that heart rate is unaffected by 50 mg of diphenhydramine, although more evidence is needed to confirm whether the same is true for loratadine, desloratadine and other OTC antihistamines.

The present study demonstrated that OTC antihistamines diphenhydramine, loratadine, and/or desloratadine, taken as recommended, do not independently alter skin blood flow, mean arterial pressure, or rate-pressure product during passive heat stress. This deviates from early inquiries such as that of Mackmull (1948) who showed that elevated doses (≥100mg) of diphenhydramine administered intravenously significantly elevated systolic and diastolic blood pressure at rest. Moreover, Kobza (1968) reported that orally administering 20mg clemizole (Formerly marketed as Allercur/Histacur), a since-discontinued OTC antihistamine, nullified post-heat stress reductions in systolic blood pressure. Lockwood et al (2005) and McCord & Halliwill (2006) reproduced similar effects in their respective inquiries, reporting that blocking H_1 receptors with 540 mg of fexofenadine suppressed post-exercise hypotension, supporting a potential mechanism by which OTC antihistamines could impact vascular tone during heat stress. Wong et al (2004) provided some evidence of an H_1 antihistamines altering vascular tone and/or skin blood flow during heat stress, reporting that the administration of a potent H_1 antagonist pyrilamine maleate via subcutaneous microdialysis (500μm) significantly reduced skin vascular conductance during the passive heating of human participants. Contrarily, the results of the present study and prior data from our lab point to 50 mg of diphenhydramine

having no effect on mean arterial pressure during active/passive heat stress (Newhouse et al, 2024).

Our lack of findings may be due to our dose/potency of OTC antihistamine being too low and not causing the level of H_1 receptor and/or myocardial M3 and/or M2 receptor antagonism required to affect vascular or parasympathetic tone. Also, it could be due to physiological compensations in heart contractility or another cardiovascular factor masking true effects. Participants were observed to reach values for skin blood flow and local sweat rate indicative of their maximum physiological thermal response in 96% and 93% of trials respectively. Thus, it is unlikely that our lack of significant results was due to insufficient heat stress. However, our *a priori* G*power sample size calculation utilized an effect size (d= 1.13) relating to meaningful differences in local sweat rate of the forearm (Kenefick et al, 2012; Rutherford et al, 2021). For this reason, our sample size (n=10) may limit our cardiovascular data.

Perceptual Findings

Thermal perception, its influence over thermal behaviour, and the important role that it plays in human thermoregulation during heat stress can at times be understated in research on thermal physiology (Schlader et al, 2010). To provide a comprehensive assessment of OTC antihistamines' safety during heat stress, it is necessary to understand how the drugs might alter individuals' perception of heat stress. Speculatively, if a molecule were to blunt perceived thermal comfort or sensation, it could lead to avoiding cooling behaviours and undesired over-exposure to heat stress (Schlader et al, 2010).

Second/third-generation H_1 antihistamines desloratadine and loratadine are considered safer alternatives to first-generation H_1 antihistamines like diphenhydramine as they do not cross the blood-brain barrier and cause sedation (Paton & Webster, 1985). From this, and evidence of

diphenhydramine having analgesic properties, it is scientifically plausible that diphenhydramine could affect thermal perception during heat stress (Rumore & Schlichting, 1985).

Contrarily, the present study demonstrated that neither diphenhydramine (50 mg), loratadine (10 mg), or desloratadine (5 mg) alter thermal comfort or sensation during passive heat stress. Further, previous data from our lab also reported that 50mg of diphenhydramine has no effect on thermal perception during active heat stress in a sample of 20 healthy adults (Newhouse et al, 2024). However, additional scientific evidence assessing OTC antihistamines' effects on thermal perception is scarce. Thus, further research is required to confirm whether OTC antihistamines can alter thermal perception, thermal behaviours, and HRI risk.

Implications

AR is a respiratory condition affecting up to a quarter of Canadians causing symptoms such as rhinorrhea, fatigue, congestion and general discomfort (Bousquet et al, 2020; Keith et al, 2012). Factors involved with anthropogenic climate change will predictably increase both the concentration of airborne allergens that contribute to AR symptoms and the severity/frequency of extreme heat events over the coming decade (Corden & Millington, 2001; D'Amato et al, 2015; Vogel et al, 2019). Several public health authorities currently advise individuals to refrain from all antihistamine medications during extreme heat events or during any heat stress, limiting a popular treatment option for many individuals who relieve their AR symptoms with antihistamines bought OTC (Ajmani et al, 2017; Casa et al, 2015; Coco et al, 2016; OSHA, 2011; Roberts et al, 2023; WHO, 2011).

The results of the present study provide initial evidence for the lack of an effect and perhaps contraindicate current heat safety advice echoed by public health authorities including the WHO, OSHA, NIOSH, ACSM, NATA and academic journals such as JAMA (Casa et al,

2015; Coco et al, 2016; OSHA, 2011; O'Connor & DeGroot, 2024; Roberts et al, 2023; WHO, 2011). Our preliminary findings suggest that OTC antihistamine allergy medications, taken at manufacturer-recommended doses, do not affect human sudomotor or cardiovascular responses during heat stress. The lack of significant findings in our study adds initial evidence to support the continued use of OTC antihistamines such as diphenhydramine, loratadine, and desloratadine to relieve AR symptoms during periods of heat stress. However, continued research is required to comprehensively understand the HRI risk posed by OTC antihistamines before this knowledge is translated into policy or practice.

Delimitations and Limitations

The scope of this study is delimited to young healthy adults in correspondence with our inclusion/exclusion criteria. Similarly, our results can only be generalized to individuals taking manufacturer-prescribed doses of diphenhydramine (Benadryl®), loratadine (Claritin®), or desloratadine (Aerius®) prophylactically. No evidence using human samples/subjects on whether acute AR reactions alter the muscarinic binding affinity of H_1 antihistamines currently exists. However, studies such as Hayashi et al, (2022) using *in-vitro* mice samples have suggested M3 receptors modulate immunity responses in lung tissue. Speculatively, if cutaneous M3 receptors exhibit similar modulation of immune responses in humans, M3 receptor antagonism from H_1 antihistamines may cause different effects during acute AR versus the prophylactic administration utilized in our study. To this end, our results should not be extended to individuals who are actively suffering from AR symptoms. Similarly, our results cannot be generalized to any clinical populations or individuals taking antihistamines on consecutive days before terminal elimination of the drug. Our results are only preliminary and should not be extended to real-world or active heat stress settings although some literature supports

diphenhydramine having no effect on sweating during active heating (Newhouse et al, 2024). It remains unclear whether subsequent bouts of heat stress or chronic heat exposure over extended periods (such as during a heat wave) accumulates in the body and might alter our results. It also remains unclear whether prescribing antihistamines other than diphenhydramine, loratadine & desloratadine, or higher doses of these medications, would alter our results.

Problematically, hormonal changes during the luteal phase of the female menstrual cycle raise baseline core temperature and increase sweat onset threshold and thermosensitivity which has undeniably limited female sample sizes and data in research on thermal physiology, especially in repeated-measures designs (Stanhewicz & Wong, 2020). Moreover, it has been suggested that progestin from hormonal IUDs may impair sweating and heat dissipation during heat stress (Stachenfeld et al, 2000).

Contrarily, new evidence from Kirby et al (2024) suggests any influence of progestin from IUDs is not physiologically meaningful considering females' sweating response during active heat stress. The same study also suggests the alterations in sweating females experience during their luteal phase are unlikely to be practically meaningful regardless of IUD use (Kirby et al, 2024). Further, Grucza et al (1993) show evidence that quadriphasic changes in females' sweating response are dampened by regular use of oral contraceptives such that they become more uniform through one's cycle. Considering our sample (n=5) of female participants, one was not prescribed a continuous-cycle contraceptive or IUD and was unable to have their trials booked during the menstrual phase of their cycle and separated by ~28 days due to scheduling difficulties. Although this participant's data may have been affected by menstrual hormones, omitting the participants' data from our statistical analyses did not alter any of our results. Taken with the findings of Grucza et al (1993) and Kirby et al (2024), it is unlikely any independent

effect of menstrual hormones on temperature regulation confounded our results, although more data would be needed to validate this conclusion. Until the relationship between OTC antihistamines and thermoeffector suppression is better understood, there is uncertainty as to whether our sample of females (n=5) has adequate statistical power to make sex-segregated observations. Because evidence exists suggesting there are sex-dependent differences in postjunctional cholinergic sensitivity, and the fact females are generally underrepresented in research on thermophysiology, it is increasingly important that future studies on OTC antihistamines and sweating focus on testing statistically powered samples of female participants (Gagnon & Kenny, 2011).

Although an effective and highly objective research design, randomized double-blind crossover protocols can still be subject to influences from masking and sampling biases (Kaptchuk, 2001). Further, participants in our study may have had some inclination to which trial they received diphenhydramine from feelings of sleepiness.

Considering limitations to our passive heating protocol, exposed skin on participants' head, neck and left arm was left uncovered by our water perfusion garment and may introduce a small degree of measurement error from evaporative heat losses. These differences were deemed negligible but nevertheless introduce the potential for error from fluctuations in ambient conditions such as temperature, humidity, and airflow between treatment legs (Rutherford et al, 2021). Of note, a one-way rmANOVA on the ambient conditions in-lab during experimental trials showed no main effects of treatment leg (Four levels: PLA, DPH, LOR, DES) on mean ambient temperature (°C, $F_{(1.912, 17.21)}$=2.598, p=0.105) or mean ambient humidity (RH%, $F_{(2.272, 20.45)}$=0.791, p=0.482), although no data was collected on airflow. Due to the high degree of heat stress and discomfort involved in our protocol, a degree of measurement interference was

introduced from moisture within the water perfusion garment and the movement of participants. Skin blood flow (Via laser-doppler flowmetry) and heart rate (Via four-lead electrocardiogram) were particularly susceptible to interference from participants' movements and moisture. The ventilated sweat capsule and capacitance hygrometry have reportedly large cohen's *d* effect sizes (~1.13) for measuring local sweat rate during high heat stress (Kenefick et al, 2012; Rutherford et al, 2021). The measurement technique is sensitive to subtle differences in placement and can be a source of measurement error considering intra-individual regional variability in sweat gland density, recruitment, and output (Rutherford et al, 2021). Nevertheless, we did show a similar lack of effects at both the forearm and chest. Calculations for sweat onset and thermosensitivity were completed as functions of change in body temperature as heating duration was determined by esophageal temperature and not time. Calculations for whole-body sweat rate utilize body weight measurements taken before and after heat stress divided by heating time and do not account for fluctuations across non-steady state and steady state sweat rates. Blood pressure was measured on participants' right upper arm using automated sphygmomanometry. These measurements were utilized for calculations of mean arterial pressure and rate-pressure product using one observation every ten minutes. Future research could improve by taking more frequent observations of arterial pressure during heating or using continuous methods such as a finger blood pressure cuff. Self-reports of thermal perception (thermal sensation and comfort) and sleepiness taken throughout trials are subjective and can be influenced by external factors or context biases such as unrelated anxiety or lighting (Crucianelli et al, 2024; Te Kulve et al, 2018).

Because this study tests a novel relationship between OTC antihistamines and sweating, there is uncertainty that our sample size has the necessary power to extend our lack of findings to

the greater population of young healthy adults. Out of the 26 individuals that initially agreed to participate, 16 participants were deemed ineligible per our inclusion criteria or withdrew before completing all four experimental trials. Drop-out participants generally cited discomfort with the insertion of the esophageal temperature probe or passive heating protocol as reasons for their withdrawal. Regardless, sample size G*power calculations conducted a priori suggested we were adequately powered at n=8 to detect meaningful differences in local sweating using the ventilated sweat capsule at high heat stress (Rutherford et al, 2021). Although we recruited an adequate sample (n=10) of participants, it may be that there is large inter-individual variability in the way OTC antihistamines affect persons' local sweating response, and we simply did not test enough individuals to observe this would-be difference. It is also important to note our *a priori* G*power sample size calculation utilized an effect size (d= 1.13) that reflects the ventilated capsules' power to detect the "smallest meaningful difference" in local sweat rate of the forearm during high heat stress. However, what is "meaningful" is arbitrary and depends on context. Rutherford et al (2021) define a "meaningful" difference in their article as being outside the day-to-day intraindividual standard deviation, which is reportedly ~0.20 $mg/cm^2/min^1$ concerning local sweat rate (Rutherford et al, 2021). Considering the present dataset, the largest mean difference in local sweat rate of the forearm at Δ1.5°C T_{body} was ~0.09 $mg/cm^2/min^1$ between placebo and desloratadine treatment legs. For context, this is 55% or 0.11 $mg/cm^2/min^1$ shy of the smallest "meaningful" difference in local sweat rate accepted in the analyses of Rutherford et al (2021). Another way to gauge "meaningful" differences in whole-body sweat rate could be by comparing the treatment effects of OTC antihistamines to other factors that influence sweating and HRI risk such as acclimation status. Using a crossover design and 10 participants, Poirier et al (2016) reported mean differences in whole-body sweat rate of ~2.0 g/min following a 14-day

acclimation protocol, an established primary-prevention strategy for HRI (Barry et al, 2020; Poirier et al, 2016). Our largest observed difference in whole-body sweat rate was 0.26 g/min between placebo and desloratadine treatment legs (See Table 2 in Results). For context, this is only 13% of the alteration in whole-body sweat rate that Poirier et al (2016) observed in response to their acclimation protocol. Further, a post-hoc G*power sample size test for one-way within-subjects 1x4 rmANOVA (alpha = 0.05, beta = 0.80) suggests a sample of only 3 participants would be required to observe alterations in whole-body sweat rate comparable to the ~2.0 g/min change reported by Poirier et al (2016). Considering our comprehensive lack of findings across all the sudomotor response variables measured in our study, it is unlikely that the added power of recruiting more young adults would alter local and whole-body sweating enough to cause clinically meaningful sweating impairment.

Both *a priori* and post-hoc G*Power sample size calculations were performed using local and whole-body sweat rate values to address our primary research question on sudomotor responses to heat stress. To this end, our lack of significant findings on cardiovascular and perceptual variables may be a result of statistical underpowering. However, it is noteworthy that our results align with previous reports of OTC-dose diphenhydramine having no effect on heart rate during exertion/heat stress (Montgomery & Duester, 1992; Newhouse et al, 2024; Scavone et al, 1998).

Lastly, our correlation analysis was limited as the Pearson correlation test is designed to measure the strength of linear relationships, whilst none of the physiological responses we measured follow perfectly linear response curves during passive heating.

Despite these limitations, our exploratory study provides preliminary evidence that OTC diphenhydramine (50 mg), loratadine (10 mg) and desloratadine (5 mg) have no effect on

thermoeffector responses to passive heat stress. Future research should aim to expand on our results by addressing these limitations and garner a comprehensive understanding of whether OTC antihistamines pose an HRI risk to the general public, clinical populations, or specific sectors such as the athletes, the military, or individuals residing in heat-prone areas.

Conclusion

Over the coming decade, climate change will exacerbate the allergenicity and duration of the pollen season, and the risk and intensity of extreme heat events (Corden & Millington, 2001; D'Amato et al, 2015; Meehl & Tebaldi, 2004; Vogel et al, 2019). Currently, public health authorities advise against taking all antihistamine medications during periods of heat stress, believing the drugs may impair thermoregulatory responses and contribute to HRI risk (Casa et al, 2015; Coco et al, 2016; OSHA, 2011; O'Connor & DeGroot, 2024; Roberts et al, 2023; WHO, 2011). Our data provides empirical evidence that OTC antihistamines diphenhydramine (Benadryl®), loratadine (Claritin®), and desloratadine (Aerius®) taken at manufacturer-recommended doses, do not alter human sudomotor, cardiovascular, and/or perceptual responses to heat stress or increase individuals' susceptibility to HRI. Future research must be conducted to address the limitations and delimitations of our study before this knowledge is translated into policy or practice. It remains unknown whether ingesting OTC antihistamines during chronic heat exposure, prescribing higher doses, or chronic use of diphenhydramine, loratadine, and/or desloratadine might impair thermoeffector responses to heat stress long-term. It is also unknown whether non-prophylactic oral administration such as after or while experiencing AR symptoms might alter either drug's metabolism and/or effects during heat stress.

As climate change progresses, research inquiring of the HRI risk posed by frequently utilized medications will be vital to protect members of the public. For this reason, it is

imperative researchers continue investigating the relationship between antihistamines and human thermoregulation to fully understand the implications of anthropogenic climate change on individuals who rely on these medications to manage their AR symptoms.

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