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# Heat Stress Responses to Exercise: related mechanisms and biomarkers

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## Abstract

The pathophysiology of heat stress occurs when the body's environmental and physiological responses exceed its ability to maintain homeostasis. When internal heat signals or external factors raise body temperature beyond a certain limit that the cooling mechanisms can effectively manage, the resulting increase in core temperature triggers response pathways that themselves induce physiological stress. The primary response mechanisms to heat stress include sweating, peripheral vasodilation, and shivering as thermogenic responses—all of which are activated by elevated temperatures and may seem counterproductive to the body's requirements, yet they operate through a neuromuscular and hormonal feedback system. Genetic factors influence individual heat tolerance; for instance, certain populations have variations in heat shock proteins (HSP70) and ion channels (TRPV1, RYR1) that enhance their heat response and tolerance. Additionally, individuals with higher relative VO2 max levels demonstrate greater heat tolerance, as those who are physically trained exhibit more sudomotor activity and effective evaporative cooling compared to untrained individuals. Furthermore, individuals who acclimatize to heat over time develop improved thresholds for heat stress, enabling them to better regulate internal and cardiovascular temperature stresses during exposure. This knowledge is crucial for populations at risk and in situations where physical exertion is required in hot conditions.

**Keywords:** Thermoregulation, cutaneous vasodilation, aerobic capacity, genetic adaptation, environmental factors, homeostasis.

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## Introduction

An individual's changes both internally and externally result in signals being sent to the sensory organs and receptors of the body. These signals are sent to the cerebral cortex for processing so that the individual can make sense of the sensory information being received (Bernard, 1879). This process will produce both conscious actions and reflexive actions. Conscious actions occur when the individual breaks away from relaxation and enjoyment (Giaja, 1938). Subconscious actions are triggered in response to challenges and threats that may disturb the balance within the internal environment (homeostasis) (Adolph, 1964). The internal medium must operate within a specific range. The range of certain characteristics of the fluid that bathes the cells of the body (extracellular fluid) that is crucial for life delineates the boundaries of this range. Stress is recognized as these chemical and physical alterations that disturb or put this balance at risk (N. A. Taylor, 2019). Selye called them "stressors," a label that is still commonly used (Selye, 1950, 1973). This analysis seeks to understand the subconscious and physiological responses of a body against stress whilst focusing on normal adults. The elderly, however, face a considerable drop in their ability to deal with stress due to sedentary behaviors. It is also important to note that stress is easier to identify than deal with (Chakravarthy, 2008) As most of the elderly people suffering from sedentary aging syndrome show significant physical stress signs. Whatever the age, stressors act on everyone differently (Kenney, 2017). Some stressors can be dealt with internally and some externally. For example, the body experiences short-term effects from stress. Adolph termed these effects as "adaptations". These physiological responses mark the onset of stress on the body. Other variables such as heart rate are considerably less fixed than some physiological variables, for example, temperature, which changes minimally. This explains why some of the body's internal systems are regulated and controlled to help maintain an internal balance. These matters will be examined in further depth in the upcoming sections. Consequently, during situations of light stress, it is often seen that several of the body's regulated variables are relatively

constant. In contrast, others change markedly due to the internal regulatory system's attempt to achieve homeostasis (Adolph, 1955; Brooks, 1969).

**External and Internal Sources of Thermal Stress**

There is a widely held belief that shifts in the body's thermal energy content originate predominantly from external (exogenous) sources that directly impact the radiative, convective, and dry heat exchanges as well as evaporative heat loss between the body and its surroundings which in turn affects the tire tissue temperature (Epstein & Moran, 2006). In this context, we can think about external stressors that result from a combination of changes in ambient temperature and water vapor pressure and nonionizing radiation which includes radio waves, microwaves, infrared, and near-ultraviolet exposures (Ken Parsons, 2007). Considering that thermal energy would always disperse from high thermal energy zones to lower ones due to the Second Law of Thermodynamics, the movement would happen at a rate that is proportional to the amount of interference or gradient (Newton's cooling law (we see how thermal energy is lost and or conserved by the surrounding temperature (N. A. Taylor, 2019). When the surrounding temperature exceeds the skin, it becomes impossible to conserve heat and as a result, heat can only be lost through perspiration(Fourier, 1972). Since humans are sweating specialists, increases in the water vapor content of the air make the evaporation of sweat and heat loss much more difficult. As a result, in dry climates, people better tolerate heat exposure than in the tropics (Carnot, 1872).

**Climate Variability and the Origins of Human Species**

The World Meteorological Organization has disclosed that the increase in levels of CO2 in the atmosphere since the 1940s has shot up at a pace almost 100 times faster than what it was at the end of the last ice age period. This anthropogenic phenomenon of global warming, in addition to other greenhouse gases, is causing shocking climatic changes such as, but not limited to, rising temperatures and increasingly severe

weather. Climate change may not be a recent occurrence, but it still forms a professional hazard due to the extreme climatic changes sometimes causing extensive destruction and new species to populate the planet. The Archaic Homo Sapiens, for example, experienced extremely rapid temperature shifts 250,000 years ago (Nelson, Heath, & Prosser, 1984). Those who evolved in Africa, alongside other regions, were subjected to harsh climatic conditions that forced species that require certain thermal conditions to die out and give rise to Sapiens. In addition, like all mammals and birds, they had high metabolic rates, along with behavioral and physiologically mediated control systems that managed their body temperatures by modulating the production of heat and the loss of heat (Section Concepts of Mammalian Homoeothermy) (Cabanac, 1979). In other words, they actively restricted their body temperature from varying in correspondence with shifts in the surrounding thermal conditions (ectothermy or poikilothermy: i.e., non-mammalian and non-bird animals), but rather, they maintained a relatively constant deep body temperature (endothermy or homoeothermy) (Havenith & van Middendorp, 1990). It has been established that when there is continuous heating respiration, convective, and radiative heat loss, then in shivering thermogenesis function, the body produces heat energy that is almost three times higher than the resting metabolic rate (N. A. S. Taylor, Taylor, Maloney, & de Dear, 2022). That mechanism conferred upon early man an amount of cold resistance which could be augmented by learned behavioral strategies such as clothing and shelter. This is self-evident among all sentient beings and even unicellular lifeforms. Indeed, all living organisms use behavioral thermoregulation, which is prevalent among ectotherms and endotherms alike which proves that it is the most basic form of regulating body temperature (Gowlett, 2001). Ectotherms also possess the ability to utilize their skin networks for regulating heat energy. “It would be unnecessarily burdensome to require the evolutionary process to create a new system to solve a problem already solved by an existing system,"(Satinoff, 1978). That vasomotor regulatory mechanism, shivering thermogenesis, and

nonshivering thermogenesis are believed to occur simultaneously while sweating, a characteristic exclusive to mammals, is accepted later Non-shivering thermogenesis (NST) generates body heat without relying on shivering (Giaja, 1938). Brown adipose tissue (BAT) serves as the main site for this process which maintains body temperature regulation. The mitochondria within brown fat cells produce heat through a protein named UCP1 while bypassing ATP production (W. Montagna, 1971). Infants and small animals rely heavily on this mechanism to regulate their body temperature (Stevens, 1973). It appears that even during selection, there was a preference for tolerating heat that would enable endurance-based strategies for hunting and escaping, as well as for persistence hunting that takes place over several hours and often during the hottest part of the day (Ruben, 1995). Before the African climatic shift, the selective pressure for dissipating heat was not as strong. But with the appearance of savanna and tropical environments, the rules changed radically (Lieberman, 2015). Since the majority of mammals are anesthetists, heat dissipation during rest was possible and effective, but not while running (Bramble & Lieberman, 2004). Instead, they opted to accept some of the thermal burden brought on by vigorous exercise, and whooping rest to remove heat. This was effective in an environment where everyonشبe was playing by the same rules, but with the introduction of Homo sapiens, things got more difficult. They had developed eccrine sweat glands, which are believed to have been co-selected with bipedalism and endurance, and tool use (Folk & Semken, 1991; William Montagna, 2012).

**Measures of Stress and Strain**

Physical or chemical stimuli are grouped in a category called “stress.” This category of stimuli, along with its associated functions, is called “strain.” Knowing the essence of these stresses is relevant, yet, for as long as these stresses are within the circumferences of allowing the balance of the internal milieu of the body to remain undisturbed, there is no threat to the vital functions of the body(Edition, 2001). Interestingly, humans, who evolved in tropical regions, seem to have

better tolerance to more severe drops in body temperature compared to humans who are suffering from severe increases in temperature(Robinson, 1963). This could perhaps be the condition at which the Earth had colder climatic conditions when the early humans emerged (Pugh, Corbett, & Johnson, 1967; Stocks, Taylor, Tipton, & Greenleaf, 2004). Physically, "heat stress" is a heat load with a propensity to increase body heat storage and increase deep body temperature. The magnitude of heat stress is controlled by six properties. Heat generated as a by-product of metabolism, particularly with exercise, is typically the largest source of heat. Four climatic variables, air temperature, mean radiant temperature, ambient vapor pressure, and air velocity, determine rates of heat loss from skin and respiratory surfaces to the external environment. Finally, when there is clothing present, the environmental rate of heat loss is reduced. Heat stress differs from "heat strain" in that the latter refers to the physiological response to a heat load, for example, increases in deep body temperature or heart rate (M. N. Cramer, Gagnon, Laitano, & Crandall, 2022).

**Indicators for Measuring Thermal Stress**

If someone were to make a guess, the easiest method for assessing thermal stress or physiological strain would be the measurement of temperature. However, outer environmental conditions such as Strain energy are not only impacted by the surrounding region’s heat. The vapor pressure of the air can be an important determining factor, too (Fanger, 1970). Therefore, combining these two variables into one single index to quantify external stress may look easy and straightforward, but the quest for an acceptable index has stretched for over a century and the methods derived from this quest are referred to as effective temperature scales (perceived) or rational indices (Epstein & Moran, 2006). The first group emerged to equalize thermal comfort for office workers with formal dress codes (effective temperature). The more ‘rational’ ones are based on thermodynamic processes and most of them are used by thermal physiologists (Ken Parsons, 2007). The

most frequent indicator of thermal stress is the WBGT or Wet Bulb Globe Temperature, and it was designed as an adjunct to the effective temperature scale (Yaglou & Minard, 1957). While there has been some effort to account for the vapor pressure of water (more commonly known as a wet bulb temperature), it has relied largely on a compromise method of achieving thermal comfort which is based more on social acceptability than robust physiological evidence (K. Parsons, 2006). Still, this index has been adopted by the Occupational Safety and Health Administration, the International Organization for Standardization, the National Institute for Occupational Safety and Health, and the American College of Sports Medicine (Control, 2018). There is hope that these decisions have been reached based on practical considerations instead of scientific ones (Armstrong et al., 2007). The WBGT index has significant limitations. First, this index is unable to account for variations in metabolic heat production, and since heat-related illnesses rarely occur in low-activity jobs, this flaw has serious implications. Second, as air temperature increases, there is an exaggerated emphasis on dry temperatures. Third, the consideration of air velocity, which significantly affects forced convection and evaporation, is inadequate in hot and humid conditions, and it has less sensitivity at speeds above 1.5 meters per second. Fourth, this index does not take into account changes in skin temperature or skin wetness, both of which contribute to the vapor pressure gradient. Fifth, core body temperature, heart rate, and overall sweating will vary under equivalent weather conditions. While a WBGT of 28 degrees Celsius is more stressful than 18 degrees Celsius, conditions with the same WBGT are not equally stressful. Finally, and perhaps as damaging as the first limitation, the applicability of this index for clothed workers varies from merely lower to completely inappropriate when wearing encapsulating suits (Budd, 2008). The Effective Temperature (ET) index is one of the oldest and most common thermal comfort indicators (Equation 1). This index incorporates air temperature, relative humidity, and wind speed as combined factors that affect the overall heat sensation. The formula for calculating ET is: In this formula, T is the air temperature in degrees

Celsius, and RH is the relative humidity in percent. This paper explains how this index can be used to help professionals to understand the environment and to take action to improve thermal comfort (Heating & Engineers, 1928).

(Equation 1)

$$ET = (T - 10)(1 - RH/100)$$

The Effective Temperature (ET) index, while useful in assessing thermal comfort in specific situations, refers to the challenge of making broad generalizations about thermal stress due to the complex interaction between environmental and physiological factors.

**Generalisations Concerning Thermal**

Heat stress is a condition in which the body undergoes pressure and strain from high temperature. Genetic factors may predispose certain individuals to become more sensitive to changes in temperature. Such sensitization may be attributed to gene mutations in some receptors and heat shock proteins, including TRPV1, RYR1, and HSP70 (Ritossa, 1962). HSP70 protects cells from heat stress through protein stabilization and inhibition of degradation. Mutations in HSP70 can disrupt protein production and heat stress adaptation. For instance, the HSPA1B variant is associated with a higher risk of heat stroke in humans under extreme heat (Alele, Otto, Malau-Aduli, & Malau-Aduli, 2022). A 2010 study demonstrated that polymorphisms of the HSP70.1 gene are associated with the response of peripheral blood mononuclear cells to heat shock, suggesting an influence of these variants on heat tolerance in dairy cattle and certain polymorphisms of the HSP70 gene lead to increased heat-activated protein misfolding and cellular damage (Basiricò et al., 2011). The skin and tissue TRPV1 ion channel plays a significant role in sensing high temperature and heat pain. TRPV1 gene mutations influence heat sensitivity. individuals with the TRPV1 rs8065080 polymorphism had altered pain thresholds and elevated heat intolerance. UCP protein genes within the mitochondria are important in thermoregulation and heat production. They enhance energy

expenditure and heat production in cells (Argyropoulos & Harper, 2002). Gene mutations are linked with different thermoregulatory traits. UCP1 polymorphisms affect metabolic rates and adaptive thermogenesis, which determines heat stress tolerance. The RYR1 receptor of skeletal muscle regulates calcium and muscle contraction (Nedergaard et al., 2001). Genetic variations can cause temperature sensitivity to become elevated, and this can cause thermogenic disorders like malignant hyperthermia (MH), which is a severe reaction to anesthetics and heat (Kampinga et al., 2009). RYR1 mutations that enhance the susceptibility to MH under heat stress. In thermoconformers, ambient temperature directly affects body temperature and metabolism. This is indicated by the Arrhenius equation and the temperature coefficient, Q10. According to studies, biological reactions in the majority of animals double or triple with each 10°C increase. These regulations are practiced by birds and mammals, utilizing active thermoregulation to attain homeothermy (Gillooly, Brown, West, Savage, & Charnov, 2001). The human body temperature is 36.5-37.0°C and skin temperature of approximately 33°C, regardless of environmental variations (Armstrong et al., 2007). Overheating, overcooling, or chemical imbalances can stress thermoregulation and cause body temperature regulation to deviate. For instance, core temperature may rise by 1.5°C during steady-state exercise before sweating or shivering begins to restore equilibrium. athletes who had certain genetic variants in HSP70 and TRPV1 experienced greater thermoregulatory strain in the heat, highlighting the impact of genetics in heat stress adaptation (Bosson et al., 2020). Thermoreceptors in the skin detect temperature, which has an effect on the perception of the body. Tissues of the body from the inside also differ in terms of temperature, affecting comfort levels. there are thermal comfort ranges that depend on genetics, prior exposure, as well as acclimatization. Thermal preference by the season shows variability in heat tolerance (Fanger, 1970).

## Regulators of Temperature Control: Internal Factors

Building on the foundational concepts of energy exchange and human thermoregulatory control mechanisms, the focus now shifts to the various intrinsic morphological and physiological traits that affect heat stress responses in healthy individuals. These traits can impact thermoeffector loops at different points, but current understanding of their modulatory effects largely depends on measurements of core body temperature and thermoeffector activities. Some of these traits have been studied in relation to the responses of postjunctional thermoeffector organs, and sympathetic skin nerve activity (SSNA) has been recorded in certain instances. These findings are acknowledged where applicable. However, there is a notable lack of research on how these characteristics might affect thermoafferent signaling and the integration of thermoafferent input.

### Structural Features

The parameters and composition of the body's passive system are of great importance in the determination of the heat stress response. Here, we cover the influence of body mass, body surface area, and surface area to mass ratio, and body composition and highlight the relevance of morphological variables in the evaluation of the individual impact of different physiological characteristics (Gordon, 2012).

### Body Mass

The Mass has several thermodynamic implications. Metabolic rate increases with body mass, and therefore, heat production is higher in heavier subjects (Kleiber, 1947; Miller, Ross, Rapp, Roede, & Opitz, 1980). Mass also acts as a heat sink, and the rise in deep body temperature is inversely related to body mass. It would follow that at a constant absolute rate of metabolic heat production, a larger mass should minimize the rise in deep body temperature for a given regulatory control of thermoeffector responses. Several investigations have shown a strong negative relationship between body mass and end-exercise deep body temperature during cycling (i.e., non-weight-bearing exercise) at a constant absolute work rate (Havenith, 2001),

absolute heat production, and constant relative intensity. Cramer and Jay illustrated the independent effect of body mass by comparing deep body temperature responses to cycling at the same heat production rates between heavier (mean: 91.5 kg) and lighter (mean: 67.6 kg) subjects who were matched for age, sex, and heat acclimation (Matthew N Cramer & Jay, 2014). At 500 and 600 W of heating, the heavier group had 0.3–0.4°C lower rectal temperatures due to a larger heat sink. Ravanelli et al noted that in uncompensable conditions, the rectal temperature rise was 0.7°C less in heavier individuals (mean: 100.0 kg) than in lighter individuals (mean: 65.8 kg) when cycling at 520 W in heat-humid conditions (Matthew N Cramer & Jay, 2016). Heat production and mass affect deep body temperature responses, and therefore both must be considered when groups of varying body size are being compared (e.g., children and adults, men and women, and individuals with and without obesity). Cramer and Jay compared deep body temperature responses of larger and smaller mass groups while cycling at fixed heat production rates (W/kg) in a compensable climate [~25°C, 37% RH]. Despite a 23.9-kg difference in mass and varying rates of heat production, rectal temperature increments were similar at 6.5 and 9.0 W/kg. In a ~35°C climate, the 9.0 W/kg experiment showed similar rises in deep body temperatures, validating this method in varying ambient conditions. There were also no differences between groups for sweat onset or thermosensitivity. These findings indicate that comparisons of deep body temperature between unmatched groups should be conducted at the same mass-specific heat production in compensable environments (Kenny & Jay, 2011).

**Morphological Considerations in Heat Stress**

The relationship between shape and heat loss in humans is allometric, i.e., has the same shape but differs in size and segmental proportions. As we increase in size, our volumes (masses) increase more rapidly than our skin surface area. Larger individuals thus have a lower specific surface area than small ones; infants exposed to cold lose heat more quickly than adults. This phenomenon is true across all animal species,

where larger-bodied animals maintain more stable deep body temperatures. The morphological features of these organisms also influence their responses to changes in the thermal environment; smaller organisms tend to be metabolic specialists, while their larger counterparts are mostly cutaneous vascular responders. Proof will be provided (under the section Morphological Determinants of Cutaneous Blood Flow and Sweating) that body morphology also influences the autonomic mechanism of choice for heat loss in humans, which largely consists of three effectors: eccrine sweat glands, cutaneous blood vessels, and skeletal muscles (Bergmann, 1848).

**Eccrine Sweat Glands**

Water traverses the skin in both liquid (active sweating) and gaseous (transepidermal water loss) forms. Nevertheless, when ambient temperatures exceed skin temperatures, the sole remaining physiological mechanism for heat dissipation is the stimulation of eccrine sweating. The normal adult possesses an average of 2.03 million active glands (95% confidence interval: 1.72 to 2.34 million). The distribution of the glands is not uniform, with the lowest densities on the lower limbs and the greatest densities, more than 300 glands per square centimeter, on the palmar surface and soles of the feet (Kenzo Sato, Kang, Saga, & Sato, 1989). The arrangement of high densities of glands on soles and palms is assumed to be a relic of arboreal life and more particularly with Sahelanthropus tchadensis, but it has also a profound thermolysis function (Manabu Shibasaki & Crandall, 2010). When temperatures hit 34°C (93°F) or more, our bodies rely solely on sweating to cool down, as we can't lose heat to the environment. We have around 2 million sweat glands in our skin that help with this process. Sweat covers most of our skin, but it isn't distributed evenly. The amount and location of sweat can change depending on the heat level. Typically, we sweat most on the forehead and back, followed by the front of the torso, shoulders, head, and neck. The arms, legs, palms, and soles sweat the least (Manabu Shibasaki & Crandall, 2010). On the hands, the palms sweat the least, while the back of the hands sweat the

most, and the fingertips sweat more than areas closer to the palms. On the legs, sweat is more abundant on the buttocks and the front of the thighs, and less so on the inner thighs. The inside of the lower legs and ankles tend to sweat more than the outside, and the tops of the feet sweat more than the soles (Manabu Shibasaki & Crandall, 2010). Areas like the back of the foot, forearm, back, abdomen, chest, and upper arm have roughly 100 to 120 glands per square centimeter (Baker, 2019). The armpits, thighs, and legs have about 60 to 85 glands per square centimeter, while the buttocks have the fewest, with 40 glands per square centimeter. Interestingly, having more sweat glands doesn't always lead to more sweating. For example, although the palms and soles have significantly more glands than the back—about five times more—they often sweat less, whereas the back tends to sweat more. This suggests that factors like the size of the glands and how sensitive they are might better explain why different body areas sweat at different rates (Baker, 2019). Eccrine sweat glands are surrounded by capillaries and controlled by both adrenergic and cholinergic nerves. Despite this, sweating is mainly triggered by sympathetic nerves that release acetylcholine. When acetylcholine binds to muscarinic (M3) receptors, it causes calcium ($Ca^{2+}$) to be released inside the cells and allows more $Ca^{2+}$ from outside to enter. This rise in calcium causes potassium ($K^+$) to exit and chloride ($Cl^-$) to enter the duct, which activates sodium-potassium-chloride (NKCC1) cotransporters. These bring sodium ($Na^+$), potassium ($K^+$), and chloride ($Cl^-$) into the cell. With more chloride in the coil, a negative charge helps sodium move between cells, increasing sodium chloride (NaCl) levels. This change creates an osmotic gradient that draws water into the duct through aquaporins. As fluid enters the duct, pressure pushes it to the skin's surface. During its journey through the duct, sodium ($Na^+$) and chloride ($Cl^-$) are reabsorbed, resulting in sweat that's approximately 99% water when it reaches the skin. Sodium reabsorption is driven by $Na^+$-$K^+$-ATPase pumps, forming a gradient that allows sodium to exit the duct through channels. Chloride leaves via cystic fibrosis transmembrane conductance regulators (CFTR). The concentration of ions in sweat

depends on how quickly the primary fluid is secreted and how fast ions are reabsorbed in the duct. Rapid secretion means less time for ion reabsorption, leading to sweat with higher levels of sodium and chloride (50). Acetylcholine is crucial for sweating, which helps us cool down. Research indicates that when acetylcholine is blocked, sweating nearly stops. If the enzyme that breaks down acetylcholine, called acetylcholinesterase, is blocked, we begin to sweat earlier during heat exposure (Cheshire & Freeman, 2003). Other substances released with acetylcholine can also increase sweating. For instance, calcitonin gene-related peptide enhances sweating when combined with substances that act like acetylcholine, though it doesn't cause sweating by itself. Additionally, nitric oxide and cyclooxygenase play a role in boosting sweating when our bodies need to regulate temperature. On the other hand, adrenergic agonists don't play a role in this sweating process. For more details on how eccrine sweat glands function, which are mainly responsible for our sweating, further explanations are available (Cheshire & Freeman, 2003).

**The Cutaneous Vascular Network**

Thermal energy is distributed around the body and traded with the external environment through intricate vascular circuits, with the cutaneous vasculature serving to retain and dissipate heat. In the cold, cutaneous vaso- and vasoconstriction reduce skin blood flow, but the proximity of the veins and arteries in the forearms and legs allows for counter-current heat exchanges, reducing peripherally lost heat (Weinbaum, Jiji, & Lemons, 1984). Reductions in blood flow to the hands and feet are very powerful indeed; maximal vasomotor activity reduces local flows below the metabolic requirement, and the consequences of sustained underperfusion are disabling and include reduced manual dexterity (Abramson, 1965), local pain, and nonfreezing and freezing cold injury (52). In the papillary layer, cutaneous capillaries curve backward toward the skin surface before running downward into superficial venous plexuses. The plexuses are dense, and the capillary blood flow is sluggish, allowing for rapid

thermal equilibration. The capillary densities are far higher in the hands and feet, with heat transfer being mediated by cutaneous arteriovenous anastomoses, thereby forming very good thermal radiators and insulators (53). These anastomotic channels are deeper than capillaries but, having radii ten times larger can produce a ten-thousand-fold increase in blood flow during cutaneous vasodilation if an intravascular pressure change takes place (Poiseuille's law) (54). It has been well established that the dilation of blood vessels in the skin accounts for nearly all of the increase in blood flow to the skin under heat conditions. The remaining slight increase is due to a reduction in vascular constriction during the early stages of heat stress. However, it is important to note that in hairless areas of the skin, such as the hands, feet, and ears, the increase in blood flow primarily occurs due to a reduction in vascular constriction. Although the role of hairless skin in heat dissipation cannot be overlooked, hairy skin plays a more significant role in heat loss due to its larger surface area. Early studies that used skin temperature measurements to estimate blood flow showed that under heat conditions, blood flow in the extremities, such as the legs and arms, increases, and this increase is controlled by vasodilator nerves. Based on these studies, researchers like Roddie and colleagues, as well as Edholm and colleagues, provided stronger evidence for the existence of skin vasodilation under neural control. These studies employed a method known as "venous occlusion plethysmography," which allows for the measurement of blood flow in the limbs without the need for invasive techniques (Edholm, Fox, & Macpherson, 1957). One significant advancement in interpreting these studies was the finding that the increase in blood flow in the forearm under heat conditions occurs solely in the skin layer, with no increase in blood flow in the muscles (54). Roddie and colleagues demonstrated that placing the lower limbs in warm water leads to a slight increase in blood flow in the forearm, which then significantly increases and stabilizes over time (D. Kellogg Jr, Johnson, & Kosiba, 1989). They also showed that if a drug called atropine is injected into the artery before and during severe heat, a marked and sustained increase in blood

flow occurs with a delay and less intensity, but it does not completely stop. In contrast, if atropine is injected after the onset of increased blood flow in the forearm, no reduction in blood flow is observed (55). Edholm and his colleagues showed that interruption of cutaneous nerves before and during heating either prevents or reduces significantly the increase in forearm blood flow (Edholm et al., 1957). These studies showed that vasodilator nerves control blood flow increase with heat, and that initial blood vessel dilation is through cholinergic mechanisms. Prevention of the release of norepinephrine prevents constriction of cutaneous blood vessels in cold but not dilation in heat. Similarly, prevention of cholinergic nerve impulses prevents active dilation of these vessels in heat. The results demonstrate separate nerves for dilating and constricting cutaneous blood vessels, with cholinergic stimuli essential for dilation. Kellogg and co-authors also demonstrated that muscarinic receptor blockade decreases this dilation. These findings generated the "cholinergic co-transmission" hypothesis, which proposes that signaling of cutaneous vasodilation is mediated by molecules other than acetylcholine (D. L. Kellogg Jr, Zhao, Wu, & Johnson, 2012). When examining how skin blood vessels expand, early studies suggested a connection to sweating, known as the 'bradykinin hypothesis.' This idea proposed that sweat glands release an enzyme that boosts bradykinin, leading to vessel expansion. However, further research revealed that blocking bradykinin receptors doesn’t affect vessel expansion in the heat, showing bradykinin isn’t directly responsible (D. Kellogg Jr, Liu, Kosiba, & O’Donnell, 1999). Despite this, the relationship between sweating and vessel expansion isn't ruled out. Researchers found that individuals without sweat glands neither sweat nor experience vessel expansion in heat, indicating a connection (Matthew N Cramer, Gagnon, Crandall, & Jay, 2017). While sweating doesn’t directly cause vessels to expand, studies indicate that stopping increased blood flow to the skin during heat reduces sweating (Daniel Gagnon et al., 2018). Importantly, under normal conditions, changes in skin blood flow or sweating don’t significantly affect body temperature regulation (Nicholas Ravanelli, Jay, & Gagnon, 2017).

**Skeletal Muscles**

Skeletal muscles, part of the third group of effectors, react to rapid heat loss by tightening and then shaking involuntarily (Pozos, Iaizzo, Danzl, & Mills, 1996). This shaking, known as shivering, boosts heat production up to five or six times above normal levels, but this increase can't be maintained indefinitely (Glickman, Mitchell, Keeton, & Lambert, 1967). If the body loses heat faster than it can produce it, it becomes a challenge the body can't overcome (Gale, Bennett, Green, & MacDonald, 1981; Iampietro et al., 1960). Shivering depends on blood sugar, so if blood sugar drops (hypoglycemia), it can shorten how long shivering can effectively help maintain warmth (Castellani & Young, 2016; Tikuisis, Ducharme, Moroz, & Jacobs, 1999).

**Biophysics of Human Temperature in Heat Stress**

Biological tissue structure and function depend on temperature which influences plasma membrane fluidity and transmembrane transport rates while also affecting enzymatic reactions and protein structures (Table 1). Homeothermic humans maintain their tissue temperatures at stable levels. The typical resting temperature range for deep head and thoracic tissues (deep body) is approximately between 36 and 38°C. The maintenance of deep body temperature involves continuous metabolic heat production through endothermy in combination with the regulation of metabolic heat transfer from internal tissues to the surrounding environment. Heat-acclimatized people or those who train aerobically can usually handle deep body temperatures between 38–40°C when exercising or exposed to ambient heat stress (Table 1). When deep body temperatures rise above 40°C they become a potential trigger for heat injury and heat stroke (Bouchama & Knochel, 2002; Shapiro & Seidman, 1990). Protein denaturation takes place in mammalian cells between 40–45°C which leads to protein inactivation followed by cell damage and death (Lepock, 2003; Roti Roti, 2008). Deep body temperatures that exceed 40°C do not always lead to heat illness or injury (Laitano, Leon, Roberts, & Sawka, 2019). "Studies

have shown that esophageal temperatures of 41.6–42.0°C can be reached in unacclimatized, sedated individuals during thermal therapy without causing serious heat-related issues. Similarly, elite endurance athletes often experience deep body temperatures between 41.1 and 41.9°C after competitive races, yet they show no signs of heat illness (Bynum et al., 1978; Maron, Wagner, & Horvath, 1977; Racinais et al., 2019; Robinson, 1963). For athletes, repeatedly pushing their bodies to these high temperatures during training might help them build heat tolerance by boosting the production of heat-shock proteins. These proteins play a key role in protecting other proteins from damage under extreme heat conditions (Table 2) (Bouchama & Knochel, 2002; Yamada, Amorim, Moseley, Robergs, & Schneider, 2007).

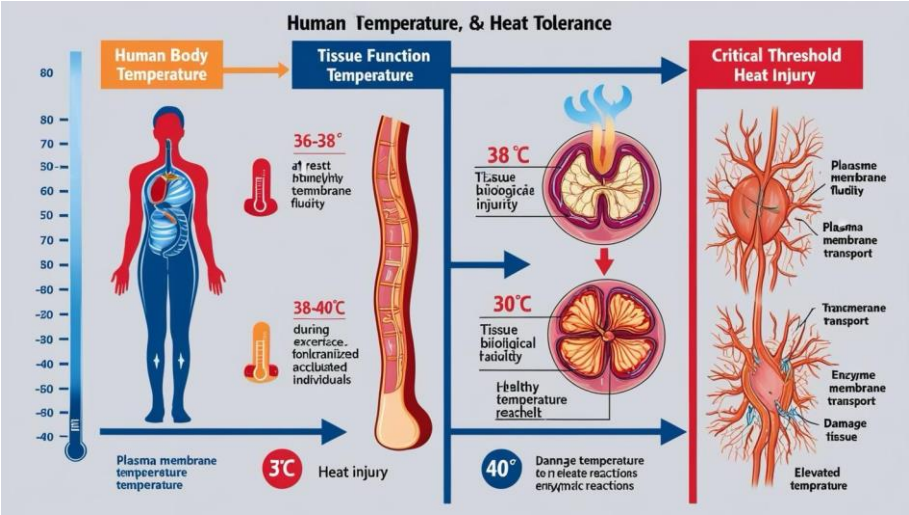


**Figure 1.** The human body maintains stable core temperatures (36–38°C at rest; 38–40°C during exercise) to support vital functions like enzyme activity and membrane transport. Temperatures above 40°C risk protein denaturation and cell damage, though heat-acclimatized individuals (e.g., athletes) can tolerate brief extremes (41–42°C) via protective heat-shock proteins. Optimal plasma membrane fluidity and enzymatic reactions occur within the 36–40°C range, while exceeding 40°C disrupts these processes, potentially leading to heat injury.

**Table 1.** Temperature Effects on Biological Tissues and Heat Tolerance Mechanisms

| Factor | Temperature Range | Physiological Impact | Adaptive Responses |
|---|---|---|---|
| **Normal Deep Body Temp** | 36–38°C | Optimal membrane fluidity, enzyme function, and protein stability. | Homeothermy maintains stability via metabolic heat production/transfer. |
| **Exercise/Heat Stress** | 38–40°C | Increased metabolic rate; manageable in acclimatized individuals. | Enhanced heat dissipation (sweating, vasodilation). |
| **Critical Threshold** | >40°C | Risk of protein denaturation, cell damage, and heat stroke. | Heat-shock proteins (HSPs) protect against protein degradation. |
| **Extreme Cases** | 41–42°C (elite athletes/therapy) | No immediate illness due to acclimatization or controlled conditions. | Repeated exposure upregulates HSPs, improving thermotolerance. |

**Table 2.** Genetic Factors Influencing Heat Tolerance

| Genetic Factor | Mechanism | Evidence/Examples |
|---|---|---|
| **HSP Gene Variants** | Polymorphisms in HSP genes (e.g., HSP70) affect protein protection efficiency. | Higher HSP70 expression linked to better survival in hyperthermic conditions (78, 86). |
| **Ion Channel Mutations** | Altered function of TRPV1 or other thermosensitive channels. | Impacts heat perception and thermoregulatory responses. |
| **Metabolic Genes** | Variations in mitochondrial efficiency (e.g., UCP3). | Influences heat production and energy expenditure during stress. |
| **ACE I/D Polymorphism** | Angiotensin-converting enzyme variants affect circulatory adaptation. | DD genotype associated with improved heat tolerance in athletes (87). |

**Gene-Related Adaptability in Heat Stress**

Thermal stress is a condition in which the body is stressed and strained by increased temperature. For genetic reasons reasons, some people may have a higher sensitivity to temperature variations. These sensitivities can be associated with certain genetic mutations such as in TRPV1, RYR1 and HSP70 which are critical for temperature responses in the body (Mayer & Bukau, 2005). The heat shock protein HSP70, which is essential in defending cells from thermal stress, assists protect cellular proteins and inhibit their degradation when heated. The body's ability to produce these proteins in response to thermal stress can be affected by different mutations in the HSP70 gene (Caterina et al., 1997). Those with certain mutations also might be more vulnerable to hotter conditions. TRPV1 ion channels that sense high temperatures and thermal pain are located on neurons in the skin and other tissues of the body and are important for temperature and pain sensation. Mutations in the TRPV1 gene have been able to change individual sensitivity

to thermal pain and temperature. Specific mutations may bring about strengthened or weakened responsiveness to heat (Nedergaard et al., 2001). UCP proteins contribute to thermogenesis and energy balance, predominantly in mitochondria. These proteins are thought to help regulate body temperature by increasing energy expenditure and heat production from cells. The role of UCP genes and their mutations in thermogenesis (adaptive thermogenesis) and heat stress response (thermal stress) is widely known. The RyR1 receptor in skeletal muscles is involved in calcium regulation and muscle contraction. Mutations in this gene may cause increased sensitivity to thermal stress and contribute to thermal disorders. (Lanner, Georgiou, Joshi, & Hamilton, 2010).

**Physiology of Human Temperature in Heat Stress**

Physiological temperature regulation is a negative feedback control system that recognizes when the set variable is being displaced through sensors that relay information to a controller that sends a command signal to turn on heat loss components to diminish the displacement of the set variable. The set variable of the temperature regulating system is deep body temperature, comprising the temperature of internal organs, including the brain. In people, deep body temperature is commonly taken from the rectum, intestines, and esophagus, but may also be assessed in arterial/venous blood(Werner, 2010). This means that there is no deep body temperature, no golden variable that is the extreme temperature that you "need" to refer to because any measurement represents the diverse thermal dynamics of the site from where the measurement is made under the studied conditions(D. Gagnon, Lemire, Jay, & Kenny, 2010). Moreover, thermal afferents are probably present in each one of these tissues, and these types of afferents together render a complete thermal afferent flow in those types of tissues during heat stress. Thus, this set variable of the person temperature control unit is the compacted space (Andrej A. Romanovsky, 2018). Of temperature in different internal organs that have thermal afferents. When deep body temperature rises, thermal input is conveyed via the spinal cord to the brain, and an efferent command emerges to trigger heat loss mechanisms arising from cutaneous vasodilation and sweating. Within this context, to activate thermoeffector heat loss, there is a prerequisite ‘load error’ that must reach a certain threshold before thermoeffetor signals are engaged (Werner, 2010). But, once turned on, the term effector output for heat loss increases in proportion to the rise in body

temperature until steady-state or maximum values are reached(Pearson et al., 2012). The activation of thermoeffector heat loss alters the heat exchange between the body and the environment, thereby minimizing the increase in deep body temperature, which is continuously adjusted to the output of the thermoeffector for heat loss(McCaffrey, Wurster, Jacobs, Euler, & Geis, 1979). As well as deep body temperature, skin temperature is one of the contributors to the thermoregulatory flow (the flow of sensory nerves, which regulate the temperature) during exposure to heat stress. Nonetheless, skin temperature is regarded as a secondary variable, since the time response of thermoeffectors and their higher performance regarding a certain thermoregulatory flow change depend on alterations in deep body temperature. During heat stress, a higher skin temperature increases the time of activation and output of the heat loss thermoeffectors, whereas a lower skin temperature decreases the activation and output to elicit a set increase in deep body temperature (MacIntyre, Bullard, Banerjee, & Elizondo, 1968). The influence of skin temperature is neurally mediated and cannot solely depend on some peripheral micro- or mesomesoscopic signal in humans. While elevated skin temperature strengthens the drive to sweat, studies have also documented that the responsiveness of eccrine sweat glands can be influenced by local skin temperature. Finally, heat-sensitive receptors may be present in skeletal muscle, helping to shape the thermoregulatory flux during heat stress, especially during exercise(Ogawa, 1970). As explained (in the subsequent section), indirect evidence has supported this possibility (though it is still unclear if it should be considered a regulated variable or auxiliary variable) within the human thermoregulation system (Wingo et al., 2010). Thermoeffectors that modulate heat loss are summarized in the following sections. Emphasis will be placed on human studies, although studies performed in animal models will be mentioned as warranted because these pathways have been studied almost exclusively in such models.

## Neural Elements of the Human Temperature Regulation System

### Afferent Pathways in Heat Stress

Scientists started noticing how sensitive animals are to heat pretty early on, especially when they looked at how skin temperature affects the body's cooling mechanisms when the brain gets warmer. If you warmed up an

animal's brain in a comfortable room, they'd start trying to cool down(Hardy, 1961). But, if you did the same experiment in a warm room, they'd cool down even more at the same brain temperature (Harold T Hammel & Pierce, 1968). This led researchers to think that our bodies regulate temperature based on a mix of 'internal' heat (from our brain and deep tissues) and 'external' heat (from our skin) (HERBERT Hensel, 1959). Interestingly, some people back then thought skin temperature was the main driver of cooling. This idea sparked some important research by Benzinger in the late 1950s and early 1960s (Benzinger, 1961). He showed that in humans, it's deep body temperature, like the temperature of the eardrum that kicks off the cooling process (Benzinger, 1959). Skin temperature, he argued, just fine-tunes how much cooling happens at a given deep body temperature. Benzinger even went so far as to say that skin temperature sensors weren't involved in actual temperature regulation and only contributed to feeling cold. This makes sense when you consider that back then, they only knew about skin sensors that fired more when the skin got cold, and less when it got warm (Benzinger, 1959, 1961). Later on, though, researchers discovered skin sensors that increased their activity when skin warmed up, first in cats and monkeys, and then in humans. At the same time, animal studies found heat-sensitive areas in other parts of the body, like the spinal cord, intestines, stomach, and muscles (Hallin, Torebjörk, & Wiesenfeld, 1982). However, we still don't have a lot of solid evidence for these heat-sensitive areas in humans (Konietzny & Hensel, 1977). Bin et al. found that a 24-degree (cutaneous temperature measured) moderate-intensity exercise bout yielded greater whole-body sweat acquisition from ingesting 37-degree (internal body temperature) water versus hot (50 degrees C) or cold (10 degrees C and 0 degrees C) (Morris, Bain, Cramer, & Jay, 2014). In addition, some of the studies identify that thermal receptors are also found in skeletal muscle. However, while the previously noted studies rely upon increased sweating and increased/decreased internal temperature concomitantly with exercise, no attention is drawn to alternate exercise-induced responses that promote sweating, such as central command (from muscle activation) and the local sudomotor response of the muscle(Todd, Gordon, Groeller, & Taylor, 2014). One study has 8 subjects who cycle in a semi-recumbent position for 35 minutes at 25 degrees centigrade at a constant load until whole-body thermal and sudomotor homeostasis is reached. Thereafter, a 24-minute series of sinusoidal load perturbations (three bouts of 8 minutes) occurs before they return to a 20-minute steady state of exercise.

The rate of forehead sweating was independently compared with esophageal temperature, mean skin temperature, and intramuscular temperature (intramuscular temperature in the vastus lateralis muscle). Sinusoidal patterns in sweating were strongly correlated with both intramuscular temperature and esophageal temperature but did not differ between temperatures(M. Shibasaki, Wilson, & Crandall, 2006). Intramuscular temperature rise also led to sweat secretion, although the phase delay between muscle heating and sweating was much shorter than that of esophageal temperature-induced sweating. The endpoint of this research suggested that heating feedback from muscle may play a part in controlling thermal sweating. The time association between eccrine sweating and intramuscular temperature, as well as the relatively shorter phase delay between them, indicate the existence of heat-sensitive components in skeletal muscles that may interact with integrative centers for thermal sweating. Different body tissues respond to heat thanks to special neurons. These neurons are found in both our central and peripheral nervous systems. The axons of these neurons are called unmyelinated C fibers. Studies from the 1950s to 1970s mainly describe how these fibers work. This text describes how our bodies sense heat through features that maintain stable responses to temperature changes and are not affected by touch (H. Hensel, 1974). The ability to perceive heat primarily involves transient receptor potential (TRP) channels in our cells. These channels open in response to temperature changes, allowing charged particles to enter, which leads to the generation of signals known as action potentials. Researchers first studied these channels in laboratory settings, focusing on the vanilloid receptor subtype 1 (TRPV1), which responds to painful heat at about 45 degrees Celsius. Other related channels, such as TRPV3, TRPV4, TRPM2, and TRPA1, also respond to heat and help us feel warmth. They cover a temperature range from harmless (30–40 degrees Celsius) to painful (>42 degrees Celsius). Research on how these channels operate at normal body temperatures or harmless heat has mainly been done using animal models (Jeon & Caterina, 2018). These studies look at animals' temperature preferences rather than automatic heat responses, resulting in mixed views on which channels detect harmless heat. Nonetheless, TRPV1 and TRPM2 are considered crucial for responding to non-painful heat sensations. TRPV1 is a protein in the body with a complex role. There's evidence that it may not be crucial for detecting harmless heat. It only activates at temperatures over 42 degrees Celsius in lab conditions, is rarely found in the brain, and isn't present

in the preoptic area of the hypothalamus (POAH) (Xiao & Xu, 2021). Mice that lack TRPV1 don't show problems with regulating their body temperature. However, when capsaicin, which activates TRPV1, is applied to the skin of mice, it stimulates neurons in the POA that are sensitive to heat and help manage heat stress. Around 10% of certain neurons in the trigeminal ganglion that have TRPV1 respond to harmless heat between 35 and 42 degrees Celsius. If these neurons are blocked in mice, it disrupts their ability to perceive heat differences. Another protein, TRPM2, seems important for sensing harmless heat, as neurons with TRPM2 activate between 34 and 42 degrees Celsius. Mice without TRPM2 find it difficult to avoid warm areas, like those at 38 degrees Celsius (Nakamura & Morrison, 2010). Neural connections about temperature regulation during heat stress. Primary somatosensory neurons situated in the skin and viscera, which gather and send information to the brain through the spinal cord, are responsible for temperature regulation. In rodents, dorsal horn neurons send projections to a brainstem nucleus located on the border between the pons and midbrain (LPBd). Activation of these neurons leads to the activation of neurons in the median preoptic nucleus (MnPO) region of the hypothalamus. The incremented activity of warm-sensitive neurons in the MnPO region increases the amount of inhibitory input to the paraventricular hypothalamus (PVH) and medial preoptic area (MPA) that provide tonic excitatory input to the dorsomedial hypothalamus (DMH)(Nakamura & Morrison, 2010). Ventral lateral preoptic area (vLPO) neurons have also been shown to be activated by harmless warming, which results in greater inhibitory input to the DMH. The notable greater portion of inhibitory DMH is because of the decreased excitatory drive to the raphe pallidus area (RPa) of the brainstem, which traditionally sends an excitatory drive to the preganglionic neurons that control the cutaneous vasoconstriction (VC) and thermogenesis. This leads to control of this pathway that passively increases skin blood flow (SkBF) and decreases heat production(Cechetto, Standaert, & Saper, 1985). On the other hand, the pathways of the human body that control the thermoeffector responses to heat loss are not yet known(Cheng, Chen, Cao, & Guo, 2016). Neuroimaging has shown that the hypothalamic preoptic area (POA) as well as a brainstem juxtafacial nucleus coordinates thermoregulation under heat stress, and the pattern of activation corresponds to the sweating output. Yet sweating output is only a shortcut to initiate certain heat loss thermoeffectors in human’s active cutaneous vasodilation (VD) and eccrine sweating production as relevant for humans,

not the suppression of cold-defense behaviors like those seen in rodents when stressed by cold. Thus, the takeaway distinctions relative to the neurocircuitry for cold-defense response link in mammals for application to humans need to be made.

**Warm Thermoafferent Feedback during Heat Stress**

We don't fully grasp how our nerves regulate heat loss. Studies in rodents indicate that temperature control involves direct signals from neurons in the hypothalamus to those in the brainstem, which manage blood vessel constriction and heat production (Hardy, 1961). In humans, however, this direct signaling doesn't appear to cause sweating or skin blood vessels to widen (H. T. Hammel, 1968). This implies humans might have distinct methods of temperature regulation that we haven't yet understood. Scientists suggest that the hypothalamus may cause heat loss indirectly through another brainstem component. In the cat, an excitatory pathway from the hypothalamus to the ventrolateral medulla has been shown using electrical stimulation. This suggests that the hypothalamus can assist in the control of heat loss mechanisms through this pathway(A. A. Romanovsky, 2004). Based on the assumption that glutamate, an excitatory amino acid, excites neurons but not axons, areas of the medulla that have been localized (between the facial nucleus and medullary triangle) are proposed as a synaptic intermediary in the neural pathway to induce sweating of the paws of cats. Moreover, a comparable region adjacent to the face (juxta facial) has also been found to become active during human sweating, and the theory is that this region could be linked directly to the sympathetic preganglionic neurons for the control of sweating(Andrej A. Romanovsky, 2018). That is, upon a temperature rise, sweat gland activity is increased, along with the modification of blood flow within the skin (Cabanac, 1979). This implies that the body responds to heat in two ways simultaneously. One of these studies measured these temporal relationships and concluded that 70 percent of the multi-unit bursts of SSNA were associated with transient changes in both skin blood flow and sweating, but just 1 percent and 10 percent were associated with transient changes in skin blood flow or sweating separately. That is, the majority of these neural activities occur concurrently with perfusion and perspiration changes. While the existence of postganglionic pseudomotor neurons has been determined through quantification of single-unit neural activity, no one is certain as to whether the dilation of cutaneous blood vessels is under the active control of

a distinct and separate population of postganglionic neurons or if this effect is realized via the same nerves innervating the eccrine sweat glands (Nakamura & Morrison, 2010). Whereas sweating has not had any studies dealing with potential efferent pathways to control active cutaneous vasodilation in human beings, despite minimal understanding of the efferent pathways between the hypothalamus and the brainstem for the control of heat loss mechanisms, the efferent neural signals produced by them have been dealt with. In human beings, sympathetic skin nerve activity (SSNA) is recordable directly from peripheral nerves using microneurography. The majority of the recordings have been multi-unit recordings of SSNA, which may be composed of activity from cutaneous, sudomotor, and possibly piloerector neurons. It is possible, though, that the increase in multi-unit SSNA during heat stress is mainly the result of augmented activity from cutaneous vasodilators and sudomotor neurons (Song et al., 2016). At the initiation of the transition from a thermoneutral to a warm environment or at the beginning of whole-body passive heat stress, a decrease in SSNA is typically observed, likely because of the elimination of cutaneous vasoconstriction. As heat stress proceeds, SSNA activity can turn off before it reappears after body and skin temperatures have passed a certain threshold for onset (Tan et al., 2016). Above this onset threshold, SSNA increases linearly with further elevations in core body temperature until it plateaus or achieves a peak response when no further increase in SSNA is measurable despite a continued rise in core body temperature. The increase in SSNA during heat stress ultimately leads to the release of neurotransmitters from postganglionic nerve terminals that target the effector organs for heat loss at the synapse. In agreement with this, the threshold for the increase in SSNA precedes the onset threshold for cutaneous vasodilation and sweating during whole-body passive heat stress. It is noteworthy that one study recorded single-unit SSNA from pseudomotor neurons during heat stress, which revealed that pseudomotor neurons are low probability firing and exhibit rhythmic cardiac and respiratory patterns (Nunneley et al., 2002). It is of interest that multi-unit SSNA bursts are primarily preceded by changes in skin resistance (sweat output), which implies that multi-unit SSNA bursts are largely due to the activation of sudomotor neurons. Later work, however, observed that most multi-unit SSNA bursts with modest body warming are preceded by a skin blood flow transient and body sweating (Egan et al., 2005). This kind of study quantified the temporal relationships and discovered that

70 percent of multi-unit SSNA bursts were accompanied by a transient alteration in skin blood flow and sweating, whereas 1 percent and 10 percent of the bursts were linked with a transient alteration in blood flow or skin sweating individually. Although the presence of postganglionic pseudomotor neurons has been identified from single-unit recordings of SSNA, it remains unclear whether active cutaneous vasodilation is mediated by a distinct and unique set of postganglionic neurons or through the same nerves that innervate the eccrine sweat glands. Studies examining the temporal relationship between bursts of multi-unit SSNA and thermoregulatory output have observed some multi-unit bursts that are only followed by an increase in skin blood flow (Michael J Farrell, Trevaks, Taylor, & McAllen, 2015). Such observations may suggest that cutaneous vasodilation is activated by a separate pool of postganglionic neurons, although a caveat to this possibility is that such bursts may represent a minority of multi-unit SSNA activity during heat stress. However, studies examining the temporal relationship between multi-unit SSNA bursts and thermal effect output generally utilized very mild levels of thermal stress, which increased the likelihood that active cutaneous vasodilation did not occur and that transient changes in skin blood flow reflected the output of cutaneous vasoconstriction. During moderate body heat that induces active cutaneous vasodilation, it has been shown that part of the multi-unit SSNA signal is preferentially associated with cutaneous vasodilation. Kamijo and colleagues recorded multi-unit SSNA during passive thermal stress in young adults who were normovolemic or hypovolemic. This study investigates sympathetic skin nerve activity (SSNA) during passive thermal stress in youth who either had normal blood volume (normovolemic) or blood volume deficiency (hypovolemic) (M. J. Farrell, Trevaks, & McAllen, 2014). The elevation of SSNA that was noted in both groups showed that passive thermal stress resulted in an elevation of multi-unit SSNA. In a single study, a component of the SSNA signal accounted for approximately 20% of the total SSNA and exhibited synchronization with the cardiac cycle. The hypovolemic group exhibited less augmentation in this component of the SSNA signal during thermal stress, whereas the remainder of the SSNA signal, not synchronized with the cardiac cycle, was similar in both groups. The hypovolemic group also exhibited reduced cutaneous vasodilation during thermal stress, although there was no difference in sweating. Further experiments demonstrated that the cardiac-cycle-related component of the SSNA signal declined during thermal stress and head-up tilt but rose following

rapid saline infusion in hypovolemic subjects. These results indicate that active cutaneous vasodilation and sweating can be regulated by distinct afferent neural pathways.

**Heat Stress and Aerobic Capacity**

Aerobic exercise stimulates cardiovascular and metabolic reactions that enhance oxygen delivery and utilization. Aerobic exercise also stimulates deep body temperature and sweating, which are significant for thermal adaptation. Heat-acclimatized and aerobically trained (high V̇O2max) subjects thus exhibit similar thermoregulatory adaptation during exercise under heat (Hellsten & Nyberg, 2015). Piwonka et al compared thermoregulatory adaptations to exercise-heat stress in untrained and well-trained individuals. Untrained participants experienced a rising deep body temperature to 39.4°C over an 85-minute walk on the treadmill under hot, dry conditions (40°C, 25% RH), whereas well-trained runners leveled out at 38.2°C. Gisolfi and Robinson then(Gisolfi & Robinson, 1969) showed that basal rectal temperature fell and rectal temperature, skin temperature, and heart rate gains were lowered through 6 weeks of interval running in temperate conditions. Findings suggested that well-trained runners were "reacclimatized" due to the stimulation of daily thermoregulatory response by training and competition (Piwonka, Robinson, Gay, & Manalis, 1965). Subsequent studies have repeated these findings, showing that fitter individuals with higher V̇O2max have superior heat tolerance and thermoregulatory competence compared to less fit subjects. In the 1970s, Nadel et al. and others demonstrated that 10 days of moderate-intensity training in a temperate environment enhanced the sweating response thermosensitivity (Nadel, Pandolf, Roberts, & Stolwijk, 1974). Adaptation was related to increased whole-body sweating for heat stress due to peripheral modification at the sweat gland level, which could involve increased responsiveness to cholinergic stimulation, possible hypertrophy of sweat glands, increased density of muscarinic receptors, or reduced activity of acetylcholinesterase(K Sato & Sato, 1983). While these findings highlight peripheral mechanisms, the potential role of increased neural temperature regulation by training cannot be excluded and is not examined. This article emphasizes that individuals with greater fitness levels (based on V̇O2max) exhibit heightened sudomotor (sweat) responsivity, which leads to heightened evaporative heat loss during exercise heat stress. Direct calorimetry

experiments by Lamarche et al found that high V̇O2max men and women showed higher rates of evaporative heat loss at higher rates of metabolic heat production (400–500 W in men, 325–400 W in women) than low-fitness subjects. High-fitness groups also showed lower esophageal temperatures during maximum heat loads, indicating better thermoregulation(Lamarche, Notley, Louie, Poirier, & Kenny, 2018). These findings show that trained individuals are more sweat-sensitive and possess a larger capacity for heat dissipation, particularly with elevated heat stress. Ravanelli et al examined the effect of an 8-week aerobic training program on thermolytic capacity by measuring the critical environmental limit for heat balance during exercise in the heat(Nicholas Ravanelli et al., 2017). Subjects cycled at 450 W in 37.5°C and 31% relative humidity, with increased ambient vapor pressure progressively until an upward inflection in esophageal temperature signaled the transition from compensable to uncompensable heat stress. Upon training, the break vapor pressure had risen from 2.98 to 3.42 kPa, showing an elevated capacity for evaporation. The elevation was the result of enhanced maximum evaporative capacity (ωmax, from 0.72 to 0.84), even as a reduced skin-air vapor pressure gradient was experienced following training. The findings reveal that training enhances evaporative heat loss by increasing the rate and density of activated sweat glands, the skin coverage area for sweat, and the ability to maintain heat balance under increased heat stress. A study conducted by Roberts et al first investigated the impact of aerobic training on the cutaneous vascular response to heat stress. After a 10-day training program, the threshold for the onset of forearm blood flow was reduced for deep body temperature, but the thermosensitivity of the response was not affected(Roberts, Wenger, Stolwijk, & Nadel, 1977). This adaptation was later found to be independent of changes in vasoconstrictor activity but perhaps linked to an increase in blood volume. Although an earlier onset of skin blood flow would theoretically enhance deep body-to-skin heat transfer, the magnitude of this adaptation is typically offset by a concomitant reduction in basal deep body temperature(Fritzsche & Coyle, 2000). This means that the relative stimulus for the increase in skin blood flow is unchanged after aerobic training, indicating that the overall thermoregulatory response is preserved despite these adaptations. Fritzsche and Coyle wrote that the trained participants showed more cutaneous and forearm blood flow responses than the untrained participants while cycling at relative intensities (50, 75, and 90% of V̇O2max)(Fritzsche & Coyle, 2000). However, this difference resulted

from their greater heat production and heat loss requirements at these intensities. In comparison to an equivalent absolute rate of heat production (9 W/kg), there were no variations in blood flow between the trained and untrained subjects. This indicates that the larger blood flow in the trained subjects is a result of their increased ability for heat production and not an adaptation to thermoregulation. Intrinsic microvascular changes that result from aerobic exercise training are enhanced endothelium-dependent cutaneous vasodilation and enhanced nitric oxide bioavailability, as evidenced by augmented responses to acetylcholine and local heating (Piwonka et al., 1965). These changes are probably mediated by increased hemodynamic shear stress and temperature; however, the contribution of temperature may be limited in temperate training conditions. As Simmons et al. observed and Fritzsche and Coyle's results corroborate, these changes would benefit most individuals with cardiometabolic disease, in which compromised vasodilation and decreased cutaneous blood flow impair thermoregulation. In the absence of disease, the real-life relevance of such adaptations, nevertheless, appears to be minimal (Fritzsche & Coyle, 2000). Complete acclimatization to heat necessitates daily exposure to physical exertion and external thermal loads that importantly increase core body and surface skin temperatures, producing profuse perspiration. Physical exertion carried out in temperate climates, even in highly trained athletes, does not adequately increase skin temperatures to maximally enhance adaptive capacity (Avellini, Shapiro, Fortney, Wenger, & Pandolf, 1982). For example, 4-day heat acclimatization at 50°C brought about additional improvement, which included greater evaporation of sweat and reduction of rectal temperature, skin temperature, and heart rate in athletes(Hessemer, Zeh, & Brück, 1986). Non-active individuals are helped the most by tough exercise regimens that bring about exceptional thermal stress, for instance, interval training that reduces rectal temperature, skin temperature, and heart rate with heat stress (Tsang, Frazer, & Hlastala, 2000). Low-intensity exercise, which minimally elevates body temperature and sweating, results in small gains, which are most likely due to enhanced muscular efficiency but not true thermoregulatory adaptation. Cold temperature exercise (e.g., swimming) increases $\dot{V}O_2max$ but not thermoregulatory adaptation, as it guarantees that heat adaptation is based on elevated body temperature and sweating and not on increased fitness or $\dot{V}O_2max$ (N. Ravanelli, Gagnon, Imbeault, & Jay, 2021; Tsang et al., 2000).

**Heat Stress Reactions during Exercise at %V̇O2max**

Research in the 1960s by Åstrand and Saltin and Hermansen determined that the variability observed among individuals in deep body temperature during exercise was reduced when exercise intensity was expressed as a set percentage of V̇O2max (relative intensity) compared to absolute oxygen uptake (V̇O2)(Astrand, 1960). Earlier studies by Christensen and Nielsen had shown that response rectal temperatures are associated with absolute exercise intensity, and thus trained subjects, with higher absolute V̇O2 and heat production, should have higher deep body temperature at the same %V̇O2max. It was argued, however, that their higher heat production is matched by heightened thermolytic capacity, e.g., higher sweat rates and skin blood flow, as a result of training. Therefore, it was customary to compare thermoregulatory responses at the same relative intensities, even in groups differing in their levels of V̇O2max(Mora-Rodriguez, 2012). The hypothesis that %V̇O2max has an independent influence on deep body temperature responses, as well as heat production, has been tested and refuted by strict research attempts. Jay et al used a comparison of subjects with high (approximately 60 mL $O2 \cdot kg^{-1} \cdot min^{-1}$) and low (approximately 40 mL $O2 \cdot kg^{-1} \cdot min^{-1}$) V̇O2max in cycling at 60% of their individual V̇O2max. The groups were well-matched in terms of body size to minimize confounding factors. The high-V̇O2max group, having greater heat production and evaporative requirements (Ereq), had greater deep body temperatures and sweat rates(Coombs, Cramer, Ravanelli, Imbeault, & Jay, 2017). When, however, both groups exercised at the same absolute heat production (∼540 W), the difference in %V̇O2max (40% vs. 58%), there were no differences in deep body temperature or sweat rate. The same has been seen in treadmill studies(Smoljanić, Morris, Dervis, & Jay, 2014). Experiments involving the use of hypoxia to manipulate %V̇O2max within the same subjects corroborated these findings. Coombs et al had participants cycle at ∼90 W (∼475 W heat production) in normoxic (45% V̇O2max) and hypoxic (62% V̇O2max) conditions. Core body temperature and sweat rates were equal, and heat production and energy expenditure requirements (Ereq) were not significantly different, despite the disparity in %V̇O2max. Conversely, when exercise was performed at 45% normoxic and hypoxic V̇O2max, hypoxia caused lowered deep body temperature and sweat rate via lowered work rate and heat production. The findings indicate that heat production, and not %V̇O2max, is the major determinant of deep body temperature and sweat rate

response to exercise. They highlight that exercise thermoregulatory responses to moderate heat stress are regulated by the heat production rate and not relative exercise intensity (%V̇O2max)(M. N. Cramer et al., 2022). Experiments were conducted in physiologically compensable environments with 100% evaporative efficiency of sweat, such that variations in maximal evaporative capacity (Emax) or evaporator capacity required (ωreq) did not influence results. The findings are in consonance with earlier observations of Christensen, Nielsen, and others that the deep body temperature and sweat rate responses are regulated to a great extent by the total heat production(Jay, Bain, Deren, Sacheli, & Cramer, 2011). Thus, for the purpose of enabling meaningful comparison of the thermoregulatory response among body size groups of similar composition, an equal absolute rate of heat production unrelated to V̇O2max is a prerequisite during exercise.

**Conclusion**

Heat stress during exercise triggers complex physiological responses aimed at maintaining thermal homeostasis, including sweating, cutaneous vasodilation, and cardiovascular adjustments. These mechanisms are influenced by intrinsic factors such as genetic predisposition (e.g., HSP70, TRPV1, and UCP variants) and extrinsic adaptations like aerobic fitness ($\dot{V}O_2max$) and heat acclimatization. While elevated core temperatures (>40°C) pose risks of protein denaturation and heat injury, certain populations—such as elite athletes and heat-acclimatized individuals—demonstrate remarkable tolerance to extreme temperatures (41–42°C), likely due to enhanced heat-shock protein expression and optimized thermoregulatory efficiency. Aerobic capacity plays a pivotal role in heat tolerance, with trained individuals exhibiting superior sudomotor activity, evaporative cooling, and cardiovascular stability under thermal stress. However, thermoregulatory responses are primarily governed by absolute metabolic heat production rather than relative exercise intensity ($\%\dot{V}O_2max$), emphasizing the need for standardized comparisons across fitness levels. Morphological factors (e.g., body mass, surface area-to-mass ratio) further modulate heat exchange, while neural and vascular pathways fine-tune effector responses. In spite of progress, there remain gaps in our knowledge regarding the neural circuits of human thermoregulation, genetic adaptation in humans, and long-term consequences of repeated heat stress. Future research priorities include: molecular mechanisms – role of TRP channels and HSPs in heat sensitivity;

clinical applications – interventions in vulnerable groups (the elderly, sedentary, patient populations); environmental interactions – heat acclimatization protocols for manual work, sport, and climate change resilience. Overall, genetic, physiological, and environmental factors dictate the response to heat stress. These findings, when combined, can enhance safety measures, optimize sports performance, and reduce heat-related threats in a warming world

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