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STATE OF THE ART
REVIEWS

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Heat, Athletes, and Immunity

Abstract: *During exercise, body temperature rises as a result of increased energy metabolism and heat absorbed from the environment. In response to this rise in body temperature, blood flow increases and stress hormones are released. Together, blood flow and stress hormones stimulate increases in the number of circulating leukocytes and alterations in various aspects of immune function, including cytokine production. The extent of changes in leukocyte numbers, cytokine concentrations, and immune cell function depends on how high body temperature rises and the intensity and duration of exercise. In general, increases in body temperature of ≤1.8°F (1°C) induce mild changes in immune function, and such changes are unlikely to increase the risk of illness in athletes, firefighters, and military personnel who regularly exercise in hot conditions. More severe immune disturbances during exercise in extreme heat (≥106°F or 41°C) may contribute to classical symptoms of heatstroke.*

Keywords: hyperthermia; heatstroke; cytokines; inflammation; lipopolysaccharide

During exercise in hot weather, the body absorbs heat from the environment (Figure 1). In addition, metabolic reactions to sustain energy production during exercise raise body temperature. Approximately 40% of energy derived from the metabolism of glucose and free fatty acids is used to fuel muscle contractions, whereas the remaining 60% is converted to body heat. In response to increases in body temperature during exercise, cardiac output increases to deliver more blood to contracting muscle and also to the skin for convective and evaporative cooling.

Alterations in immune function during exercise in the heat have important implications for athletes, military personnel, and firefighters. Strenuous exercise can increase the risk of developing upper respiratory illness,[1-4] and immune changes during exercise in the heat may contribute to the symptoms of heatstroke.[5] Immune changes in response to exercise in the heat may be due to a variety of factors, which include the following[6]:

- A direct effect of elevated body temperature
- Stress hormones released in response to elevated body temperature
- Stress hormones released independently of changes in body temperature
- Blood flow and leukocyte trafficking
- Oxidative stress
- A combination of these factors.

Particular attention has focused on the role of stress hormones in regulating changes in the immune system during exercise in hot conditions. Catecholamines released from the adrenal medulla, such as epinephrine and norepinephrine, regulate changes in cardiac output and blood flow during exercise in the heat (Figure 1). Exercise in the heat also stimulates the release of cortisol from the adrenal cortex and growth hormone from the pituitary gland. These physiological responses to exercise in the heat influence the immune system during exercise in the heat in 2 main ways. First, increased blood flow and stress hormones mobilize leukocytes from bone marrow and also from the endothelial surface of blood vessels in the lungs. Second, by binding to surface receptors on immune cells, stress

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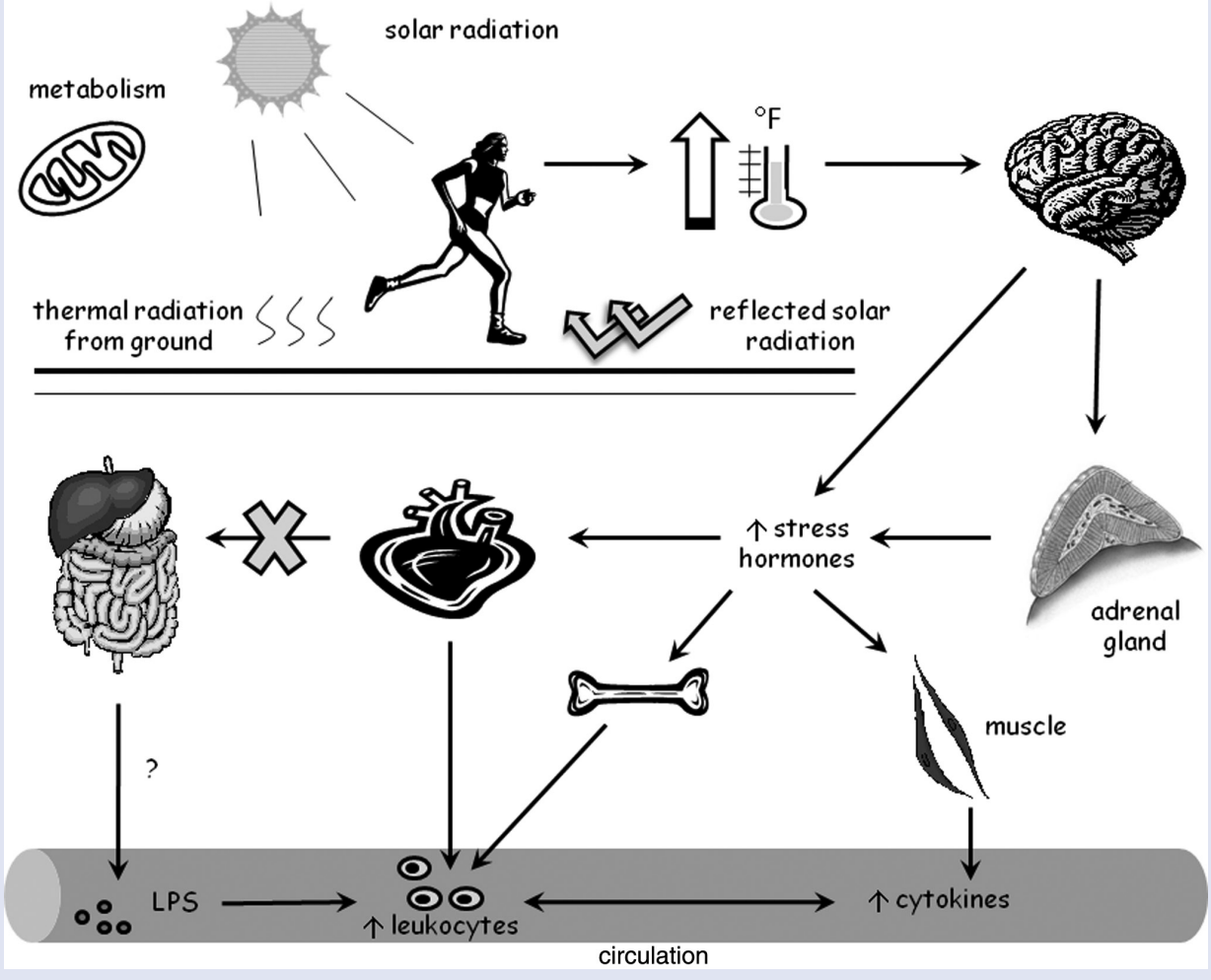
Figure 1.

Flow diagram indicating processes of heat gain, hormonal changes, and blood flow that regulate immune changes during exercise in the heat. A rise in body temperature stimulates the hypothalamus and adrenal gland to release stress hormones such as catecholamines, growth hormone, and cortisol. These stress hormones alter cardiac output and blood flow to the gastrointestinal tract, skeletal muscle, and skin. Increased blood flow mobilizes leukocytes from bone marrow and the endothelial lining of blood vessels. Cytokines, such as interleukin-6, are also released from muscle into the circulation. Lower blood flow to the gastrointestinal tract may cause leakage of lipopolysaccharide into the circulation, which may in turn stimulate leukocytosis and systemic cytokine production.



hormones alter signaling pathways within these cells that modulate the functional activity of these cells. Cytokines produced by immune cells in response to a rise in body temperature may also influence circulating leukocyte numbers and immune cell activity in an autocrine and paracrine manner. Exercise in hot conditions also increases oxidative stress,[7] and oxidative stress may alter some aspects of immune function, such as cytokine production.[8,9]

The purpose of this review is to provide a brief summary of the effects of heat stress and exercise on the distribution and activity of various types of immune cells. The potential role of exercise-induced immune changes in heat injury is also discussed. Interested readers are directed to other reviews for more comprehensive information.[5,6]

Passive Heating and Circulating Leukocytes

To understand the influence of body temperature on the immune system, several studies have investigated the influence of passive heating of humans on

Table 1.

Effects of Passive Heating on Circulating Leukocyte Subsets

Passive Heating	Difference in Body Temperature	% Difference in Cell Counts Immediately After Heating	Reference
1 h 20 min sitting in water at 102°F vs 73°F (39°C vs 23°C)	3°F (1.6°C)	Lymphocytes 20% higher Neutrophils 15% higher Monocytes 75% higher	10
3 h sitting in air at 104°F vs 73°F (40°C vs 23°C)	1.6°F (1°C)	Lymphocytes similar Neutrophils similar Monocytes similar	27
2 h sitting in water at 101°F vs 96°F (38.5°C vs 35.3°C)	4°F (2.3°C)	Neutrophils 60% higher	12
2 h sitting in water at 103°F vs 94°F (39.5°C vs 34.5°C)	5°F (2.3°C)	Lymphocytes 30% higher Neutrophils 40% higher Monocytes similar	13

the number of various different cell types in the circulation. In general, these studies have investigated changes in circulating leukocyte numbers between sitting in air or water 95°F to 113°F (34.5°C-45°C). Among these studies (see Table 1), circulating leukocyte numbers appear to increase only when body temperature exceeds 100°F (38°C), which is similar to body temperatures observed during strenuous exercise.[10-13] Changes in the numbers of lymphocytes, granulocytes, and monocytes with passive heating are variable; none of these cell types are individually responsive to heat stress. Growth hormone and the chemokine granulocyte-colony stimulating factor (G-CSF) mediate the leukocytosis that occurs with passive heating in humans[14] and mice.[15] In contrast, cortisol and β-adrenergic and β-endorphin receptors do not influence leukocytosis to the same extent.[14,15]

Passive Heating and Circulating Cytokines

Cytokines represent a group of proteins that mediate cross-talk between different cells of the immune system and the release of immune cells from bone marrow. They are an integral component in the inflammatory responses to infection and tissue injury. Passive heating of humans for 1 to 2 hours at 101°F to 103°F (38.5°C-39.5°C; raising body temperature to ≥101°F or 38.5°C) increases the plasma concentrations of the proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 and the chemokines G-CSF and IL-8.[12,16] The cellular sources of these cytokines likely include T helper 1 lymphocytes and macrophages.[17] G-CSF and IL-8 mobilize neutrophils in the circulation[18,19] and may therefore partially regulate the neutrophilia that occurs with a rise in body temperature.[15]

Passive Heating and Immune Cell Function

The effects of passive heating on neutrophil function are equivocal. Some researchers have reported that 2 hours of passive heating of humans at 101°F (38.5°C; raising body temperature to 101°F or 38.5°C) reduces neutrophil production of the proteolytic enzyme elastase.[12] In contrast, others have reported that 6 hours of passive heating of cancer patients at 107°F (41.5°C) raises neutrophil bactericidal capacity,[20] whereas 2 hours of passive heating of humans at 103°F (raising body temperature to 103°F) does not alter neutrophil production of reactive oxygen species.[21] Some of this disparity may be due to differences in the temperature and period of heat exposure. The effects of passive heating on lymphocyte, monocyte, and natural killer cell functions are more consistent. Hyperthermia increases the production of the cytokines IL-1, IL-2, and interferon (IFN)-γ by lymphocytes and monocytes stimulated with mitogens in both healthy humans and cancer patients.[11,22] Hyperthermia also stimulates natural killer cell activity.[13,22,23] These immune-stimulatory effects of hyperthermia may be useful in the treatment of cancer patients. The systemic factors that enhance the function of lymphocyte, monocyte, and natural killer cells following hyperthermia are uncertain. Blocking the actions of stress hormones does not alter natural killer cell activity in response to passive heating.[14] Autocrine or paracrine factors may therefore play a role.

Exercise, Heat Stress, and Circulating Leukocytes

Compared with passive heating, exercise in hot conditions raises body temperature to at least the same extent but stimulates a stronger stress hormone response.[24] This greater stress hormone response to exercise likely reflects greater demand for blood flow to contracting skeletal muscle to support oxygen, fuel mobilization, and provide nutrient supply and also to the skin for cooling. Several studies have investigated whether exercise in the heat promotes leukocytosis. The results from these studies generally demonstrate that circulating leukocyte numbers increase when body temperature increases ≥1.8°F (1°C) during exercise in the heat (Table 2).[10,25-27] Lymphocytes and monocytes tend to increase to a greater extent than neutrophils following exercise in the heat. In contrast, more mild heat stress during

Table 2.

Effects of Exercise in the Heat on Circulating Leukocytes

Exercise	Difference in Body Temperature	% Difference in Cell Counts Immediately After Exercise	Reference
40 min cycling at 75% VO_{2max} in water at 102°F vs 73°F (39°C vs 23°C)	2.3°F (1.3°C)	Lymphocytes 30% higher Neutrophils similar Monocytes similar	10
40 min cycling at 75% VO_{2max} in water at 102°F vs 73°F (39°C vs 23°C)	3.1°F (1.7°C)	Lymphocytes 10% higher Neutrophils 30% higher Monocytes similar	26
30 min cycling at 50% VO_{2max} in air at 104°F vs 73°F (40°C vs 23°C)	1.3°F (0.7°C)	Lymphocytes 40% higher Neutrophils similar Monocytes 40% higher	27
1 h cycling at 60% VO_{2peak} in air at 100°F vs 64°F (46°C vs 8°C)	1.8°F (1°C)	Lymphocytes 60% higher Neutrophils 20% higher	30
1 h 30 min cycling at 60% VO_{2max} in air at 90°F vs 64°F (32°C vs 18°C)	0.5°F (0.9°C)	Lymphocytes 10% higher Neutrophils 10% higher Monocytes similar	28
1 h 15 min cycling at 55% VO_{2peak} in air at 100°F vs 72°F (38°C vs 22°C)	2.2°F (1.2°C)	Lymphocytes 10% higher Neutrophils 25% higher	25
1 h cycling at 55% VO_{2peak} in water at 95°F vs 64°F (35°C vs 18°C)	2°F (1.1°C)	Lymphocytes similar Neutrophils similar Monocytes similar	33
2 h cycling at 60% VO_{2max} in water at 86°F vs 68°F (30°C vs 20°C)	1.1°F (0.6°C)	Lymphocytes 10% lower Neutrophils 20% higher Monocytes 25% higher	32
2 h running at 58% VO_{2max} in water at 101°F vs 96°F (38.5°C vs 35.3°C)	3.6°F (2.3°C)	Neutrophils similar	12
1 h 30 min cycling at 70% VO_{2peak} in air at 95°F vs 59°F (35°C vs 15°C)	1.4°F (0.8°C)	Lymphocytes similar Neutrophils similar Monocytes similar	35
1 h running at 90% anaerobic threshold in air at 82°F vs 64°F (28°C vs 18°C)	2°F (1.1°C)	Lymphocytes similar Neutrophils similar Monocytes similar	29

References 12, 25, 26, 29, 30, 32.

exercise does not promote any significant leukocytosis.[28-31] The rise in body temperature and stress hormones accounts for most of the increase in circulating leukocyte numbers during exercise in the heat.[10,26] In the hours after exercise in the heat, circulating leukocytes either remain higher or return to baseline in a similar manner to that after exercise in thermoneutral conditions.* Leukocyte responses to repeated bouts of exercise in short succession (45-minute rest) are generally greater in hot conditions.[27]

Exercise, Heat Stress, and Circulating Cytokines

Fewer studies have investigated the effects of exercise in the heat on circulating cytokines. Cytokine responses to exercise in hot conditions are potentially important because cytokines regulate leukocyte trafficking and function. IL-6 is the most commonly measured cytokine after exercise in the heat, but the magnitude of changes in IL-6 varies widely between studies (Table 3). This variability may relate to differences in ambient temperature and the duration and intensity of exercise. Perhaps not surprisingly, plasma cytokine concentrations increase to a greater extent during exercise in the heat at ≥70% VO_{2max} compared with ≤60% VO_{2max}. Plasma IL-6 concentration increases during exercise in the heat,[12,33-35] most likely in response to greater depletion of muscle glycogen.[36,37] IL-6 may stimulate production of IL-10 and IL-1ra during the latter stages of exercise.[38] The plasma TNF-α concentration also increases during exercise in hot conditions,[28,34,35] but the cellular source of TNF-α is unknown.[35,39] The chemokines G-CSF and IL-8 also increase during exercise in the heat, but they play a limited role in regulating changes in circulating neutrophils.[12,28] Extracellular heat shock protein 70 is classified as a chaperokine,[40] and it increases within the circulation following exercise in the heat.[41]

Exercise, Heat Stress, and Immune Cell Function

Alterations in circulating leukocytes and cytokines during exercise in the heat may

Table 3.

Effects of Exercise in the Heat on Circulating Cytokines

Exercise	Difference in Body Temperature	% Difference in Cytokines Immediately After Exercise	Reference
1 h cycling at 55% VO_{2peak} in water at 95°F vs 64°F (35°C vs 18°C)	2°F (1.1°C)	IL-6 50% higher	33
1 h running at 90% anaerobic threshold in air at 82°F vs 64°F (28°C vs 18°C)	2°F (1.1°C)	IL-6 40% higher	29
40 min cycling at 75% VO_{2max} in water at 102°F vs 73°F (39°C vs 23°C)	3.1°F (1.7°C)	IL-6 50% higher IL-1ra 3× higher TNF-α 15× higher IL-12 12× higher	34
2 h running at 58% VO_{2max} in water at 101°F vs 96°F (38.5°C vs 35.3°C)	3.6°F (2.3°C)	IL-6 1.6× higher G-CSF 8× higher	12
1 h 30 min cycling at 60% VO_{2max} in air at 90°F vs 64°F (32°C vs 18°C)	0.5°F (0.9°C)	IL-6 15% higher IL-1ra 70% higher TNF-α 15% higher IL-8 25% higher IL-10 120% higher G-CSF 70% higher	28
1 h 30 min cycling at 70% VO_{2peak} in air at 95°F vs 59°F (35°C vs 15°C)	1.4°F (0.8°C)	IL-6 3.5× higher TNF-α 1.6× higher	35

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IL, interleukin; TNF, tumor necrosis factor.

influence the functional activity of various immune cells. As a marker of neutrophil activation, plasma myeloperoxidase concentration increases to a similar extent after exercise in hot and thermoneutral conditions.[28,29] Similarly, neutrophil production of elastase decreases after exercise in both hot and thermoneutral conditions.[31] In contrast, neutrophil superoxide production[25] and plasma calprotectin concentrations are higher after exercise in the heat compared with exercise in thermoneutral conditions.[28] Exercise in hot conditions differentially influences specific lymphocyte functions. Lymphocyte proliferation decreases or increases,[25,27] whereas immunoglobulin production increases after exercise in the heat compared with exercise in thermoneutral conditions.[27] These divergent responses may reflect differences in the relative proportions of circulating lymphocyte subsets between exercise in hot versus thermoneutral conditions.[25,27] Natural killer cell activity is similar after exercise in hot and thermoneutral conditions.[25,30,33] Finally, the salivary immunoglobulin A secretion rate decreases after exercise in both hot and thermoneutral conditions.[42]

Exercise in the Heat and Susceptibility to Illness

Evidence implicating immune changes in severe heat injury comes from studies of military personnel and individuals on religious pilgrimages to Mecca. Lymphocyte activation is suppressed in military recruits with exertional heat injury (body temperature 104.7°F or 40.4°C) compared with military recruits without exertional heat injury (body temperature 101.5°F or 38.6°C).[43] The number of circulating leukocytes, T-suppressor (CD8+), and natural killer (CD16+, CD56+) cells are higher, whereas the number of T-helper (CD4+) and B cells are lower in individuals with heatstroke (body temperature 106.6°F or 41.4°C).[44,45] Furthermore, in individuals with heatstroke, the number of T-suppressor cells correlates with body temperature (Pearson correlation $r = 0.75$, $P = .007$, $n = 11$).[45] Some of these lymphocyte responses may result from systemic cytokine release during heatstroke.[46-48]

A dual pathway model has been proposed to account for the role of cytokines in the etiology of heatstroke.[5] The first pathway suggests that elevated circulating concentrations of pyrogens such as gram-negative bacteria (eg, lipopolysaccharide) during exercise in the heat stimulate a systemic inflammatory response.[5] This may occur as a result of reduced blood flow (hypoxia) and opening of tight junctions in the gastrointestinal tract during exercise (Figure 1).[49] Lipopolysaccharide activates the complement cascade and the synthesis of prostaglandin E_2 and pyrogenic cytokines such as IL-1 and TNF-α. Prostaglandin E_2 and cytokines then stimulate the hypothalamus, resulting in a febrile response.[50] The second pathway suggests that exercise itself—if sufficiently intense or prolonged—suppresses the production of T-helper cytokines (eg, IL-2, TNF-α, IL-12) and promotes the production of T-helper 2 cytokines (eg, IL-6, IL-10). This shift in the Th1/Th2 balance may increase susceptibility to leakage of lipopolysaccharide into the circulation during exercise.[5]

No research has directly examined whether exercise in the heat increases the risk of viral infection. Addressing this

issue is problematic for 2 reasons. First, in a field setting, it is difficult to separate the effects of exercise and added heat stress on the immune system. Furthermore, viral infection is unpredictable, and large numbers of subjects would be required to capture and evaluate the incidence of infection following exercise in the heat in a field setting. Second, inducing viral infection in humans following exercise in hot conditions raises ethical issues. Our current knowledge is therefore limited to in vitro research, which indicates that kidney cells exposed to ~108°F (42°C) for 6 hours are more susceptible to viral infection compared with kidney cells not exposed to this form of heat shock.[51] Other research indicates that acute infection before exercise in the heat increases the severity of heat illness, possibly by raising basal hyperthermia.[52]

Gastrointestinal illness is common among military personnel who exercise in hot conditions.[53] This illness may be linked, in part, to the presence of bacteria in the gastrointestinal system and the circulation. The role of lipopolysaccharide as a factor driving cytokine responses to exercise is controversial. A number of studies have reported that prolonged endurance exercise increases plasma lipopolysaccharide concentration.[47,54-61] In contrast, others have found no change in plasma lipopolysaccharide concentration after a 100-mile footrace, despite high plasma cytokine concentrations after the race.[62] Doubts exist concerning the specificity of laboratory methods used to measure plasma lipopolysaccharide concentration.[63]

Conclusion

Exercise in the heat induces major changes in blood flow and a robust stress hormone response. These physiological responses induce modest changes in circulating leukocyte numbers and cytokine concentrations and alter the activity of some immune cells. The relatively small body of existing literature does not support the concept that athletes, firefighters, or military personnel are at greater risk of illness following exercise in the heat compared with exercise in more moderate temperatures. More research is required to examine whether exercise in hot conditions increases the risk of viral infection and bacteria-related gastrointestinal illnesses. A critical threshold for the rise in body temperature during exercise may exist, perhaps ~6°F (3.5°C), beyond which systemic inflammatory responses may contribute to symptoms of heatstroke. Further work is warranted, particularly in the field, to improve our understanding of the effects of heat stress during exercise on the immune system. AJLM

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