# THE IMMUNE RESPONSE TO EXERCISE

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## INTRODUCTION

When discussing the acute physiological response to exercise, the first actors that come into mind are the respiratory and cardiocirculatory systems. However, extensive research indicates that the immune system also responds to physical activity both acutely and chronically. Exercise induces a humoral as well as a neuroendocrine response, with increases in plasma cytokines, adrenaline and cortisol, which both influence and are modulated by glucose metabolism and ultimately impact immune function. Two frameworks have been classically used in the field of exercise immunology. The "open window theory"[1] describes acute changes in cellular and humoral immunity that can occur after a bout of exercise, whereby a decrease in lymphocyte subpopulations and markers of humoral immunity suggest that immune function may be temporarily compromised and proneness to infections increased. The "J-shaped-curve"[2] (see Figure 3) models the relationship between regular exercise intensity and risk of upper respiratory tract infections (URTI). It suggests that with moderate physical activity the risk of URTI is lower than that of a sedentary individual, but this risk may be higher with increasing levels of exercise. Understanding these relationships is especially important in elite sport, given the high training volumes to which athletes are subject, which may temporarily compromise immune function and increase susceptibility to infections, especially during congested periods.

## NEUROENDOCRINE RESPONSE TO EXERCISE

*Two axes are activated at exercise onset that drive the immune response: the sympathoadrenal and the hypothalamic-pituitary-adrenal (HPA) axes*[3].

### *1. The Sympathoadrenal System*

At the onset of exercise, the hypothalamus initiates the neuroendocrine response by activating two distinct axes (Figure 1). The first and immediate acting one is the sympathoadrenal system, which leads to the release of adrenaline. This is the main signal that induces the mobilization and redistribution of leucocytes that are marginated along the vascular endothelium, particularly NK cells and cytotoxic T-lymphocytes, which results in a transient increase in circulating leucocyte numbers during exercise. It also enhances IL-10 production[4], which has both pro- and anti-inflammatory properties. However, the effects of adrenaline are short-lived, and plasma concentrations decline quickly after exercise has stopped.

### *2. The hypothalamic-pituitary-adrenal (HPA) axis*

In contrast to the immediate acting sympathoadrenal system, the HPA axis is responsible for the release of cortisol in a more delayed manner. Cortisol exerts an immunosuppressive effect during and after exercise[4] by reducing lymphocyte activation and proliferation as well as circulating lymphocyte counts. It also reduces pro-inflammatory cytokine production (for example, IL-1, IL-2, IL-6 and IFN-γ) by T CD4+, T CD8+ and NK cells and attenuates cytotoxic activity. Additionally, cortisol contributes to the reduction of circulating immune cells after exercise by redistributing them to peripheral tissues such as the lungs, intestine, skin and muscle.

Increases in plasma catecholamines and cortisol are proportional to exercise duration[4]. Higher intensities are also associated with more pronounced hormonal responses, which may lead to greater reductions in immune cell numbers and functions. The interplay between the sympathoadrenal system and the HPA axis accounts for the immediate and delayed alterations observed in immune parameters during and after exercise.

## CYTOKINES

*Exercise elicits an inflammatory cascade in which IL-6 is key.*

Although exercise acts as an inflammatory stimulus as evidenced by an increase in circulating inflammatory cytokines, the resulting immune response differs from that observed during an infection. In the latter, early pro-cytokines IL-1 and TNF-α, produced mainly by macrophages, initiate the inflammatory response and

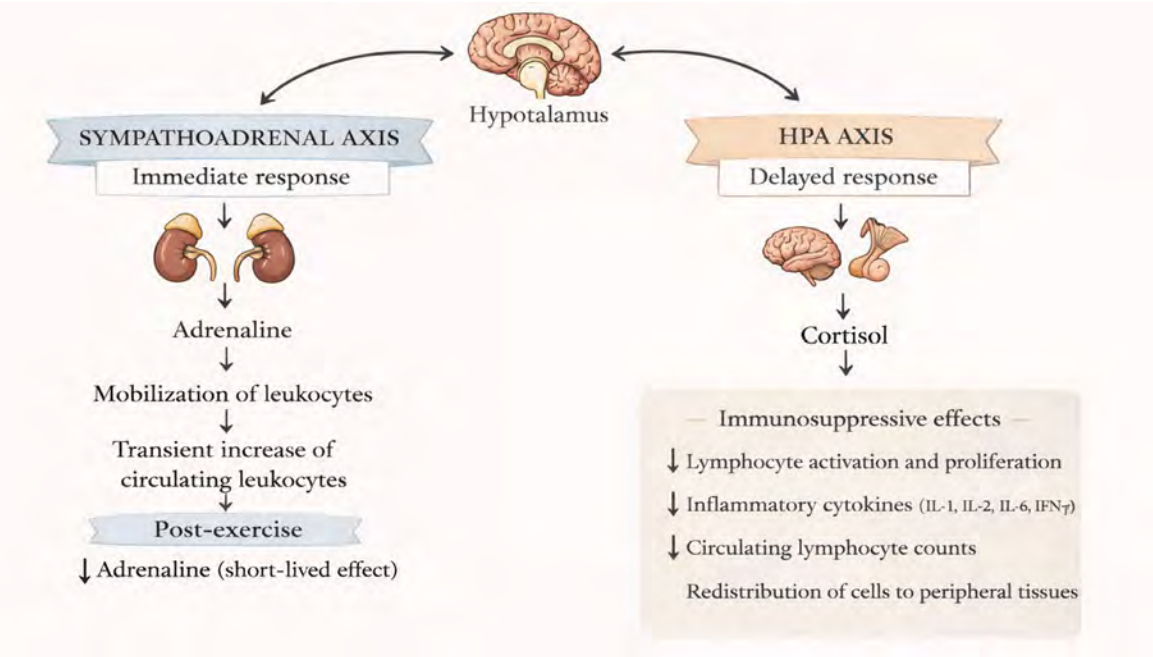


**Figure 1:**
The neuroendocrine response to exercise. Exercise induces a response from both, the sympathoadrenal and the HPA axes. Image generated using AI (OpenAI).

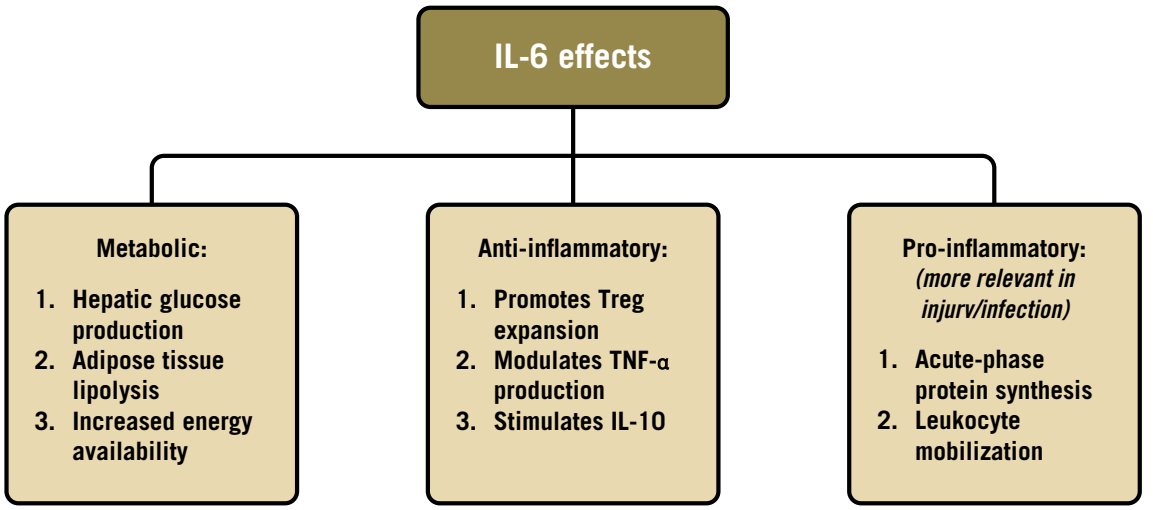


**Figure 2:**
Effects of IL-6.

promote IL-6 production by multiple cell types, including macrophages, which subsequently induces hepatic synthesis of acute-phase reactants. However, in the context of exercise, this cascade is regulated differently. IL-6 is predominantly produced by skeletal muscle cells, not macrophages, and is largely independent of IL-1 and TNF-α, both of which have shown variable responses to exercise across studies[3]. This IL-6 produced by skeletal muscle cells exerts primarily anti-inflammatory and metabolic regulatory effects (Figure 2). It acts as a mediator of anti-inflammatory pathways, mainly by promoting T regulatory cell expansion and modulating the production of other pro-inflammatory cytokines, such as TNF-α. Another important effect is stimulating the secretion of IL-10, which has anti-inflammatory properties[3]. As part of its metabolic effects, IL-6 increases energy availability by stimulating hepatic glucose production and lipolysis in adipose tissue. Nonetheless, it also mediates pro-inflammatory responses, such as acute-phase protein synthesis, leukocyte (especially neutrophil) mobilization and immune cell redistribution, and therefore plays a crucial role as a modulator of the immune response to exercise.

LINKS TO GLUCOSE METABOLISM

One of the primary roles of these three systems (sympathoadrenal, HPA axis, and IL-6 signaling) is to ensure an adequate supply of glucose and therefore energy availability during exercise. This is not only needed by active muscle cells but also by immune cells, whose activity, and therefore need for energy, increases during exercise. Consequently, decreases in blood glucose stimulate the secretion of cortisol in order to counteract such reductions, and ingestion of carbohydrate has been found to attenuate exercise-induced increases in cortisol and adrenaline[5,6,7].

EFFECTS OF PHYSICAL ACTIVITY ON THE IMMUNE RESPONSE

*Two models exist to describe the relationship between exercise and the immune system.*

*1. The Open Window Theory*

The "open window theory"[1] suggests that immune function is compromised in the first hours after vigorous exercise and therefore, susceptibility to infections during this time is higher. There is an increase in total leucocytes, in particular neutrophils and lymphocytes during and immediately after

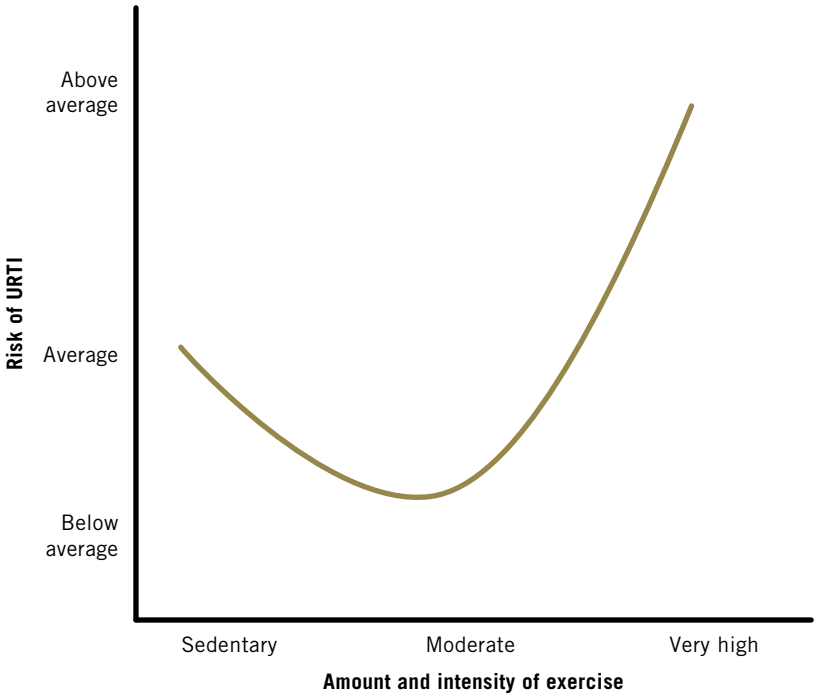


**Figure 3:** The J-shaped curve. The risk of URTI is lowest with moderate levels of physical activity, average with low levels of activity and increases progressively with higher training loads. Adapted from Nieman, 1994[1].

physical activity. However, during the post-exercise period total lymphocyte counts as well as subsets, such as NK cells, quickly decrease below pre-exercise (baseline) levels and remain so in the first hours after a bout of intense exercise, which is then interpreted as an "open window" (for infections) effect. Immune cell functions, such as macrophage phagocytic activity, are impaired during this time period. Cell counts remain below baseline for 24 hours, during which immune surveillance can be compromised. This may result in an increased susceptibility to pathogens. Since professional athletes have training sessions daily or almost daily, and sometimes more than once per day, it is possible that a new training session takes place before immune parameters return to baseline and a progressive decrease ensues, potentially resulting in an increasingly impaired immune function.

*2. The J-Shaped Curve*

The "J-shaped curve"[2] (Figure 1) is a model that shows the relationship between the intensity of regular exercise and the risk of URTI. The model posits that with moderate physical activity the risk of URTI decreases when compared to that of a sedentary individual, and that this risk is higher with increasing levels of exercise[2]. Regular exercise of moderate intensity seems to enhance the immune response to pathogens and protect against infections. It should be noted, though, that elite athletes are subject to higher workloads when compared to non-athletes. As illustrated by the J-shaped curve, this may result in an increased risk of infections acutely, for example during periods of intense training or a congested schedule, as well as chronically.

*Immune markers are altered after exercise*

Natural killer (NK) cells are a subtype of lymphocytes that exert cytotoxic activity without requiring previous sensitization and play a crucial role as a first line of defense against viruses and tumor cells. Because of this, they have been vastly studied in the field of exercise immunology[8]. They are considered one of the main lymphocyte subpopulations being responsible for the "open window," given that their circulating numbers decrease after exercise. This may contribute to a reduced capacity to defend against pathogens entering the body, assuming that a reduction in their numbers also involves an impaired overall function.

Markers of humoral immunity are involved in the "open window" theory as well, and several have been found to decrease after intense exercise. One of these parameters is salivary IgA (sIgA), which has received much attention given its function as part of the first line of defense against pathogens, specifically against viruses entering the upper airways. A decrease in its concentration could produce an impaired capacity to prevent viral attachment to mucosal cells. Indeed, in American football players, lower levels of sIgA were found during

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congested periods of training[9]. Moreover, incidence of URTI during these periods of higher load and lower sIgA was increased[9]. However, reports of decreased sIgA have not been as homogeneous as in the case of lymphocytes. Some studies have found no changes in sIgA after exercise[8]. While this may be due to methodological differences, for example the time of sample collection, or reporting methods (e. g. concentration vs. production rate), it may also indicate that some parameters respond differently to different types of exercise or to variable intensities.

Two more parameters have also been repeatedly investigated. The first one is cortisol, due to its key role in the physiological response to stress (see subsection "The HPA Axis"), such as vigorous exercise. The second one is IL-6 (see subsection "Cytokines"), because of its role as mediator of the acute-phase response. As has been discussed, cortisol, due to its immunosuppressive and anti-inflammatory effects, may contribute to an "open window" effect in the post-exercise period by decreasing circulating numbers of inflammatory cells and inhibiting their functions. IL-6 is released to the bloodstream by contracting muscle during exercise. Indeed, higher serum concentrations have been reported after exercise[2]. The study of these two parameters contributes to a better understanding of the complex processes that take place during and after exercise.

The decrease in lymphocyte counts after strenuous physical activity was initially thought to be caused by cell apoptosis[10]. However, more recent evidence suggests that, in fact, a redistribution of these cells into the muscle tissue and organs takes place[10]. Furthermore, it appears to be senescent lymphocytes that are mobilized after exercise, which most likely come from peripheral rather than lymphatic organs, such as lymph nodes, the spleen and Peyer's patches[10]. However, redistribution may not entirely explain decreases below baseline values (i.e. before exercise), and it is still possible that a certain degree of cell apoptosis occurs. Mobilization of senescent lymphocytes can prevent accumulation of aging and possibly less functional cells, and promote production of naïve T-cells[10], which might contribute to immune competence across the lifespan. This suggests that immune function may be compromised acutely, particularly after intense or strenuous exercise, but enhanced in the long term, especially with moderate physical activity.

*The acute immune response to exercise is highly dependent on intensity and duration*

Studies in exercise immunology have been carried out with different exercise intensities (low, moderate and high) and stimuli (aerobic vs. resistance, short vs. prolonged). Low- to moderate-intensity exercise enhances T-cell function and is associated with increased levels of the anti-inflammatory cytokine IL-10[9] and minor increases in IL-6. On the other hand, high-intensity exercise elicits a marked increase in catecholamines and cortisol secretion[11], leading to a more pronounced reduction in lymphocytes and an "open window" for infection. IL-10 and IL-6 act as modulators, contributing to the regulation of the inflammatory response. Like lower intensities, short duration exercise induces only minor alterations in immune parameters, potentially without an impaired immune function. With prolonged exercise, such as marathon running or prolonged cycling, there is a more pronounced secretion of cortisol, which reduces T lymphocyte and NK cells after exercise and may increase the risk of URTI.

Endurance exercise induces a greater increase in plasma IL-6 when compared to resistance exercise. Other anti-inflammatory effects of predominantly aerobic exercise include increased secretion of IL-10 and reduced production of TNF-α[12]. These differences may be caused by a greater muscle damage during and after resistance training, which likely promotes a more pro-inflammatory state through IL-1 production by macrophages infiltrating damaged muscle tissue.

CONCLUSIONS

The immune response to physical activity is dependent on a complex interplay of multiple factors. Exercise acts as a physiological stressor, eliciting a response from the sympathoadrenal and HPA axes, which release adrenaline and cortisol to the bloodstream, as well as activation of the cytokine cascade, with IL-6 playing a main role, thereby orchestrating the immune system response to exercise. Evidence suggests that overall immune function can be impaired acutely after intense exercise, with reductions in circulating immune cells and their functions.

## Key Takeaways

- *The onset of exercise activates two important systems: the sympathoadrenal system and the HPA axis.*
- *The sympathoadrenal system stimulates the release of adrenaline, which mobilizes marginated immune cells along the vascular endothelium, resulting in an increase in leukocytes and their subtypes during and immediately after exercise*
- *The HPA axis stimulates the release of cortisol, which contributes to a transient reduction in circulating lymphocytes and may impair immune function in the post-exercise period.*
- *The Open Window Theory suggests that immune function may be compromised in the first hours after strenuous exercise with an increased susceptibility to infections.*
- *A decrease in immune cells (lymphocytes, NK) and other alterations in markers of humoral immunity (decreased sIgA, increased immune compromise with higher serum cortisol) could leave an "open window" for pathogens to enter the body.*
- *The J-Shaped Curve is a model that has traditionally been used to depict the relationship between the amount of regular exercise and the risk of URTI.*
- *The model posits that risk of URTI is lowest with moderate physical activity when compared to sedentary individuals and increases progressively with rising levels of exercise.*

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