15 Interrelations Between Acute and Chronic Exercise Stress and the Immune and Endocrine Systems

Jonathan Peake

Introduction

Interaction between the endocrine and immune system is necessary to regulate our health. However, under some conditions, stress hormones can overstimulate or suppress the immune system, resulting in harmful consequences [1]. Stress is often considered negative, yet it is an intrinsic part of everyday life. Stress is not clearly defined; it is context-specific and depends on the nature of factors that challenge our body. Internal stimuli will elicit different stress reactions compared with external stimuli [1]. Similarly, some stressors will induce responses that may benefit survival, whereas others will cause disturbances that may endanger our health. Stress also depends on how our bodies perceive and respond to stressful stimuli [1].

Several important factors determine whether stress hormones stimulate or inhibit the immune system. These factors include [1]:

- The effects of stress on the distribution of immune cells in the body
- The duration of stress
- Hormone concentrations
- The timing of stress hormone exposure relative to the activation status of immune cells (i.e., naïve vs. activated, early vs. late activation)

J. Peake (✉)
School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia
e-mail: jonathan.peake@qut.edu.au

Exercise is a reproducible and quantifiable model of stress and is useful for studying the interactions between the endocrine and immune systems. Exercise stimulates the secretion of a variety of stress hormones, but catecholamines, cortisol and growth hormone are most closely linked with exercise-induced changes in immune function. Research on the interactions between endocrine and immune systems following acute exercise and chronic training is important. Regular exposure to mild short-term stress can potentially enhance immune function and lead to various health benefits. Conversely, prolonged exposure to the chronic stress of intense training may inhibit certain immune functions that are required for health maintenance. This chapter describes the regulatory roles of stress hormones on immune cell counts and activity during acute exercise and following chronic exercise training. Figure 15.1 summarises the immunoendocrine interactions during exercise and their potential functional significance.

Mechanisms of Interaction: In Vitro Evidence

Stress hormones modulate immune function directly by binding to cognate receptors on immune cells and indirectly by modulating the production of cytokines (e.g., IFN-γ, IL-1β, IL-6, TNF-α) [2]. Glucocorticoid receptors are

A. C. Hackney, N. W. Constantini (eds.), *Endocrinology of Physical Activity and Sport*, Contemporary Endocrinology, https://doi.org/10.1007/978-3-030-33376-8_15

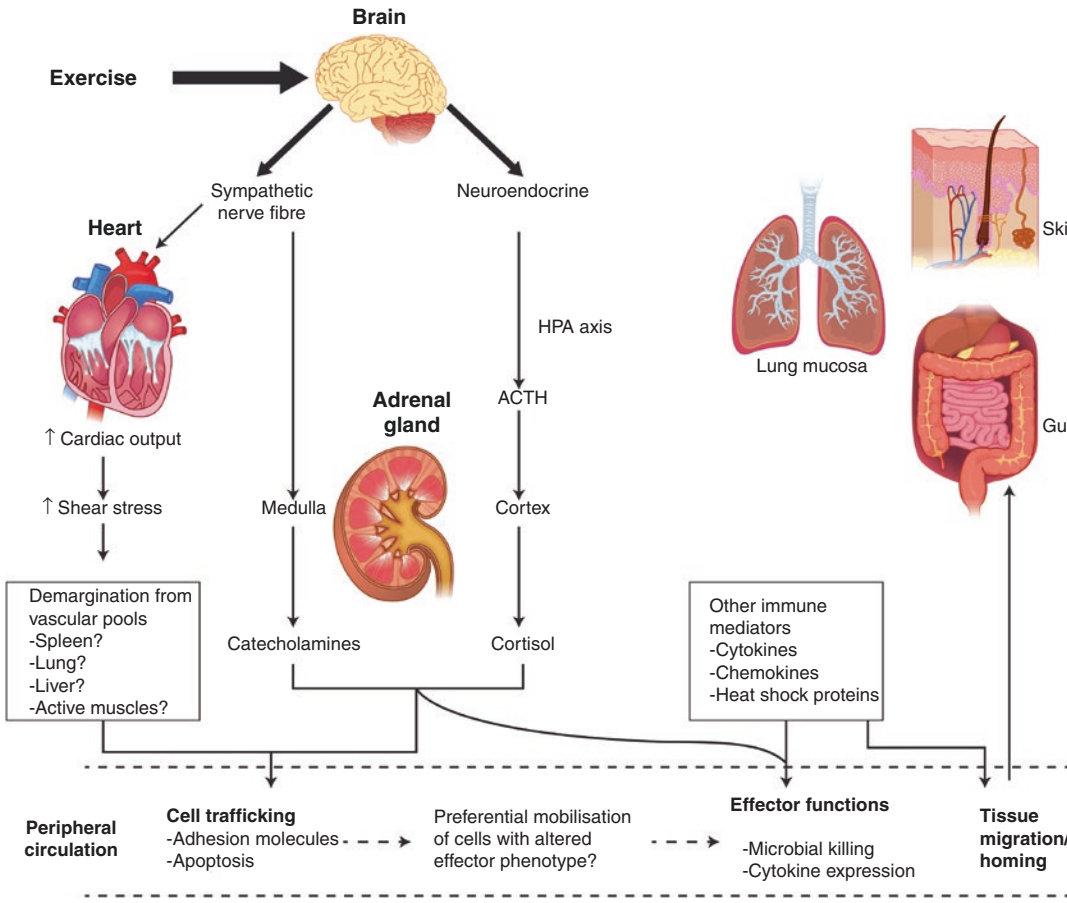

Fig. 15.1 Potential mechanisms by which stress hormone interacts with the immune system during exercise. (Modified from TOM-Systemdruck GmbH, Walsh et al. [170])

expressed on monocytes and B lymphocytes, whereas glucocorticoid receptor expression is much lower on $CD3^+$ T cells and neutrophils [3, 4]. β_2-adrenoreceptors for catecholamines are expressed on (in descending order) natural killer (NK) cells, monocytes, B lymphocytes and T suppressor lymphocytes [5]. Macrophages [6] and neutrophils [7] also express β_2-adrenoreceptors. Within T lymphocyte subpopulations, β_2-adrenoreceptors are mainly expressed in naïve $CD4^+$ T cells and T helper 1 and T helper 2 cells [8–10]. mRNA for α-adrenoreceptors is expressed by activated T cells [11] and in peripheral blood mononuclear cells of patients with juvenile rheumatoid arthritis but not healthy individuals [12]. Although B lymphocytes, monocytes and neutrophils all express growth hormone receptors [13–15], growth hormone most likely exerts its effects on the immune system by binding to prolactin receptors, which are expressed on monocytes and B and T cells [16]. Immune cells also express receptors for other stress hormones, including substance P [17], neuropeptide Y [18], corticotrophin-releasing hormone [19] and serotonin [20].

Glucocorticoids regulate the activity of immune cells by binding to glucocorticoid receptors, which in turn suppresses the transcription factors activator protein 1 (AP-1) and nuclear factor κ B (NFκB) [21]. Glucocorticoids inhibit AP-1 transcriptional activity by preventing the oncoproteins c-Fos and c-Jun from binding to the AP-1 consensus binding site in DNA [22]. Glucocorticoids inhibit NFκB transcriptional activity through two mechanisms.

Firstly, glucocorticoids can induce expression of the inhibitory protein IκB, which then prevents NFκB from translocating to the nucleus where it initiates transcription [23]. Secondly, physical interaction or cross-talk between glucocorticoid receptors and NFκB can suppress transcription [24, 25]. By suppressing the transcriptional activity of AP-1 and NFκB, glucocorticoids regulate various immune functions, including cytokine production [21]. In particular, glucocorticoids inhibit monocyte production of type 1 cytokines IL-12 and IFN-γ, which in turn favours the production of type 2 cytokines IL-4 and IL-10 by $CD4^+$ lymphocytes and peripheral blood mononuclear cells [26–29]. Type 1 cytokines regulate the activity T cytotoxic cells, NK cells and macrophages which defend against intracellular pathogens. Type 2 cytokines regulate the activity of B lymphocytes, eosinophils and mast cells, which defend against extracellular pathogens [30]. The type 1/type 2 cytokine balance determines the balance between cell-mediated vs. humoral immunity and the risk of various immune-related disorders [31]. For information on the effects of glucocorticoids on other aspects of immune function, readers are referred to other more comprehensive reviews [21, 32].

Binding of catecholamines to β_2-adrenoreceptors can inhibit IL-2 and IFN-γ and stimulate IL-4 and IL-10 production by T cells and peripheral blood mononuclear cells [26, 33, 34]. Similar to glucocorticoids, catecholamines can therefore induce a shift towards type 2 cytokine production. The combined effects of glucocorticoids and catecholamines on IFN-γ, IL-4 and IL-10 production by peripheral blood mononuclear cells are in fact additive [26]. However, there are some inconsistencies in the literature concerning the effects of β-agonists on cytokine production. Some studies report that T helper 2 lymphocytes do not respond to β-agonist stimulation [9, 35], but more recent data indicate that activated T cells do produce cytokines following β-agonist stimulation [10]. The effects of β-agonists on cytokine production may also be dose-dependent. Low concentrations of β-agonists (i.e., 1–10 nM) stimulate cytokine production, whereas high concentrations (i.e., 100 nM to 10 μM) inhibit cytokine production by T cells [10]. Downstream from cyclic AMP, β-agonists inhibit cytokine production by T cells by blocking the calcium-/calmodulin-dependent protein phosphatase calcineurin and p38 mitogen-activated protein kinase, but not NFκB [10, 36]. For information on the effects of catecholamines on other aspects of immune function, readers are referred to other more comprehensive reviews [21, 31, 37].

In comparison with glucocorticoids and catecholamines, less is known about the effects of growth hormone and prolactin on the immune system. The actions of growth hormone and insulin-like growth factor-1 (IGF-1) do not overlap entirely, but growth hormone exerts many of its actions through IGF-1. Neither growth hormone nor IGF-1 is essential for immune function, but growth hormone influences various aspects of immune cell development and activity [38]. Growth hormone inhibits apoptosis of $CD4^+$ T cells following treatment with dexamethasone [39]. Growth hormone, through binding to its receptor on the surface of T cells, may activate phosphatidylinositol 3 kinase (which regulates cell proliferation) and NFκB (which controls apoptosis through the anti-apoptosis protein Bcl2) [40]. IGF-1 also stimulates macrophages to produce reactive oxygen species [41] and increases NK cell activity [42]. Prolactin is also not essential to normal immune function [38], but it can promote lymphocyte proliferation [43] and haematopoiesis [44].

Interactions between the neuroendocrine and immune systems are bidirectional. Pro-inflammatory cytokines released from immune cells (e.g., IL-1β, IL-6 and TNF-α) mediate communication between the immune system and the central nervous system. Cytokines can alter activity of the central nervous system through humoral, neural and cellular pathways [45]. Cytokines can pass the blood–brain barrier directly [46]. Alternatively, immune cells can pass across the blood–brain barrier and release cytokines into the central nervous system [47]. Cells comprising the blood–brain barrier also secrete various cytokines [48]. Cytokines may signal the central nervous system by stimulating afferent nerves, although this concept remains

somewhat controversial [49]. One theory proposes that cytokines target the blood–brain barrier during systemic inflammation, whereas they target afferent nerves during localised inflammation [49]. Cytokines can pass back across the blood–brain barrier into the circulation following intracerebroventricular injection of lipopolysaccharide (LPS) [50]. Cytokines interact with components of the central nervous system, resulting in behavioural changes. Specifically, cytokines alter neurotransmitter function, neuroendocrine activity, neural plasticity and neural circuitry. These actions can induce fever, changes in appetite, fatigue and depression [45].

Stress Hormones and Leukocyte Mobilisation In Vivo

A number of studies have investigated the effects of stress hormones on circulating leukocyte numbers by infusing variable doses of stress hormones in healthy humans over 30 min up to 5 h. Cortisol raises the number of circulating neutrophils, whereas it suppresses the number of lymphocytes, and does not alter the number of Leu^+ NK cells [51, 52]. By contrast, adrenaline increases the number of circulating total lymphocytes and NK cells [51, 53–55]. The number of circulating monocytes also rises 1–2 h following infusion of adrenaline [53, 55, 56].

In contrast with NK cells, the effects of adrenaline and the β-agonist isoproterenol on circulating T lymphocyte subpopulations are somewhat variable. In response to these agents, the number/percentage of circulating $CD4^+$ T helper cells decreases [54, 56, 57] or increases [53, 58], whereas the number/percentage of circulating $CD8^+$ T cytotoxic cells increases [53, 54, 58], decreases [57] or remains unchanged [56, 59]. The number/percentage of circulating B lymphocytes decreases [53] or remains unchanged following infusion of adrenaline or isoproterenol [54, 56, 59]. More recent research indicates that adrenaline increases the number of circulating $CCR7{-}CD45RA^+CD8^+$ effector T cells, CD4−CD8− γ/δ T cells, $CD3^+CD56^+$ NK T-like cells, $CD16^+CD56^{dim}$ cytotoxic NK cells and $CD14^{dim}CD16^+$ pro-inflammatory monocytes. These cells most likely originate from marginated pools on the endothelial surface of blood vessels [60]. In addition to these findings, γ/δ T cells and T cells expressing chemokine receptors (CXCR2, CXCR3 and CCR5) are mobilised into the circulation following psychological stress. These responses correlate with cardiac activation [61, 62].

The effects of noradrenaline on circulating leukocytes are also variable. One study has reported that noradrenaline raised the number of circulating neutrophils, monocyte, lymphocytes and $CD16^+$ NK cells [58, 63]. Another study found no changes in the numbers of these cell types or T lymphocyte subpopulations following treatment with noradrenaline [54]. These inconsistent findings may be due to differences between these studies in noradrenaline dose and in the duration of hormone infusion and blood sampling times relative to the period of infusion.

Combined treatment with cortisol and adrenaline increases the number of circulating neutrophils for up to 12 h [52]. Growth hormone infusion in humans (2 IU) increases neutrophil number, but does not alter blood mononuclear cell subpopulations [64].

Stress Hormones and Leukocyte Function In Vivo

Several of the studies described above have also examined changes in immune cell function following infusion of stress hormones in healthy humans. Cortisol does not alter Leu^+ NK cell activity [51] or neutrophil chemotaxis or production of reactive oxygen species [65]. By contrast, adrenaline increases the activity of $CD16^+$ NK cells [53, 55]. Similarly, noradrenaline infusion in humans (16 μg/min for 1 h) also increases $CD16^+$ NK cell activity [63]. The effects of catecholamines and isoproterenol on lymphocyte proliferation vary. Isoproterenol reduces lymphocyte proliferation [54], whereas adrenaline and noradrenaline have no effect [54, 57]. This disparity may be due to variable changes in lymphocyte subpopulations in response to these agents. Adrenaline increases the number of T

cells that express IFN-γ, IL-2, IL-4 and TNF-α [53]. Adrenaline and noradrenaline infusions also raise the plasma concentrations of IL-6 and IL-1 receptor antagonist (IL-1ra) under normal resting conditions [66–68]. In contrast, adrenaline infusion prior to experimental endotoxemia reduces subsequent changes in the plasma concentrations of IL-6, IL-8 and TNF-α [69]. Hydrocortisone treatment immediately prior to experimental endotoxemia does not alter subsequent changes in plasma IL-6 concentration but attenuates plasma TNF-α concentration and increases plasma IL-10 concentration endotoxemia [70, 71]. Conversely, IL-6 and IFN-γ increase the plasma concentrations of cortisol and ACTH cortisol [72, 73], while infusion of LPS increases the plasma concentrations of adrenaline and cortisol [59].

To summarise, glucocorticoids, catecholamines and growth hormone bind to specific receptors on the surface of immune cells. This hormone-receptor binding mediates leukocyte trafficking and functional activity. In vitro, glucocorticoids and catecholamines induce a shift in the balance of type 1/type 2 cytokines towards greater production of type 2 cytokines. Growth hormone regulates immune cell activity through IGF-1 and can inhibit apoptosis of T lymphocytes. In vivo, cortisol mobilises neutrophils but reduces the number of circulating lymphocytes and does not alter circulating natural killer cell numbers. Catecholamines increase the total number of circulating lymphocytes, monocytes and natural killer cells. They also stimulate natural killer cell activity. By contrast, the effects of catecholamines on circulating lymphocyte subpopulations and lymphocyte activity are more variable. By crossing the blood–brain barrier, immune cells and cytokines can alter the function of the central nervous system.

Immunoendocrine Responses to Acute Exercise

Exercise immunologists have used various approaches to investigate the interaction between the endocrine and immune systems during exercise. On a basic level, some research has assessed the correlation between changes in stress hormones and immunological variables following exercise. Other research has examined the interactions between the endocrine and immune systems by using different exercise workloads, carbohydrate and caffeine supplementation, thermal stress or drugs. A small number of studies have also investigated how exercise-induced immune changes alter the activity of the central nervous system.

Correlations Between Stress Hormones and Immunological Variables

McCarthy et al. [74] first provided evidence that following brief, intense exercise, the number of circulating lymphocytes correlated positively with the plasma concentrations of adrenaline ($\rho = 0.67$, $p < 0.05$) and noradrenaline ($\rho = 0.68$, $p < 0.05$). Plasma adrenaline concentration also correlates positively with the number of circulating neutrophils after short, intense exercise [74, 75] and endurance exercise [76]. Rhind et al. investigated the relationships between stress hormones and immune cells following exercise. Stepwise multiple linear regression indicated that plasma adrenaline concentration accounted for some of the variation in $CD3^+$ T cells, $CD4^+$ T helper cells, $CD8^+$ T cytotoxic cells and $CD3-/CD16^+/CD56^+$ NK cells [77]. Plasma noradrenaline concentration also explained some of the variation in $CD3-/CD16^+/CD56^+$ NK cells and $CD19^+$ B cells [77]. Steensberg et al. [78] discovered that following 2.5 h running at 75% VO_{2max} (maximal oxygen uptake), the number of T helper 2 cells that produce IL-2 and IFN-γ decreases below pre-exercise values, and this response is inversely correlated with plasma adrenaline concentration. Brenner et al. [79] used stepwise multiple linear regression to examine stress hormones and immune cells following cold exposure. Plasma noradrenaline concentration accounted for some of the variation in $CD3^+$ T cells, $CD8^+$ T cytotoxic cells and $CD19^+$ B cells, whereas plasma adrenaline concentration was only linked with changes in $CD19^+$ B cells [79].

The relationship between plasma cortisol concentration and the number of circulating immune cells is more variable. Some studies report no relationship [74, 80] or an inverse relationship [81] between plasma cortisol concentration and the number of circulating neutrophils after exercise. Other studies suggest that cortisol does mediate neutrophil mobilisation following exercise [76, 77, 82, 83]. The association between plasma cortisol concentration and the number of circulating monocytes following exercise is also inconsistent [77, 81]. It does seem, however, that plasma cortisol concentration accounts for some of the variation in $CD4^+$ T helper cells and $CD19^+$ B cells following exercise [77]. These inconsistent findings may be due to variation in blood sampling points used to examine the association between plasma cortisol concentration and the number of circulating immune cells. In contrast with adrenaline, cortisol mobilises neutrophils into the circulation in a more delayed and prolonged fashion [51, 52]. Recent evidence indicates that plasma cortisol concentration correlates strongly with lymphocyte apoptosis after resistance exercise [84]. Although growth hormone can mobilise neutrophils at rest [64], there is no clear evidence to indicate that growth hormone regulates the number of circulating neutrophils following exercise [81].

Several studies suggest that stress hormones also regulate cytokine responses to exercise. The plasma concentrations of adrenaline, noradrenaline, cortisol and growth hormone correlate with the plasma concentrations of IL-6, IL-1ra, IL-12 and TNF-α following exercise in both thermoneutral and hot conditions [85–87]. The plasma concentrations of noradrenaline and cortisol also correlate with plasma IL-6 concentration following cold exposure [79, 88]. It is unclear whether hormones or cytokines are the driving factor behind these relationships. Stress hormones and cytokines regulate body temperature during exercise, albeit through distinct mechanisms [89]. Adrenaline may stimulate a small rise in plasma IL-6 concentration during exercise [68]. Alternatively, the correlation between plasma adrenaline and IL-6 concentrations following exercise may be purely coincidental, because both adrenaline and IL-6 regulate muscle glycogen depletion during exercise [90, 91]. IL-6 release from skeletal muscle during exercise correlates with arterial IL-6 concentration [92]. Treatment with the glucocorticoids hydrocortisone and dexamethasone reduces plasma IL-6 concentration during exercise [85]. However, IL-6 stimulates cortisol release at rest [72]. Further research is required to clarify the interactions between IL-6 and cortisol during exercise.

Exercise Workload, Stress Hormones and Immunological Variables

Stress hormones are released into the circulation as the intensity of exercise increases. Plasma adrenaline, noradrenaline and growth hormone concentrations rise in an exponential manner with increasing intensity [93–95]. By contrast, plasma cortisol concentration only increases above exercise intensities of >60% VO_{2max} [76, 96, 97]. Based on these hormone responses, a number of studies have compared immunological responses to exercise of variable intensity and duration.

Foster et al. [93] first provided evidence that catecholamines influence leukocyte mobilisation as a function of exercise intensity. The number of circulating granulocytes and lymphocytes increased with workload. Using the β-antagonist propranolol, they demonstrated that during exercise, catecholamines regulate changes in lymphocytes, but not granulocytes [93]. Compared with moderate-intensity exercise, the number of circulating monocytes is similar, while $CD4^+$ T helper cells, $CD8^+$ T cytotoxic cells and T cell proliferation decrease below pre-exercise values after high-intensity exercise [82, 97, 98]. Conversely, the number of $CD19^+$ B cells is higher after high- vs. moderate-intensity exercise [82]. The number of circulating NK cells and NK cell activity is similar immediately after moderate- and high-intensity exercise, while NK cells and activity decrease below pre-exercise values 2 h after high-intensity exercise [98]. These studies did not evaluate the relationship between stress hormones and these intensity-dependent

immune changes. However, it seems likely that stress hormones play a more dominant role in mediating immune changes during high-intensity exercise. The plasma concentrations of IL-6, IL-1ra and IL-10 are also higher following high- vs. moderate-intensity exercise [76, 92, 99, 100]. As discussed above, adrenaline may stimulate a minor rise in plasma IL-6 and IL-1ra concentration during exercise [66, 68], but it is more likely that IL-6 stimulates IL-1ra and IL-10 late in exercise [72].

Carbohydrate Supplementation, Stress Hormones and Immunological Variables

Cortisol and adrenaline play key roles in mediating metabolism during exercise [90, 101]. Many studies have used carbohydrate supplementation to manipulate stress hormone responses and examine the mechanisms of exercise-induced changes in immune cell counts and activity.

With the exception of a few studies [102–104], carbohydrate consumption during endurance exercise generally reduces the plasma concentrations of adrenaline, cortisol and growth hormone [105–112]. This decrease in the release of stress hormones most likely accounts for the decline in the number of circulating neutrophils and monocytes following carbohydrate ingestion during exercise [102, 103, 107, 109–111, 113]. By contrast, although carbohydrate supplementation attenuates plasma cortisol concentration, in general, it does not prevent the post-exercise decline in the number of circulating lymphocytes, lymphocyte subsets or NK cells [110, 114–118].

The effects of carbohydrate supplementation on other exercise-induced changes in immune cell function are variable. Despite changes in stress hormones, not all studies demonstrate that carbohydrate consumption maintains or increases neutrophil and monocyte function [102, 103, 107, 109, 113, 119]. Most research indicates that carbohydrate supplementation does not prevent the post-exercise decrease in lymphocyte proliferation [114, 118, 120]. However, Lancaster et al. [115] found that consuming carbohydrate reduces plasma cortisol concentration and helps to maintain the number of IFN-γ^+ $CD4^+$ and $CD8^+$ T cells and IFN-γ production by these cells during exercise. The metabolic stress of low muscle glycogen appears to increase plasma cortisol concentration and the number of circulating leukocytes, but does not alter lymphocyte proliferation during exercise [121, 122]. Carbohydrate supplementation increases IL-2- and IFN-γ-stimulated NK cell activity, but not IL-4- and IL-12-stimulated NK cell activity [116, 117]. These effects on NK cell activity are independent of changes in plasma cortisol concentration [116, 117]. Nieman et al. [123] discovered that carbohydrate ingestion during exercise reduced plasma cortisol concentration but did not alter salivary immunoglobulin A concentration (when adjusted for saliva protein concentration and secretion rate). However, changes in salivary immunoglobulin A concentration were negatively correlated with plasma cortisol concentration, and this relationship predicted the incidence of upper respiratory illness in the 2 weeks after exercise [123].

With a few exceptions [103, 106, 112], most research shows that carbohydrate attenuates the rise in plasma concentrations of IL-6, IL-10 and IL-1ra (but not IL-8 or TNF-α) following exercise [105, 108–111]. These cytokine responses to consuming carbohydrate during exercise may be partly linked to changes in catecholamine release. Carbohydrate supplementation does not influence leukocyte mRNA expression of IL-6, IL-8, IL-10 and IL-1ra or monocyte intracellular production of IL-6 and TNF-α following exercise [105, 106]. Carbohydrate ingestion attenuates the release of IL-6 from the skeletal muscle during exercise, but the effects of carbohydrate on mRNA expression of IL-6 and IL-8 in the skeletal muscle following exercise are variable [110, 111, 124, 125].

Caffeine Supplementation, Stress Hormones and Immunological Variables

Although caffeine is a well-known stimulant of the central nervous system, only a small number of studies have focused on its effects on stress

hormones and immune responses to exercise. Ingesting 6 mg caffeine 1 h before endurance exercise consistently raises plasma adrenaline concentration [126–130]. Compared with a placebo treatment, caffeine supplementation does not alter the number of circulating neutrophils following exercise or neutrophil production of reactive oxygen species [129, 130]. The number of circulating CD3−/CD56$^+$ NK cells is greater compared with a placebo treatment, whereas changes in the number of activated NK cells expressing CD69 are variable after exercise and caffeine ingestion [131, 132]. Changes in the total number of circulating lymphocytes after exercise and caffeine intake are also variable [129, 130]. The numbers of circulating CD4$^+$ T helper cells and CD8$^+$ T cytotoxic cells are lower, while the numbers of these cells that express the activation marker CD69 are greater after exercise and caffeine intake compared with a placebo treatment [126]. Caffeine supplementation also increases the concentration and secretion rate of salivary immunoglobulin A and the plasma concentration of heat shock protein 72 after exercise compared with a placebo treatment [127, 128]. This variation in the effects of caffeine on exercise-induced immune changes may be due to differences in exercise protocol, blood sampling times and the habitual caffeine intake of the study participants.

Thermal Stress, Stress Hormones and Immunological Variables

Some researchers have compared changes in stress hormones and immunological variables following exercise in hot vs. cold/thermoneutral conditions. Several studies have examined responses to exercise in hot vs. cold water. This approach appears to be more effective than comparing responses to exercise in hot vs. cold/thermoneutral ambient conditions, because water is a more effective conductor of heat than air. For detailed discussion on the effects of thermal stress on the endocrine and immune systems, interested readers should consult the comprehensive review by Walsh and Whitham [89].

Plasma stress hormone concentrations are higher following exercise in hot vs. cold water, and these responses most likely account for the higher numbers of circulating neutrophils and lymphocytes following exercise in hot water [77, 81, 133–135]. However, not all research supports a link between stress hormones and the number of circulating leukocytes following exercise in hot conditions [136, 137]. This relationship may vary depending on the demands of exercise. Within the lymphocyte subsets, CD3$^+$ T cells, CD34$^+$ T helper cells, CD8$^+$ T cytotoxic cells and CD3−/CD16$^+$/CD56$^+$ NK cells (but not CD19$^+$ B cells) are higher at the end of exercise in hot vs. cold/thermoneutral conditions [77, 122]. By contrast, the number of circulating CD3$^+$ T cells is lower 2 h after exercise in hot vs. thermoneutral conditions [122].

The effects of thermal stress on neutrophil function following exercise are also variable, with reports of an increase [138], a decrease [137] or no change [122, 134]. Thermal stress during exercise increases lymphocyte proliferation per cell (despite higher plasma cortisol concentration) [122], whereas it does not alter NK cell activity per cell [122, 139]. The plasma concentrations of IL-10, IL-1ra, IL-12 and TNF-α are consistently higher after exercise in hot vs. cold/thermoneutral conditions, whereas changes in the plasma concentrations of IL-6, IL-8 and granulocyte-colony-stimulating factor (G-CSF) are less consistent [86, 134, 136–138].

Drugs, Stress Hormones and Immunological Variables

Several studies have used drugs to manipulate stress hormone responses to exercise and examine the resultant immunological responses. The findings of these studies are equivocal, possibly because of variation in the exercise protocols, treatment periods and drugs used in these studies.

As described previously, Foster et al. [93] treated men with a single dose of the non-selective β_1-/β_2-antagonist propranolol 10 min before incremental exercise. They discovered

that during exercise, propranolol reduced the rise in the number of circulating lymphocytes, but not neutrophils or plasma catecholamine concentrations. This finding suggests that catecholamines may not regulate leukocyte mobilisation directly during incremental exercise. Instead, catecholamines may work indirectly by increasing blood flow, which strips leukocytes from the endothelial surface of blood vessels in marginal pools such as the lungs. Murray et al. [140] conducted a follow-up study in which they treated men and women with propranolol or the selective β_1-antagonist metoprolol for 1 week prior to an incremental exercise test. Neither drug reduced post-exercise plasma catecholamine concentrations compared with the control trial. However, compared with the control trial, propranolol (but not metoprolol) reduced the total number of circulating lymphocytes, numbers of $CD4^+$ T helper cells and $CD8^+$ T cytotoxic cells and NK cell numbers and activity and reduced the post-exercise decline in lymphocyte proliferation [140]. These findings suggest that circulating catecholamines may not mobilise lymphocytes into the circulation. Instead, these cells may be mobilised from the spleen in response to direct activation of β_1-/β_2-adrenergic receptors in the spleen [141].

Starkie et al. [142] treated men with the selective α_1-antagonist prazosin and the non-selective β-antagonist timolol or placebo 2 h prior to 20 min cycling at ~78% VO_{2max}. Plasma catecholamine concentrations were higher, whereas plasma cortisol concentration was lower after exercise in the drug trial compared with the placebo trial. Starkie et al. [142] attributed the greater catecholamine response in the drug trial to reduced clearance of catecholamines by β-receptors. The numbers of circulating lymphocytes and monocytes increased during exercise in both trials but were lower immediately after exercise in the drug trial compared with the placebo trial—despite the higher plasma catecholamine concentrations. This finding conflicts with other research showing that infusion of adrenaline or isoproterenol *raises* the number of circulating lymphocytes [51, 53, 54]. One possible explanation for this difference is that the drugs used in the study by Starkie et al. [142] may target different adrenergic receptors on lymphocyte compared with adrenaline or isoproterenol. The numbers of circulating IFN-γ^+ $CD3^+$ T cells, IL-2^+ $CD3^+$ T cells and IFN-γ^+ CD3−/$CD56^+$ NK cells increased during exercise in both trials. However, the numbers of these cells were lower after exercise in the drug trial compared with the placebo trial. IL-2 production by $CD3^+$ T cells and IFN-γ production by both IFN-γ^+ $CD3^+$ T cells and IFN-γ^+ CD3−/$CD56^+$ NK cells decreased during exercise similarly in both trials. These findings suggest that α- and/or β-adrenergic receptor stimulation does not regulate cytokine production by T cells and NK cells during exercise.

Mazzeo et al. [143] treated women with prazosin or placebo for 3 days before cycling for 50 min at 50% VO_{2max}. Prazosin reduced plasma IL-6 concentration after exercise compared with the placebo. Papanicolaou et al. [85] treated men with hydrocortisone, dexamethasone or a placebo 4 h before 25 min running at 78% VO_{2max}. Both hydrocortisone and dexamethasone attenuated plasma IL-6 concentration after exercise compared with the placebo.

Evidence for Interactions Between the Central Nervous and Immune Systems

As outlined above, considerable attention has focused on how stress hormones regulate immune responses to exercise. The immune system is also capable of altering the function of the central nervous system. Several studies have examined this issue, and it is likely that more research will be conducted in this area in the future. In mice, exercise-induced muscle damage stimulates macrophages residing in the brain to secrete IL-1β into the surrounding tissue [144, 145]. This response appears to increase perceptions of fatigue, reduce voluntary activity and delay recovery from exercise [146]. In humans, Steensberg et al. [147] observed that at rest, the concentrations of IL-6 and the cellular chaperone heat shock protein 72 (HSP72) are two to three

times higher in cerebrospinal fluid compared with plasma. Although exercise stimulates the systemic release of IL-6 and heat shock protein 72, their concentrations remain stable in cerebral spinal fluid, which indicates that they do not cross the blood–brain barrier [147]. The brain releases small amounts of IL-6 into the systemic circulation during exercise, and this is independent of hyperthermia [148]. The functional significance of this response is not certain. It may provide a signal to the liver to increase glucose output, or it may be a more general indication of increased neural activity during exercise [148].

Chronic Interactions Between the Endocrine and Immune Systems

Compared with the amount of research on acute exercise, fewer studies have examined interactions between stress hormones and immunological variables following chronic training. Most studies have simply documented the effects of intensified training on simultaneous changes in stress hormones and immune cell counts at rest and/or in response to acute exercise. Very few studies have specifically examined the relationship between changes in stress hormones and immune cell counts and function.

Several studies report no changes in resting plasma and urinary cortisol concentrations, immune cell counts or serum cytokine concentrations after intensified training [149–153]. Robson-Ansley et al. [154] discovered no changes in resting plasma cortisol or the number of circulating neutrophil counts but did find that resting plasma IL-6 concentration was persistently elevated following 4 weeks of intense training. Fry et al. [155] observed that resting plasma cortisol concentration decreased, while the numbers of circulating neutrophils, monocytes and lymphocytes did not change after 10 days of intense interval training. The number of circulating $CD3^+$, $CD4^+$ and $CD8^+$ T cells and $CD20^+$ B cells also remained unchanged, whereas the number of circulating $CD56^+$ NK cells decreased and $CD25^+$ T cells increased following 10 days of training [155]. It is unlikely, however, that these changes in $CD56^+$ NK cells and $CD25^+$ T cells were related to changes in plasma cortisol concentration. Smith and Myburgh [156] reported no change in resting plasma cortisol concentration but found that $CD4^+$ and $CD8^+$ T cell counts and $CD16^+/CD56^+$ NK cells decreased following 4 weeks of intense training. Makras et al. [157] observed an increase in urinary cortisol concentration, an increase in $CD4^+$ T cell count and a decrease in neutrophil count at rest after 4 weeks of military training. Ortega et al. [158] found that neutrophil phagocytic activity was higher in female athletes compared with non-athletes. In the athletes, neutrophil phagocytic activity correlated positively with plasma cortisol concentration, whereas it correlated negatively with plasma ACTH concentration. Findings from the study by Cunniffe et al. [159] suggest that elevated salivary cortisol concentration with training may reduce salivary immunoglobulin A concentration, resulting in increased susceptibility to upper respiratory illness. Some of the variability among these studies may result from differences in the physical fitness of study participants, training loads and blood sampling times.

The effects of chronic training on cortisol and immune responses to acute exercise are also variable. Verde et al. [160] reported that changes in serum cortisol concentration, $CD3^+$ T cell counts and lymphocyte proliferation after acute exercise were all attenuated following 3 weeks of intense training. Lancaster et al. [161] discovered that 2 weeks of intense training reduced plasma cortisol concentration but did not alter lymphocyte production of the type 1 cytokine IFN-γ or the type 2 cytokine IL-4. In contrast with these findings, other research indicates no effect of chronic training on exercise-induced changes in plasma and salivary cortisol concentration, immune cell counts or salivary immunoglobulin A concentration [150, 152, 162].

A small number of studies have examined changes in plasma or urinary catecholamine concentrations and immune cell counts following chronic training. Imrich et al. [150] found no changes in plasma catecholamine concentration or immune cell counts at rest or in response to acute exercise following 6 weeks of training.

Hooper et al. [163] reported that both the number of circulating neutrophils and plasma noradrenaline concentration were elevated in swimmers showing symptoms of overtraining compared with swimmers who were not overtrained after 6 months of training. However, it is unclear whether these responses were linked in any way. Mackinnon et al. [151] observed that urinary norepinephrine concentration decreased, whereas plasma noradrenaline and leukocyte counts at rest did not change following 4 weeks of intense training. Makras et al. [157] found that the ratio of adrenaline to noradrenaline in urine increased after 4 weeks of military training. This response correlated positively with $CD4^+$ T cell counts and correlated negatively with neutrophil counts.

Biological Significance of Interactions Between the Endocrine and Immune Systems

Dhabhar [1] proposes the following analogy to explain the possible significance of acute stress on the immune system. Within minutes of the onset of stress, catecholamines stimulate the body's 'soldiers' (i.e., leukocytes) to leave their 'barracks' (i.e., spleen, lung, bone marrow, lymph nodes) and enter the 'boulevards' (i.e., blood vessels and lymphatics). As stress proceeds, glucocorticoids are released which stimulate leukocytes to exit the bloodstream and enter potential 'battle stations' (i.e., skin, lung, gastrointestinal and urinary-genital tracts, mucosal surfaces and lymph nodes) in preparation for immune challenges that may occur in response to stressful stimuli [1].

In the context of exercise, the factors that stimulate the release of stress hormones are most often non-harmful. These factors may include demands for (1) increased blood flow to contracting muscle (to deliver oxygen and nutrients) and skin (for thermoregulation) and (2) release of energy substrates from the liver and adipose tissue (e.g., glucose, fatty acids, amino acids) to support muscle metabolism. Interaction between the endocrine and immune systems during exercise can therefore be considered as rather non-specific. However, stress hormones may (incidentally) prime immune cells to respond to infectious pathogens and/or airborne pollutants that invade mucosal surfaces lining the respiratory tract.

Dhabhar [1] proposed that the effects of stress on the immune system and general health depend on the duration of exposure to stress. Acute and intense stress may enhance immune function, and mild stress of moderate duration may promote immunosurveillance, while chronic stress may cause immune dysregulation [1]. Immunoprotection resulting from acute stress may lead to more effective wound healing, responses to vaccination and resistance to infection and cancer. Immunopathology resulting from severe acute stress or persistent stress may promote pro-inflammatory and autoimmune diseases. Immunosuppression resulting from chronic stress may reduce the effectiveness of wound healing and vaccination and increase the risk of infection and cancer. By contrast, chronic stress may reduce the risk of pro-inflammatory and autoimmune diseases by suppressing aspects of immune function that contribute to such conditions (e.g., T lymphocyte activity, cytokine production) [1].

Both acute exercise [164] and chronic training [165, 166] increase antibody production in response to vaccination. Mild repeated stress resulting from chronic training also improves the rate of wound healing [167], decreases the risk of upper respiratory illness [168] and reduces the prevalence and severity of various chronic diseases [169]. Although more work is needed to define their precise role, it is likely that stress hormones mediate some of these benefits of exercise.

Summary

A variety of non-harmful stimuli during exercise induce the release of stress hormones. These stress hormones influence many physiological systems, including the immune system. Stress hormones act to mobilise immune cells into the circulation and can increase or decrease the activity of these cells. The precise nature of the inter-

action between stress hormones and immune cells likely depends on multiple factors, including the intensity and duration of exercise, the physical fitness of exercising individuals and environmental conditions. Some stress hormones (e.g., catecholamines) influence immune cell activity mainly during exercise, whereas others (e.g., cortisol) may have a more delayed effect on immune function during the later stages of exercise and/or after exercise. Nutritional interventions such as carbohydrate and caffeine supplementation can alter the secretion of stress hormones during exercise, but these alterations do not always result in changes in immune function. Immunoendocrine interactions during exercise may serve to promote some aspects of health. However, further research is needed to understand the biological significance of such interactions in more detail.

References

1. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation. 2009;16:300–17.
2. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005;5:243–51.
3. Bartholome B, Spies CM, Gaber T, Schuchmann S, Berki T, Kunkel D, et al. Membrane glucocorticoid receptors (mGCR) are expressed in normal human peripheral blood mononuclear cells and up-regulated after in vitro stimulation and in patients with rheumatoid arthritis. FASEB J. 2004;18:70–80.
4. Miller AH, Spencer RL, Pearce BD, Pisell TL, Azrieli Y, Tanapat P, et al. Glucocorticoid receptors are differentially expressed in the cells and tissues of the immune system. Cell Immunol. 1998;186:45–54.
5. Maisel AS, Harris T, Rearden CA, Michel MC. Beta-adrenergic receptors in lymphocyte subsets after exercise. Alterations in normal individuals and patients with congestive heart failure. Circulation. 1990;82:2003–10.
6. Liggett SB. Identification and characterization of a homogeneous population of beta 2-adrenergic receptors on human alveolar macrophages. Am Rev Respir Dis. 1989;139:552–5.
7. Marinetti GV, Rosenfeld SI, Thiem PA, Condemi JJ, Leddy JP. Beta-adrenergic receptors of human leukocytes. Studies with intact mononuclear and polymorphonuclear cells and membranes comparing two radioligands in the presence and absence of chloroquine. Biochem Pharmacol. 1983;32:2033–43.
8. Swanson MA, Lee WT, Sanders VM. IFN-gamma production by Th1 cells generated from naive CD4+ T cells exposed to norepinephrine. J Immunol. 2001;166:232–40.
9. Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. J Immunol. 1997;158:4200–10.
10. Loza MJ, Foster S, Peters SP, Penn RB. Beta-agonists modulate T-cell functions via direct actions on type 1 and type 2 cells. Blood. 2006;107:2052–60.
11. Bao JY, Huang Y, Wang F, Peng YP, Qiu YH. Expression of alpha-AR subtypes in T lymphocytes and role of the alpha-ARs in mediating modulation of T cell function. Neuroimmunomodulation. 2007;14:344–53.
12. Roupe van der Voort C, Heijnen CJ, Wulffraat N, Kuis W, Kavelaars A. Stress induces increases in IL-6 production by leucocytes of patients with the chronic inflammatory disease juvenile rheumatoid arthritis: a putative role for alpha(1)-adrenergic receptors. J Neuroimmunol. 2000;110:223–9.
13. Bresson JL, Jeay S, Gagnerault MC, Kayser C, Beressi N, Wu Z, et al. Growth hormone (GH) and prolactin receptors in human peripheral blood mononuclear cells: relation with age and GH-binding protein. Endocrinology. 1999;140:3203–9.
14. Rapaport R, Sills IN, Green L, Barrett P, Labus J, Skuza KA, et al. Detection of human growth hormone receptors on IM-9 cells and peripheral blood mononuclear cell subsets by flow cytometry: correlation with growth hormone-binding protein levels. J Clin Endocrinol Metab. 1995;80:2612–9.
15. Hattori N, Saito T, Yagyu T, Jiang BH, Kitagawa K, Inagaki C. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. J Clin Endocrinol Metab. 2001;86:4284–91.
16. Pellegrini I, Lebrun JJ, Ali S, Kelly PA. Expression of prolactin and its receptor in human lymphoid cells. Mol Endocrinol. 1992;6:1023–31.
17. Lai JP, Douglas SD, Ho WZ. Human lymphocytes express substance P and its receptor. J Neuroimmunol. 1998;86:80–6.
18. Petitto JM, Huang Z, McCarthy DB. Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: evidence of low levels of mRNA expression and (125I)NPY binding sites. J Neuroimmunol. 1994;54:81–6.
19. Radulovic M, Dautzenberg FM, Sydow S, Radulovic J, Spiess J. Corticotropin-releasing factor receptor 1 in mouse spleen: expression after immune stimulation and identification of receptor-bearing cells. J Immunol. 1999;162:3013–21.
20. Cloez-Tayarani I, Petit-Bertron AF, Venters HD, Cavaillon JM. Differential effect of serotonin on cytokine production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells: involvement of 5-hydroxytryptamine2A receptors. Int Immunol. 2003;15:233–40.

21. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol. 2002;20:125–63.
22. Adcock IM, Brown CR, Shirasaki H, Barnes PJ. Effects of dexamethasone on cytokine and phorbol ester stimulated c-Fos and c-Jun DNA binding and gene expression in human lung. Eur Respir J. 1994;7:2117–23.
23. Ramdas J, Harmon JM. Glucocorticoid-induced apoptosis and regulation of NF-kappaB activity in human leukemic T cells. Endocrinology. 1998;139:3813–21.
24. Caldenhoven E, Liden J, Wissink S, Van de Stolpe A, Raaijmakers J, Koenderman L, et al. Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids. Mol Endocrinol. 1995;9:401–12.
25. Ray A, Prefontaine KE. Physical association and functional antagonism between the p65 subunit of transcription factor NF-kappa B and the glucocorticoid receptor. Proc Natl Acad Sci U S A. 1994;91:752–6.
26. Salicru AN, Sams CF, Marshall GD. Cooperative effects of corticosteroids and catecholamines upon immune deviation of the type-1/type-2 cytokine balance in favor of type-2 expression in human peripheral blood mononuclear cells. Brain Behav Immun. 2007;21:913–20.
27. Gayo A, Mozo L, Suarez A, Tunon A, Lahoz C, Gutierrez C. Glucocorticoids increase IL-10 expression in multiple sclerosis patients with acute relapse. J Neuroimmunol. 1998;85:122–30.
28. DeKruyff RH, Fang Y, Umetsu DT. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4+ lymphocytes by inhibiting IL-12 production. J Immunol. 1998;160:2231–7.
29. Blotta MH, DeKruyff RH, Umetsu DT. Corticosteroids inhibit IL-12 production in human monocytes and enhance their capacity to induce IL-4 synthesis in CD4+ lymphocytes. J Immunol. 1997;158:5589–95.
30. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci. 2002;966:290–303.
31. Calcagni E, Elenkov IJ. Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. Ann N Y Acad Sci. 2006;1069:62–76.
32. Zen M, Canova M, Campana C, Bettio S, Nalotto L, Rampudda M, et al. The kaleidoscope of glucocorticoid effects on immune system. Autoimmun Rev. 2011;10:305–10.
33. Panina-Bordignon P, Mazzeo D, Lucia PD, D'Ambrosio D, Lang R, Fabbri L, et al. Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. J Clin Invest. 1997;100:1513–9.
34. Agarwal SK, Marshall GD. Beta-adrenergic modulation of human type-1/type-2 cytokine balance. J Allergy Clin Immunol. 2000;105:91–8.
35. Ramer-Quinn DS, Baker RA, Sanders VM. Activated T helper 1 and T helper 2 cells differentially express the beta-2-adrenergic receptor: a mechanism for selective modulation of T helper 1 cell cytokine production. J Immunol. 1997;159:4857–67.
36. Riether C, Kavelaars A, Wirth T, Pacheco-Lopez G, Doenlen R, Willemen H, et al. Stimulation of beta-adrenergic receptors inhibits calcineurin activity in CD4(+) T cells via PKA-AKAP interaction. Brain Behav Immun. 2011;25:59–66.
37. Kin NW, Sanders VM. It takes nerve to tell T and B cells what to do. J Leukoc Biol. 2006;79:1093–104.
38. Dorshkind K, Horseman ND. The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocr Rev. 2000;21:292–312.
39. Dobashi H, Sato M, Tanaka T, Tokuda M, Ishida T. Growth hormone restores glucocorticoid-induced T cell suppression. FASEB J. 2001;15:1861–3.
40. Jeay S, Sonenshein GE, Postel-Vinay MC, Kelly PA, Baixeras E. Growth hormone can act as a cytokine controlling survival and proliferation of immune cells: new insights into signaling pathways. Mol Cell Endocrinol. 2002;188:1–7.
41. Warwick-Davies J, Lowrie DB, Cole PJ. Growth hormone is a human macrophage activating factor. Priming of human monocytes for enhanced release of H2O2. J Immunol. 1995;154:1909–18.
42. Kooijman R, Willems M, De Haas CJ, Rijkers GT, Schuurmans AL, Van Buul-Offers SC, et al. Expression of type I insulin-like growth factor receptors on human peripheral blood mononuclear cells. Endocrinology. 1992;131:2244–50.
43. Clevenger CV, Russell DH, Appasamy PM, Prystowsky MB. Regulation of interleukin 2-driven T-lymphocyte proliferation by prolactin. Proc Natl Acad Sci U S A. 1990;87:6460–4.
44. Woody MA, Welniak LA, Sun R, Tian ZG, Henry M, Richards S, et al. Prolactin exerts hematopoietic growth-promoting effects in vivo and partially counteracts myelosuppression by azidothymidine. Exp Hematol. 1999;27:811–6.
45. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther. 2011;130:226–38.
46. Banks WA, Erickson MA. The blood–brain barrier and immune function and dysfunction. Neurobiol Dis. 2010;37:26–32.
47. Engelhardt B. The blood-central nervous system barriers actively control immune cell entry into the central nervous system. Curr Pharm Des. 2008;14:1555–65.
48. Verma S, Nakaoke R, Dohgu S, Banks WA. Release of cytokines by brain endothelial cells: a polarized response to lipopolysaccharide. Brain Behav Immun. 2006;20:449–55.
49. Quan N. Immune-to-brain signaling: how important are the blood–brain barrier-independent pathways? Mol Neurobiol. 2008;37:142–52.

50. Chen G, McCuskey RS, Reichlin S. Blood interleukin-6 and tumor necrosis factor-alpha elevation after intracerebroventricular injection of Escherichia coli endotoxin in the rat is determined by two opposing factors: peripheral induction by LPS transferred from brain to blood and inhibition of peripheral response by a brain-mediated mechanism. Neuroimmunomodulation. 2000;8:59–69.
51. Tonnesen E, Christensen NJ, Brinklov MM. Natural killer cell activity during cortisol and adrenaline infusion in healthy volunteers. Eur J Clin Investig. 1987;17:497–503.
52. Davis JM, Albert JD, Tracy KJ, Calvano SE, Lowry SF, Shires GT, et al. Increased neutrophil mobilization and decreased chemotaxis during cortisol and epinephrine infusions. J Trauma. 1991;31:725–31.
53. Kittner JM, Jacobs R, Pawlak CR, Heijnen CJ, Schedlowski M, Schmidt RE. Adrenaline-induced immunological changes are altered in patients with rheumatoid arthritis. Rheumatology (Oxford). 2002;41:1031–9.
54. Van Tits LJ, Michel MC, Grosse-Wilde H, Happel M, Eigler FW, Soliman A, et al. Catecholamines increase lymphocyte beta 2-adrenergic receptors via a beta 2-adrenergic, spleen-dependent process. Am J Phys. 1990;258:E191–202.
55. Kappel M, Tvede N, Galbo H, Haahr PM, Kjaer M, Linstow M, et al. Evidence that the effect of physical exercise on NK cell activity is mediated by epinephrine. J Appl Physiol. 1991;70:2530–4.
56. Tvede N, Kappel M, Klarlund K, Duhn S, Halkjaer-Kristensen J, Kjaer M, et al. Evidence that the effect of bicycle exercise on blood mononuclear cell proliferative responses and subsets is mediated by epinephrine. Int J Sports Med. 1994;15:100–4.
57. Januszkiewicz A, Essen P, McNurlan MA, Ringden O, Garlick PJ, Wernerman J. A combined stress hormone infusion decreases in vivo protein synthesis in human T lymphocytes in healthy volunteers. Metabolism. 2001;50:1308–14.
58. Schedlowski M, Hosch W, Oberbeck R, Benschop RJ, Jacobs R, Raab HR, et al. Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms. J Immunol. 1996;156:93–9.
59. Richardson RP, Rhyne CD, Fong Y, Hesse DG, Tracey KJ, Marano MA, et al. Peripheral blood leukocyte kinetics following in vivo lipopolysaccharide (LPS) administration to normal human subjects. Influence of elicited hormones and cytokines. Ann Surg. 1989;210:239–45.
60. Dimitrov S, Lange T, Born J. Selective mobilization of cytotoxic leukocytes by epinephrine. J Immunol. 2010;184:503–11.
61. Bosch JA, Berntson GG, Cacioppo JT, Dhabhar FS, Marucha PT. Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: a potential pathway linking immunologic reactivity to cardiovascular disease. Brain Behav Immun. 2003;17:251–9.
62. Anane LH, Edwards KM, Burns VE, Drayson MT, Riddell NE, van Zanten JJ, et al. Mobilization of gammadelta T lymphocytes in response to psychological stress, exercise, and beta-agonist infusion. Brain Behav Immun. 2009;23:823–9.
63. Kappel M, Poulsen TD, Galbo H, Pedersen BK. Effects of elevated plasma noradrenaline concentration on the immune system in humans. Eur J Appl Physiol. 1998;79:93–8.
64. Kappel M, Hansen MB, Diamant M, Jorgensen JO, Gyhrs A, Pedersen BK. Effects of an acute bolus growth hormone infusion on the human immune system. Horm Metab Res. 1993;25:579–85.
65. Burns AM, Keogan M, Donaldson M, Brown DL, Park GR. Effects of inotropes on human leucocyte numbers, neutrophil function and lymphocyte subtypes. Br J Anaesth. 1997;78:530–5.
66. Sondergaard SR, Ostrowski K, Ullum H, Pedersen BK. Changes in plasma concentrations of interleukin-6 and interleukin-1 receptor antagonists in response to adrenaline infusion in humans. Eur J Appl Physiol. 2000;83:95–8.
67. Keller P, Keller C, Robinson LE, Pedersen BK. Epinephrine infusion increases adipose interleukin-6 gene expression and systemic levels in humans. J Appl Physiol. 2004;97:1309–12.
68. Steensberg A, Toft AD, Schjerling P, Halkjaer-Kristensen J, Pedersen BK. Plasma interleukin-6 during strenuous exercise: role of epinephrine. Am J Phys. 2001;281:C1001–4.
69. Jan BU, Coyle SM, Oikawa LO, Lu SE, Calvano SE, Lehrer PM, et al. Influence of acute epinephrine infusion on endotoxin-induced parameters of heart rate variability: a randomized controlled trial. Ann Surg. 2009;249:750–6.
70. Barber AE, Coyle SM, Marano MA, Fischer E, Calvano SE, Fong Y, et al. Glucocorticoid therapy alters hormonal and cytokine responses to endotoxin in man. J Immunol. 1993;150:1999–2006.
71. van der Poll T, Barber AE, Coyle SM, Lowry SF. Hypercortisolemia increases plasma interleukin-10 concentrations during human endotoxemia—a clinical research center study. J Clin Endocrinol Metab. 1996;81:3604–6.
72. Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Phys. 2003;285:E433–7.
73. de Metz J, Sprangers F, Endert E, Ackermans MT, ten Berge IJ, Sauerwein HP, et al. Interferon-gamma has immunomodulatory effects with minor endocrine and metabolic effects in humans. J Appl Physiol. 1999;86:517–22.
74. McCarthy D, MacDonald I, Grant M, Marbut M, Watling M. Studies on the immediate and delayed leucocytosis elicited by brief (30 min) strenuous exercise. Eur J Appl Physiol. 1992;64:513–7.
75. Suzuki K, Sato H, Kikuchi T, Abe T, Nakaji S, Sugawara K, et al. Capacity of circulating neutrophils

to produce reactive oxygen species after exhaustive exercise. J Appl Physiol. 1996;81:1213–22.
76. Peake JM, Wilson G, Hordern M, Suzuki K, Nosaka K, Yamaya K, et al. Changes in neutrophil receptor expression, degranulation and respiratory burst activity after moderate and high intensity exercise. J Appl Physiol. 2004;97:612–8.
77. Rhind SG, Gannon GA, Shek PN, Brenner IK, Severs Y, Zamecnik J, et al. Contribution of exertional hyperthermia to sympathoadrenal-mediated lymphocyte subset redistribution. J Appl Physiol. 1999;87:1178–85.
78. Steensberg A, Toft AD, Bruunsgaard H, Sandmand M, Halkjaer-Kristensen J, Pedersen BK. Strenuous exercise decreases the percentage of type 1 T cells in the circulation. J Appl Physiol. 2001;91:1708–12.
79. Brenner IK, Castellani JW, Gabaree C, Young AJ, Zamecnik J, Shephard RJ, et al. Immune changes in humans during cold exposure: effects of prior heating and exercise. J Appl Physiol. 1999;87:699–710.
80. Hansen MK, O'Connor KA, Goehler LE, Watkins LR, Maier SF. The contribution of the vagus nerve in interleukin-1beta-induced fever is dependent on dose. Am J Physiol Regul Integr Comp Physiol. 2001;280:R929–34.
81. Cross MC, Radomski MW, Vanhelder WP, Rhind SG, Shephard RJ. Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocyte subsets. J Appl Physiol. 1996;81:822–9.
82. Gabriel H, Schwarz L, Steffens G, Kindermann W. Immunoregulatory hormones, circulating leucocyte and lymphocyte subpopulations before and after endurance exercise of different intensities. Int J Sports Med. 1992;13:359–66.
83. Suzuki K, Totsuka M, Nakaji S, Yamada M, Kudoh S, Liu Q, et al. Endurance exercise causes interaction among stress hormones, cytokines, neutrophil dynamics, and muscle damage. J Appl Physiol. 1999;86:1360–7.
84. Kruger K, Agnischock S, Lechtermann A, Tiwari S, Mishra M, Pilat C, et al. Intensive resistance exercise induces lymphocyte apoptosis via cortisol and glucocorticoid receptor-dependent pathways. J Appl Physiol. 2011;110:1226–32.
85. Papanicolaou DA, Petrides JS, Tsigos C, Bina S, Kalogeras KT, Wilder R, et al. Exercise stimulates interleukin-6 secretion: inhibition by glucocorticoids and correlation with catecholamines. Am J Physiol Endocrinol Metab. 1996;34:E601–5.
86. Rhind SG, Gannon GA, Shephard RJ, Buguet A, Shek PN, Radomski MW. Cytokine induction during exertional hyperthermia is abolished by core temperature clamping: neuroendocrine regulatory mechanisms. Int J Hyperth. 2004;20:503–16.
87. Singh A, Papanicolaou DA, Lawrence LL, Howell EA, Chrousos GP, Deuster PA. Neuroendocrine responses to running in women after zinc and vitamin E supplementation. Med Sci Sports Exerc. 1999;31:536–42.
88. Rhind SG, Castellani JW, Brenner IK, Shephard RJ, Zamecnik J, Montain SJ, et al. Intracellular monocyte and serum cytokine expression is modulated by exhausting exercise and cold exposure. Am J Physiol Regul Integr Comp Physiol. 2001;281:R66–75.
89. Walsh NP, Whitham M. Exercising in environmental extremes: a greater threat to immune function? Sports Med. 2006;36:941–76.
90. Febbraio MA, Lambert DL, Starkie RL, Proietto J, Hargreaves M. Effect of epinephrine on muscle glycogenolysis during exercise in trained men. J Appl Physiol. 1998;84:465–70.
91. Steensberg A, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, et al. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. J Physiol. 2001;537:633–9.
92. Helge JW, Stallknecht B, Pedersen BK, Galbo H, Kiens B, Richter EA. The effect of graded exercise on IL-6 release and glucose uptake in human skeletal muscle. J Physiol. 2003;546:299–305.
93. Foster NK, Martyn JB, Rangno RE, Hogg JC, Pardy RL. Leukocytosis of exercise: role of cardiac output and catecholamines. J Appl Physiol. 1986;61:2218–23.
94. McMurray RG, Forsythe WA, Mar MH, Hardy CJ. Exercise intensity-related responses of beta-endorphin and catecholamines. Med Sci Sports Exerc. 1987;19:570–4.
95. Weltman A, Pritzlaff CJ, Wideman L, Weltman JY, Blumer JL, Abbott RD, et al. Exercise-dependent growth hormone release is linked to markers of heightened central adrenergic outflow. J Appl Physiol. 2000;89:629–35.
96. Davies CT, Few JD. Effects of exercise on adrenocortical function. J Appl Physiol. 1973;35:887–91.
97. Nieman D, Miller A, Henson D, Warren B, Gusewitch G, Johnson R, et al. Effect of high-intensity versus moderate-intensity exercise on lymphocyte subpopulations and proliferative response. Int J Sports Med. 1994;15:199–206.
98. Tvede N, Kappel M, Halkjaer-Kristensen J, Galbo H, Pedersen BK. The effect of light, moderate and severe bicycle exercise on lymphocyte subsets, natural and lymphokine activated killer cells, lymphocyte proliferative response and interleukin 2 production. Int J Sports Med. 1993;14:275–82.
99. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. Eur J Appl Physiol. 2005;95:514–21.
100. Scott JP, Sale C, Greeves JP, Casey A, Dutton J, Fraser WD. Effect of exercise intensity in the cytokine response to an acute bout of running. Med Sci Sports Exerc. 2011;43:2297–306.
101. Del Corral P, Howley ET, Hartsell M, Ashraf M, Younger MS. Metabolic effects of low cortisol during exercise in humans. J Appl Physiol. 1998;84:939–47.

102. Bishop N, Blannin A, Robson P, Walsh N, Gleeson M. The effects of carbohydrate supplementation on immune responses to a soccer-specific exercise protocol. J Sports Sci. 1999;17:787–96.
103. Henson D, Nieman D, Nehlsen-Cannarella S, Fagoaga O, Shannon M, Bolton M, et al. Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing. Med Sci Sports Exerc. 2000;32:1384–9.
104. Peake J, Wilson G, Mackinnon L, Coombes JS. Carbohydrate supplementation and alterations in neutrophils, and plasma cortisol and myoglobin concentration after intense exercise. Eur J Appl Physiol. 2005;93:672–8.
105. Nieman DC, Henson DA, Davis JM, Dumke CL, Utter AC, Murphy EA, et al. Blood leukocyte mRNA expression for IL-10, IL-1Ra, and IL-8, but not IL-6, increases after exercise. J Interf Cytokine Res. 2006;26:668–74.
106. Starkie RL, Angus DJ, Rolland J, Hargreaves M, Febbraio MA. Effect of prolonged, submaximal exercise and carbohydrate ingestion on monocyte intracellular cytokine production in humans. J Physiol. 2000;528:647–55.
107. Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Henson DA, Utter A, Davis JM, et al. Effects of mode and carbohydrate on the granulocyte and monocyte response to intensive, prolonged exercise. J Appl Physiol. 1998;84:1252–9.
108. Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Henson DA, Utter A, Davis JM, et al. Influence of mode and carbohydrate on the cytokine response to heavy exertion. Med Sci Sports Exerc. 1998;30:671–8.
109. Bishop NC, Gleeson M, Nicholas CW, Ali A. Influence of carbohydrate supplementation on plasma cytokine and neutrophil degranulation responses to high intensity intermittent exercise. Int J Sport Nutr Exerc Metab. 2002;12:145–56.
110. Nieman DC, Davis JM, Henson DA, Gross SJ, Dumke CL, Utter AC, et al. Muscle cytokine mRNA changes after 2.5 h of cycling: influence of carbohydrate. Med Sci Sports Exerc. 2005;37:1283–90.
111. Nieman DC, Davis JM, Henson DA, Walberg-Rankin J, Shute M, Dumke CL, et al. Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. J Appl Physiol. 2003;94:1917–25.
112. Nieman DC, Henson DA, Smith LL, Utter AC, Vinci DM, Davis JM, et al. Cytokine changes after a marathon race. J Appl Physiol. 2001;91:109–14.
113. Nieman D, Fagoaga O, Butterworth D, Warren B, Utter A, Davis J, et al. Carbohydrate supplementation affects blood granulocyte and monocyte trafficking but not function following 2.5 hours of running. Am J Clin Nutr. 1997;66:153–9.
114. Henson DA, Nieman DC, Pistilli EE, Schilling B, Colacino A, Utter AC, et al. Influence of carbohydrate and age on lymphocyte function following a marathon. Int J Sport Nutr Exerc Metab. 2004;14:308–22.
115. Lancaster GI, Khan Q, Drysdale PT, Wallace F, Jeukendrup AE, Drayson MT, et al. Effect of prolonged exercise and carbohydrate ingestion on type 1 and type 2 T lymphocyte distribution and intracellular cytokine production in humans. J Appl Physiol. 2005;98:565–71.
116. McFarlin BK, Flynn MG, Hampton T. Carbohydrate consumption during cycling increases in vitro NK cell responses to IL-2 and IFN-gamma. Brain Behav Immun. 2007;21:202–8.
117. McFarlin BK, Flynn MG, Stewart LK, Timmerman KL. Carbohydrate intake during endurance exercise increases natural killer cell responsiveness to IL-2. J Appl Physiol. 2004;96:271–5.
118. Nieman DC, Henson DA, Gojanovich G, Davis JM, Murphy EA, Mayer EP, et al. Influence of carbohydrate on immune function following 2 h cycling. Res Sports Med. 2006;14:225–37.
119. Bishop NC, Blannin AK, Walsh NP, Gleeson M. Carbohydrate beverage ingestion and neutrophil degranulation responses following cycling to fatigue at 75% VO_{2max}. Int J Sports Med. 2001;22:226–31.
120. Koch AJ, Potteiger JA, Chan MA, Benedict SH, Frey BB. Minimal influence of carbohydrate ingestion on the immune response following acute resistance exercise. Int J Sport Nutr Exerc Metab. 2001;11:149–61.
121. Bishop NC, Walsh NP, Haines DL, Richards EE, Gleeson M. Pre-exercise carbohydrate status and immune responses to prolonged cycling: I. Effect on neutrophil degranulation. Int J Sport Nutr Exerc Metab. 2001;11:490–502.
122. Mitchell JB, Dugas JP, McFarlin BK, Nelson MJ. Effect of exercise, heat stress, and hydration on immune cell number and function. Med Sci Sports Exerc. 2002;34:1941–50.
123. Nieman DC, Henson DA, Fagoaga OR, Utter AC, Vinci DM, Davis JM, et al. Change in salivary IgA following a competitive marathon race. Int J Sports Med. 2002;23:69–75.
124. Febbraio MA, Steensberg A, Keller C, Starkie RL, Nielsen HB, Krustrup P, et al. Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. J Physiol. 2003;549:607–12.
125. Starkie RL, Arkinstall MJ, Koukoulas I, Hawley JA, Febbraio MA. Carbohydrate ingestion attenuates the increase in plasma interleukin-6, but not skeletal muscle interleukin-6 mRNA, during exercise in humans. J Physiol. 2001;533:585–91.
126. Bishop NC, Fitzgerald C, Porter PJ, Scanlon GA, Smith AC. Effect of caffeine ingestion on lymphocyte counts and subset activation in vivo following strenuous cycling. Eur J Appl Physiol. 2005;93:606–13.
127. Bishop NC, Walker GJ, Scanlon GA, Richards S, Rogers E. Salivary IgA responses to prolonged

intensive exercise following caffeine ingestion. Med Sci Sports Exerc. 2006;38:513–9.
128. Whitham M, Walker GJ, Bishop NC. Effect of caffeine supplementation on the extracellular heat shock protein 72 response to exercise. J Appl Physiol. 2006;101:1222–7.
129. Walker GJ, Dziubak A, Houghton L, Prendergast C, Lim L, Bishop NC. The effect of caffeine ingestion on human neutrophil oxidative burst responses following time-trial cycling. J Sports Sci. 2008;26:611–9.
130. Walker GJ, Caudwell P, Dixon N, Bishop NC. The effect of caffeine ingestion on neutrophil oxidative burst responses following prolonged cycling. Int J Sport Nutr Exerc Metab. 2006;16:24–35.
131. Fletcher DK, Bishop NC. Effect of a single and repeated dose of caffeine on antigen-stimulated human natural killer cell CD69 expression after high-intensity intermittent exercise. Eur J Appl Physiol. 2011;111:1329–39.
132. Fletcher DK, Bishop NC. Effect of a high and low dose of caffeine on antigen-stimulated activation of human natural killer cells after prolonged cycling. Int J Sport Nutr Exerc Metab. 2011;21:155–65.
133. Brenner IK, Zamecnik J, Shek PN, Shephard RJ. The impact of heat exposure and repeated exercise on circulating stress hormones. Eur J Appl Physiol. 1997;76:445–54.
134. Niess AM, Fehrenbach E, Lehmann R, Opavsky L, Jesse M, Northoff H, et al. Impact of elevated ambient temperatures on the acute immune response to intensive endurance exercise. Eur J Appl Physiol. 2003;89:344–51.
135. Severs Y, Brenner I, Shek PN, Shephard RJ. Effects of heat and intermittent exercise on leukocyte and sub-population cell counts. Eur J Appl Physiol. 1996;74:234–45.
136. Starkie RL, Hargreaves M, Rolland J, Febbraio M. Heat stress, cytokines and the immune response to exercise. Brain Behav Immun. 2005;19:404–12.
137. Laing SJ, Jackson AR, Walters R, Lloyd-Jones E, Whitham M, Maassen N, et al. Human blood neutrophil responses to prolonged exercise with and without a thermal clamp. J Appl Physiol. 2008;104:20–6.
138. Peake J, Peiffer J, Abbiss C, Nosaka K, Laursen P, Suzuki K. Body temperature and its effect on leukocyte mobilisation, cytokines and markers of neutrophil activation. Eur J Appl Physiol. 2007;102:391–401.
139. Brenner IK, Severs YD, Shek PN, Shephard RJ. Impact of heat exposure and moderate, intermittent exercise on cytolytic cells. Eur J Appl Physiol. 1996;74:162–71.
140. Murray DR, Irwin M, Rearden CA, Ziegler M, Motulsky H, Maisel AS. Sympathetic and immune interactions during dynamic exercise. Mediation via a beta 2-adrenergic-dependent mechanism. Circulation. 1992;86:203–13.
141. Kruger K, Lechtermann A, Fobker M, Volker K, Mooren FC. Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav Immun. 2008;22:324–38.
142. Starkie RL, Rolland J, Febbraio MA. Effect of adrenergic blockade on lymphocyte cytokine production at rest and during exercise. Am J Physiol Cell Physiol. 2001;281:C1233–40.
143. Mazzeo R, Donovan D, Fleshner M, Butterfield G, Zamudio S, Wolfel E, et al. Interleukin-6 response to exercise and high-altitude exposure: influence of alpha-adrenergic blockade. J Appl Physiol. 2001;91:2143–9.
144. Carmichael MD, Davis JM, Murphy EA, Carson JA, Van Rooijen N, Mayer E, et al. Role of brain macrophages on IL-1beta and fatigue following eccentric exercise-induced muscle damage. Brain Behav Immun. 2010;24:564–8.
145. Carmichael MD, Davis JM, Murphy EA, Brown AS, Carson JA, Mayer E, et al. Recovery of running performance following muscle-damaging exercise: relationship to brain IL-1beta. Brain Behav Immun. 2005;19:445–52.
146. Carmichael MD, Davis JM, Murphy EA, Brown AS, Carson JA, Mayer EP, et al. Role of brain IL-1beta on fatigue after exercise-induced muscle damage. Am J Physiol Regul Integr Comp Physiol. 2006;291:R1344–8.
147. Steensberg A, Dalsgaard MK, Secher NH, Pedersen BK. Cerebrospinal fluid IL-6, HSP72, and TNF-alpha in exercising humans. Brain Behav Immun. 2006;20:585–9.
148. Nybo L, Nielsen B, Pedersen BK, Moller K, Secher NH. Interleukin-6 release from the human brain during prolonged exercise. J Physiol. 2002;542:991–5.
149. Dressendorfer RH, Petersen SR, Moss Lovshin SE, Hannon JL, Lee SF, Bell GJ. Performance enhancement with maintenance of resting immune status after intensified cycle training. Clin J Sport Med. 2002;12:301–7.
150. Imrich R, Tibenska E, Koska J, Ksinantova L, Kvetnansky R, Bergendiova-Sedlackova K, et al. Repeated stress-induced stimulation of catecholamine response is not followed by altered immune cell redistribution. Ann N Y Acad Sci. 2004;1018:266–72.
151. Mackinnon LT, Hooper SL, Jones S, Gordon RD, Bachmann AW. Hormonal, immunological, and hematological responses to intensified training in elite swimmers. Med Sci Sports Exerc. 1997;29:1637–45.
152. Ndon JA, Snyder AC, Foster C, Wehrenberg WB. Effects of chronic intense exercise training on the leukocyte response to acute exercise. Int J Sports Med. 1992;13:176–82.
153. Mujika I, Chatard JC, Geyssant A. Effects of training and taper on blood leucocyte populations in competitive swimmers: relationships with cortisol and performance. Int J Sports Med. 1996;17:213–7.
154. Robson-Ansley PJ, Blannin A, Gleeson M. Elevated plasma interleukin-6 levels in trained male triathletes

following an acute period of intense interval training. Eur J Appl Physiol. 2006;99:353–60.
155. Fry RW, Morton AR, Garcia-Webb P, Crawford GP, Keast D. Biological responses to overload training in endurance sports. Eur J Appl Physiol. 1992;64:335–44.
156. Smith C, Myburgh KH. Are the relationships between early activation of lymphocytes and cortisol or testosterone influenced by intensified cycling training in men? Appl Physiol Nutr Metab. 2006;31:226–34.
157. Makras P, Koukoulis GN, Bourikas G, Papatheodorou G, Bedevis K, Menounos P, et al. Effect of 4 weeks of basic military training on peripheral blood leucocytes and urinary excretion of catecholamines and cortisol. J Sports Sci. 2005;23:825–34.
158. Ortega E, Barriga C, De la Fuente M. Study of the phagocytic process in neutrophils from elite sportswomen. Eur J Appl Physiol. 1993;66:37–42.
159. Cunniffe B, Griffiths H, Proctor W, Davies B, Baker JS, Jones KP. Mucosal immunity and illness incidence in elite rugby union players across a season. Med Sci Sports Exerc. 2011;43:388–97.
160. Verde T, Thomas S, Shephard RJ. Potential markers of heavy training in highly trained distance runners. Br J Sports Med. 1992;26:167–75.
161. Lancaster G, Halson S, Khan Q, Drysdale P, Wallace F, Jeukendrup AE, et al. Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2 T lymphocytes. Exerc Immunol Rev. 2004;10:91–106.
162. McDowell SL, Hughes RA, Hughes RJ, Housh TJ, Johnson GO. The effect of exercise training on salivary immunoglobulin A and cortisol responses to maximal exercise. Int J Sports Med. 1992;13:577–80.
163. Hooper SL, Mackinnon LT, Howard A, Gordon RD, Bachmann AW. Markers for monitoring overtraining and recovery. Med Sci Sports Exerc. 1995;27:106–12.
164. Edwards KM, Burns VE, Reynolds T, Carroll D, Drayson M, Ring C. Acute stress exposure prior to influenza vaccination enhances antibody response in women. Brain Behav Immun. 2006;20:159–68.
165. Woods JA, Keylock KT, Lowder T, Vieira VJ, Zelkovich W, Dumich S, et al. Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: the immune function intervention trial. J Am Geriatr Soc. 2009;57:2183–91.
166. Keylock KT, Lowder T, Leifheit KA, Cook M, Mariani RA, Ross K, et al. Higher antibody, but not cell-mediated, responses to vaccination in high physically fit elderly. J Appl Physiol. 2007;102:1090–8.
167. Keylock KT, Vieira VJ, Wallig MA, DiPietro LA, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am J Physiol Regul Integr Comp Physiol. 2008;294:R179–84.
168. Nieman DC. Is infection risk linked to exercise workload? Med Sci Sports Exerc. 2000;32:S406–11.
169. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports. 2006;16(Suppl 1):3–63.
170. Walsh N, et al. Position statement. Part one: Immune function and exercise. Exerc Immunol Rev. 2011;17:6–63.