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

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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).

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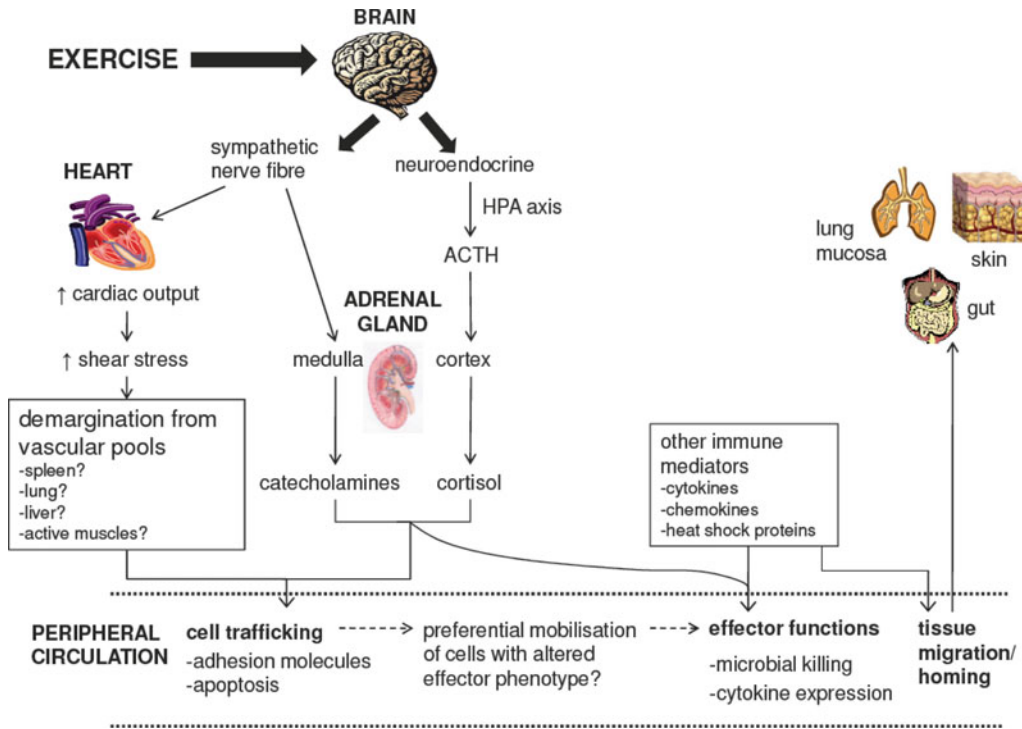


Fig. 1. Potential mechanisms by which stress hormone interact with the immune system during exercise. Reprinted, with permission, from TOM-Systemdruck GmbH, Walsh N et al., Position statement. Part one: Immune function and exercise. *Exercise Immunology Review* 2011;17: 6–63.

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)

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 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-1 β , IL-6, TNF- α) (2). Glucocorticoid receptors are 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, 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, 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 (NF κ B) (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 NF κ B transcriptional activity through two mechanisms. Firstly, glucocorticoids can induce expression of the inhibitory protein I κ B, which then prevents NF κ B from translocating to the nucleus where it initiates transcription (23). Secondly, physical interaction or cross-talk between glucocorticoid receptors and NF κ B can suppress transcription (24, 25). By suppressing the transcriptional activity of AP-1 and NF κ B, glucocorticoids regulate various immune functions, including cytokine production (21). In particular, glucocorticoids inhibit monocyte production of the type 1 cytokines IL-12 and IFN- γ , which in turn favours the production of the 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 μ M) 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 NF κ B (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 NF κ B (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 bi-directional. Pro-inflammatory cytokines released from immune cells (e.g. IL-1 β , 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 $\mu\text{g}/\text{min}$ 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 leucocyte 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% $\dot{V}O_{2max}$, 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 $>60\% \dot{V}O_{2\max}$ (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 skeletal muscle during exercise, but the effects of carbohydrate on mRNA expression of IL-6 and IL-8 in 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 $\sim 78\% \dot{V}O_{2\max}$. 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% $\dot{V}O_{2\max}$. 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% $\dot{V}O_{2\max}$. 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-1 β 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 increase 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: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 interaction 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.

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