HIGHLIGHTED TOPIC | Exercise and Inflammation

Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity

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What is striking about dangerous exercise is that in almost every instance, the interrelated stress, inflammatory, and immune systems play a significant role. A key concept that has emerged over the past several decades is that exercise, even in healthy people, leads to a robust inflammatory response characterized by mobilization of leukocytes and an increase in their numbers in the central circulation, and an increase in circulating potent inflammatory mediators like IL-6, the latter a pleiotropic cytokine (11, 103) produced by immune cells (44), a variety of tissues [like adipocytes (125)], and directly from the active muscle tissue (104, 125, 129, 131). Brief exercise stimulates innate immunity at the systemic level, as well as setting the stage for local, muscle inflammatory responses.

It has been known for decades that individual bouts of exercise lead to an increase in circulating leukocytes and even stem cells (1, 10, 24, 91, 114, 158). This is a remarkably reproducible, substantial, somewhat dose-dependent phenomenon known to exist in children and adults, as well as in other mammals (34, 55, 64, 105). Lymphocytes, monocytes, and natural killer (NK) cells increase rapidly with the onset of exercise but begin to decrease immediately on its cessation. Circulating neutrophils increase more slowly and may remain...
elevated for up to several hours, long after the initiating bout of exercise ends (93, 112, 155). We now know that exercise as brief in duration as 6 min can mobilize leukocytes (120); thus the physical activity-related increase in these critical circulating innate immune cells happens frequently in the daily lives of many humans and other mammals.

In 1999, Ostrowski and coworkers (97) presented a model of the immune and inflammatory response to exercise in healthy people. They noted that strenuous exercise led to increased circulating levels of proinflammatory mediators, but simultaneously, “... cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise.” Moreover, the idea that initial stimulus of the inflammatory system “awakens” both pro- and anti-inflammatory response pathways is seen not only in exercise, but in other conditions, like sepsis and burn injury (107, 111), as well.

Until fairly recently, the potential biological significance of exercise-induced immune responses was either ignored or minimized as simply another typical manifestation of the global response to all sorts of physiological and psychological “stress or danger” stimuli mediated in common through neuroendocrine activity and chemical mediators like cortisol, growth hormone, epinephrine, and norepinephrine, all of which can alter immune function (82, 83, 96, 99, 119). However, the emerging view is that while exercise clearly elicits a brain “danger” response, central stimulation of neuroendocrine pathways alone do not account for all of the inflammatory and immune responses known to accompany brief bouts of exercise (130). Indeed, in studies that have attempted to compare the inflammatory response to exercise with psychosocial stress, exercise was found to alter immune mediators far more profoundly (50). Unlike psychosocial stress, exercise is accompanied by target tissue metabolic signals (e.g., profound change in pH, lactic acid, temperature, PO2, and PCO2) that themselves can independently alter immune mediators [like heat shock proteins (38, 73)] and leukocyte function (76). There is even evidence that exercise may be accompanied by translocation of gut bacteria into the central circulation, causing a classic antigen-mediated systemic immune response (18, 58, 85). Finally, in recent years, Pedersen, Febbraio, and their collaborators have made the groundbreaking discovery that working muscle tissue itself produces immune mediators like IL-6 and IL-8 (2, 37).

We now know that the change in numbers of circulating immune cells following exercise is also accompanied by a change in the gene-expression profile of these cells (25, 39). In our laboratory, Connolly et al. (25) showed that a relatively brief bout of heavy exercise significantly altered the expression of hundreds of genes in peripheral blood mononuclear cells (PBMCs). Following 30 min of heavy exercise, we found changes in PBMC genes reflecting a range of responses including pro-inflammatory responses, e.g., prostaglandin D2 synthase (PTGDS) (145), cathepsin W (CTSW) (72), MIP 1β (CCL4) (109), and heat shock 70-kDa protein 1B (HSPA1B) (118); anti-inflammatory responses, e.g., dual-specificity phosphatase 1 (DUSP1) (75), interleukin-1 receptor antagonist (IL1RA) (53), cystatin (CST7) (70), and aldo-keto reductase family 1, member C3 (AKR1C3) (113); and even growth factors, e.g., epieregulin (EREG) (160), early growth response-1 (EGR-1) (32), and endothelial growth factor (EGF FL) (156).

The bulk of the gene responses were transient and returned to baseline, or even below baseline, by 1 h of recovery. Whether these documented changes in the gene expression in circulating immune cells in response to exercise occur because of direct effects on the cells themselves, or, alternatively, by mobilizing cells with different gene expression profile patterns from various depots, is not known. Whatever the mechanism may prove to be, while exercise can quickly stimulate pro-inflammatory gene responses in PBMCs, anti-inflammatory signals are also put into play that rapidly quench the development of a potentially deleterious inflammatory state within circulating immune cells.

DANGEROUS EXERCISE

The usual balance between the pro- and anti-inflammatory exercise responses is occasionally upset, however, and when it is, disease may result. In the following, we review several examples of failed homeostatic inflammatory responses to exercise.


Injury and overuse. Musculoskeletal sports injuries range from the common condition of delayed-onset muscle soreness to frank breaks, tears, and dislocations, and invariably involve acute inflammation (22, 102, 106, 146). Indeed, as shown in Fig. 1, Carp and coworkers (22) recently demonstrated that even local musculoskeletal (work-related) injuries can lead to increases in systemic levels of mediators like TNF-α and IL-1β that indicate inflammation. It is, however, not at all clear if the initial inflammatory response is beneficial or harmful and, consequently, whether or not the early inflammation should be treated (15, 152). As noted by Tidball (141), muscle repair in response to injury consists of a “complex picture in which inflammatory cells promote both injury and repair, through the combined actions of free radicals, growth factors, and chemokines.” In a recent elegant study, Tidball and Wehling-Hendricks (142) compared the different regulatory functions of macrophages that infiltrate damaged muscle early after the insult (in the first 2 days) with those that appear in the muscle during days 2–4. Remarkably, their studies demonstrated that the later invading macrophages played more active roles in stimulating muscle repair, perhaps through interacting with resident satellite cells, while the early-invading macrophages played key roles in removing damaged tissue.

Thus the optimal balance of immune/inflammatory responses in sports injuries may depend not only on the profile of infiltrating types of leukocytes but even on the conditions (systemic? local?) that might differentiate functional pathways within a leukocyte subpopulation but even on the conditions (systemic? local?) that might differentiate functional pathways within a leukocyte subpopulation itself. Since these inflammatory/immune cells in the tissues likely originate from circulating immune cells in the circulation, it is reasonable to speculate that factors within the circulation might alter the function of these cells upon reaching target tissues. Interestingly, Lessner and coworkers (79) demonstrated that in the case of atherosclerotic lesions, growth of plaques was augmented through recruitment of monocytes from the circulation. The interaction of circulating immune cells, their tissue counterparts, and growth and repair in response to exercise remains a poorly investigated area.

With overuse syndromes or repeated injuries, the inflammatory response becomes chronic and can exacerbate, rather than ameliorate, the underlying injury (9). A number of investiga-
Exercise-associated allergic responses are uncommon, but when they do occur, can have severe consequences. For example, anaphylaxis is a severe form of allergic reaction that can lead to shock and death if not treated promptly. Exercise-induced anaphylaxis is a rare but potentially life-threatening condition that can occur during or after exercise, especially in individuals with a history of food allergies or other allergies.

The neutrophil is a type of white blood cell that plays a crucial role in inflammation and immune responses. In chronic lung disease or rheumatoid arthritis (RA), neutrophils can become dysregulated, leading to chronic inflammation. Exercise can exacerbate this dysregulation by releasing reactive oxygen species (ROS) that can damage tissue.

The word "anaphylaxis" was coined by Charles Richet in 1913 and refers to a systemic allergic reaction that occurs when an antigen previously encountered in the body binds to IgE antibodies, leading to the release of histamine and other inflammatory mediators. Recent research has suggested that anaphylaxis can be IgE dependent in most cases, but some cases may be independent of IgE.

Fig. 1. Evidence that regional musculoskeletal injury can lead to a systemic inflammatory response. Twenty-two individuals with a history of upper-extremity work-related musculoskeletal injury due to overuse of no longer than 12 wk duration were included. Using the upper-body musculoskeletal assessment (UBMA), in which higher scores indicate greater severity of the work-related disuse injury, these investigators found that increasing injury severity was significantly associated with increasing systemic levels of inflammatory indicators: C-reactive protein, TNF-α, IL-1β, and IL-6. Whether this chronic inflammatory state also influences immune cells rendering them more reactive to additional exercise is not known. Data are from Carp et al. (22).

Fig. 2. Exercise anaphylaxis. Exercise anaphylaxis is a rare but potentially life-threatening condition that can occur during or after exercise in individuals with a history of food allergies or other allergies. It is characterized by a rapid onset of symptoms including hypotension, urticaria, and wheezing. The mechanism of exercise anaphylaxis has yet to be identified, but research suggests that anaphylaxis can be IgE dependent or independent of IgE.
the circulation as a result of exercise-associated redistribution of blood flow (133), the stage is then set for a more profound immune response like anaphylaxis.

**Exercise-induced bronchoconstriction.** An imbalance of the pro- and anti-inflammatory leukocyte responses to exercise may also play a role in a significant clinical manifestation of asthma, exercise-induced bronchoconstriction (EIB)—the transient reduction in lung function due to airway obstruction that occurs after vigorous exercise. EIB is a common feature of asthma (particularly in children), estimated to occur in about 60–80% of asthmatic children (27), and exercise is the most common stimulus for inducing an attack in asthmatic children (5). There are recent data suggesting that EIB may be high in athletes (69). Despite the clinical importance of the phenomenon, the mechanism of EIB remains controversial, and EIB is often underdiagnosed (7, 17, 21, 122). The fact that many of the exercise-induced immune responses in healthy people involve increases of some of the same mediators [e.g., ICAM (3, 128)] and leukocytes [e.g., neutrophils (13)] that play a role in bronchoconstriction in asthmatics leads to the notion that leukocyte responses might be involved in the mechanism of EIB.

Controversy has surrounded the mechanisms responsible for EIB for decades (49, 88). Two theories, both resulting from airway dehydration associated with exercise, have predominated: 1) airway thermal flux (i.e., cooling and rewarming); and 2) increased airway osmolarity. These events, it is hypothesized, trigger an inflammatory response in the airway. There are inconsistencies, however, with clinical and experimental observations regarding both mechanisms (7). Moreover, despite some promising results in the early 1980s, the research into the role of inflammatory cells and cytokines in EIB had dwindled (29, 77, 78) until fairly recently.

There is now a growing body of data suggesting that leukocytes may be abnormal in asthmatics. For example, Mann and Chung (84) recently demonstrated increased expression on circulating neutrophils of the adhesion molecules CD11b and CD35 and of resistance to the effects of prednisolone, all evidence for increased neutrophil activation. Gounni and coworkers (51) demonstrated that there exists a subpopulation of circulating neutrophils in asthmatic subjects that express the IgE receptor FceRI and that when engaged, this receptor activates the neutrophils. The authors speculated that these neutrophils may play a role in asthma airway pathology by contributing to local inflammation and aggregation of lymphocytes.

There is also substantial data demonstrating abnormalities in lymphocytes in children (as young as 24 mo) and adults with asthma. In particular, lymphocytes obtained from peripheral blood in asthmatics demonstrate a predominance of T-helper lymphocyte type 2 (TH2, IL-4 producing) immune responses relative to TH1 (IFN-\(\gamma\)) producing) (33, 124). Moreover, Tsumori and colleagues (147) showed that T cells from asthmatic subjects, in particular TH2 cells, preferentially migrate to bronchial tissue (see Fig. 3), and de Blic and colleagues (28) found that bronchoalveolar lavage samples obtained from highly symptomatic children with asthma show substantially increased ratios of the protein products IL-4/IFN-\(\gamma\). Thus there is a direct line of evidence linking altered T-cell cytokine production from lymphocytes found in the circulation to levels
dangerous, deleterious consequences of exercise (asthma, anaphylaxis) are not more common? Obviously, for most people, the exercise-associated pro-inflammatory responses are blunted almost immediately by anti-inflammatory mediators stimulated simultaneously by the bout of physical activity. One theme that does emerge from the examples described above and from the recent literature is that exercise could become dangerous when and if an individual’s leukocytes had been rendered more responsive than normal to the additional immune stimulus of exercise.

In this scenario (Fig. 2), prior activation of leukocytes is sufficient to upset the normally balanced immune/inflammatory stimulation by exercise, and, consequently, the circulating immune cells “behave badly.” In the case of food-induced exercise anaphylaxis, as noted above, our model suggests that food-sensitized immune cells [possible lymphocytes or macrophages (136)] are relatively innocuous until they are redistributed from gut-associated circulatory depots, like the spleen, into the central circulation where they interact with larger numbers of immune cells, including basophils and mast cells, and cause a systemic response.

In the case of asthma, the prior activation of leukocytes may be the result of genetic or environmental factors. As noted, there is increasing data supporting the idea of an imbalance between the T helper type 1 (Th1) and Th2 lymphocytes in asthmatic subjects (90) that may be worsened with exercise (54). In addition, a particularly relevant group is the TIM genes (T-cell, immunoglobulin, mucin domain-containing molecules), which play a role in determining Th1 or Th2 function of lymphocytes (71). The genetics of asthma and atopy is the subject of much current research, speculation, and debate (68, 121). Many of the suspected genes are involved in regulation of immune cell function through mediators like TNF and IL-4. We identified the set of genes that were found to be both affected by exercise in PBMCs [Connolly et al. (25)] study and that have been associated with asthma [from a recent meta-analysis by Ober and Hoffjan (94)]. We found seven genes that overlapped in these two studies (Table 1), providing a potential road map for investigation into physiological pathways that might link exercise with bronchoconstriction (66, 100, 101, 137, 138).

It is now clear that EIB is worsened when people exercise under conditions of excessive air pollution. As noted recently by McConnell et al. (87), “incidence of new diagnoses of asthma is associated with heavy exercise in communities with high concentrations of ozone; thus, air pollution and outdoor exercise could contribute to the development of asthma in

Table 1. Seven genes that are both linked to asthma and whose expression in PBMCs is influenced by 30 min of exercise in healthy adults

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Gene Symbol</th>
<th>Role in Asthma</th>
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<tbody>
<tr>
<td>T-box 21</td>
<td>TBX21</td>
<td>Influences naive T-cell development</td>
</tr>
<tr>
<td>Adrenergic, β2- receptor, surface</td>
<td>ADRB2</td>
<td>Potentially important source of variability in the response to β2-agonist drugs</td>
</tr>
<tr>
<td>Prostaglandin D2 receptor (DP)</td>
<td>PTGDR</td>
<td>Involved in the control of inducible cyclooxygenase (COX-2) and its metabolites</td>
</tr>
<tr>
<td>Signal transducer and activator of transcription 4</td>
<td>STAT4</td>
<td>Mediates responses to interleukin-12 in lymphocytes and regulating the differentiation of T helper cells</td>
</tr>
<tr>
<td>Arachidonate 5-lipoxygenase</td>
<td>ALOX5</td>
<td>Encodes 5-lipoxygenase; involved in leukotriene role in aspirin-sensitive asthma</td>
</tr>
<tr>
<td>Prostaglandin E receptor 2 (subtype EP2), 53 kDa</td>
<td>PTGER2</td>
<td>Involved in the control of the inducible cyclooxygenase (COX-2) and its metabolites</td>
</tr>
<tr>
<td>Chemokine (C-C motif) ligand 5</td>
<td>CCL5</td>
<td>Promotes Th2 dominance</td>
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</table>

The genes listed were found to significantly increase expression following exercise in young adult men [data from Connolly et al. (25)] and were observed to be linked with asthma in at least one published study [data from Ober and Hoffjan (94)]. PBMC, peripheral blood mononuclear cells; Th2, T-helper type 2 lymphocyte.
children.” This idea is corroborated by recent work from Frampton and coworkers (45) (Table 2) showing that exposure to ultrafine particles in air pollution (<100 nm) in combination with exercise can influence activation of circulating lymphocytes and expression of key adhesion molecules like ICAM-1 on other leukocytes. These authors also found that the effect of the ultrafine particles on circulating leukocytes was different in asthmatic subjects compared with nonasthmatic controls. Thus we speculate that one contributing mechanism to EIB may be the combined influence of environmental stress and genetic predisposition rendering circulating leukocytes more susceptible to the innate immune signal from brief exercise.

Intercurrent illness, acute or chronic, activates the immune system, and with exercise, exercise modulation of previously activated leukocytes may occur. Surprisingly, despite much popular focus about whether physical training with intercurrent illnesses like colds and flu is dangerous, there is very little research on what happens to immune function when exercise is performed in the face of active immune responses to viral illness. School guidelines about when children can return to play following acute common illnesses such as asthma are varied and inconsistent (4). Inflammatory mediators like IL-6 than observed in controls in both children and adults (56, 143). In systemic lupus erythematosis, a systemic autoimmune disease (134), brief exercise leads to abnormal cortisol, pro-inflammatory cytokines like IL-6, exercise leads to larger acute increases in cytokines in both children and adults (150, 159). Intriguingly, obesity is now clearly associated with chronic low-grade inflammation with elevated circulating leukocytes and cytokines in both children and adults (14, 30, 60). Collectively, these clinical examples do suggest that exercise in the context of the chronically ill individual could potentially lead to deleterious consequences through mechanisms that involve a pathological combination of exercise stimulation of immune signals with leukocytes previously affected by other stress, inflammatory, or immune mediators.

**SUMMARY: IS EXERCISE AN “IMMUNIZATION”?**

This review of the existence of substantial immune-modulated pathophysiological effects of exercise substantiates the idea that the immune and inflammatory consequences of physical activity may play a role in the health benefits of exercise and leads to the question, “Is exercise an immunization?” In the most general sense, immunizations promote health by altering the immune system in a manner that prevents disease. Vaccinations specifically stimulate immunity with modified antigens that “educate” the immune system but without causing disease. Is exercise a powerful enough immune modulator that, like a killed or attenuated virus, actually causes a robust immune response to invoke the creation of specific memory cells in adaptive immunity to generate a long-term alteration in future immune responses?

There are increasing data suggesting that exercise, more specifically, levels of fitness and associated body composition, can alter the immunological response to vaccination. Smith and coworkers (126), for example, showed in vivo an age-related reduction in the primary antibody and memory T-cell response in humans to a novel antigen. Remarkably, the age-related

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### Table 2. Summary of UFP exposure effects on circulating leukocytes

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Adhesion Molecules</th>
<th>Lymphocyte Subsets and Activation</th>
<th>Leukocyte Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPREST (n = 12 healthy subjects): 2-h exposure to 10 μg/m³ UFPs or filtered air at rest</td>
<td>No effects</td>
<td>No effects</td>
<td>No effects</td>
</tr>
<tr>
<td>UPDOSE (n = 12 healthy subjects): 2-h exposure with intermittent exercise for each subject (10 μg/m³ UFPs; 25 μg/m³ UFPs, and filtered air)</td>
<td>Decreased monocyte CD54 Decreased PMN CD49d (males)</td>
<td>Increased CD25+ T-cells (females)</td>
<td>Decreased monocytes and basophils (females)</td>
</tr>
<tr>
<td>UP50 (n = 16 healthy subjects): 2-h exposure to 50 μg/m³ UFPs and air with intermittent exercise as in UPDOSE</td>
<td>Decreased monocyte CD18 and CD54 (males) Decreased PMN CD18 and increased CD11a</td>
<td>Increased CD25+ T-cells</td>
<td>Decreased eosinophils</td>
</tr>
<tr>
<td>UPASTHMA (n = 16 asthmatic subjects): 2-h exposure with intermittent exercise as in the UPDOSE (10 μg/m³ UFPs and air)</td>
<td>Decreased monocyte CD11b. Decreased PMN CD54 and increased CD62L (males) Decreased eosinophil CD11b</td>
<td>Decreased CD4+ T-cells</td>
<td>Decreased eosinophils and basophils</td>
</tr>
</tbody>
</table>

The combination of exercise and exposure to ultrafine particles (UFP) had marked effects on circulating immune cells. PMN, polymorphonuclear leukocyte. Data are from Frampton et al. (45).

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impairment was attenuated in those older individuals who had maintained a physically active lifestyle, but the mechanisms for this beneficial effect remain unknown. Edwards and coworkers (35) suggested that acute eccentric exercise might influence the antibody response to the influenza vaccine by acting as a local adjuvant. They found that the antibody response was enhanced by exercise in women but reduced in men. In contrast, exercise increased the cell-mediated response in men but not in women. Again, the mechanisms for these intriguing effects are not yet understood. Finally, earlier work in the authors’ laboratory (36), demonstrated a reduced specific antibody response to tetanus in obese, physically inactive children and adolescents. Factors such as a lower vaccination dose relative to body size, or reduced absorption from the injection site due to increased adipose tissue or related to reduced immune response due to the chronic low-grade inflammation expressed by the higher levels of IL-6 could all have contributed to this finding.

Recently, several investigators have begun to focus on the longer term effects of exercise and physical activity on the cell-surface expression of toll-like receptor 4 (TLR-4) on immune cells (41, 42, 48, 74, 89). The TLRs are transmembrane proteins responsible for recognizing pathogens and are seen as a link between innate immune function (the latter, clearly stimulated by exercise) and adaptive immunity (132). Collectively, these observations suggest that exercise can downregulate surface expression the TLR-4 on immune cells. Thus these observations may explain how repeated exercise can lead to a sort of immune “tolerance,” part of the mechanisms through which the immune and inflammatory signals of exercise are balanced. In the right dose, might this exercise-induced tolerance help ameliorate conditions like EIB? Although some data are compelling, whether being physically fit protects against EIB has not yet been conclusively determined (81).

Exercise could also modify immune responses indirectly through the well-described anatomic and metabolic adaptations to repeated physical activity. Increased muscle mass, improved oxygen delivery to working muscle, and more mitochondria could all act in concert to lessen the muscle-derived stress signals noted above: heat, hypoxia, and acidosis. Might some of the established health-promoting effects of exercise (reduction of cardiovascular disease risk) result from exercise alterations of the immune system? Obviously, much work needs to be done in all of these areas.

What is clear from the existence of dangerous exercise is that the immune responses caused by exercise are real and robust. Like pharmaceutical therapies, prescribing exercise as therapy, an activity that is gaining in acceptance throughout the medical community (e.g., 95, 123, 127, 139), must be predicated on understanding the risks and benefits of exercise as thoroughly as possible. Only in this manner can the “right” dose be achieved. Finally, a greater understanding of dangerous exercise is likely to yield new knowledge that is useful not only in the context of exercise physiology but also in shedding new light on the role of the immune system as it adjusts to daily life perturbations such as physical activity.

GRANTS

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