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TITLE

PHYSICAL EXERCISE AS A HUMAN MODEL OF LIMITED INFLAMMATORY RESPONSE

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Physical exercise as a human model of limited inflammatory response[1]

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Abstract: An inflammatory response represents a fundamental series of humoral and cellular reaction cascades in response to infection, tissue injury, and related insults. An excessive response is commonly seen under the pathological conditions of trauma, sepsis, and burns. It is becoming increasingly evident that most, if not all, of the distinguishing features of a classical inflammatory response are detectable in an exercising individual, namely mobilization and activation of granulocytes, lymphocytes, and monocytes; release of inflammatory factors and soluble mediators; involvement of active phase reactants; and activation of the complement and other reactive humoral cascade systems. While the manifestation of many exercise-induced immune and related changes has been reported and confirmed repeatedly, the underlying mechanisms triggering and modulating the elicited immune responses are, at best, poorly understood. Unlike the exaggerated and sometimes uncontrollable inflammatory response in septic and trauma patients resulting in morbidity and mortality, strenuous and severe exercise normally elicits an inflammatory response of a subclinical nature to facilitate the repairing process for site-specific tissue damage. Regardless of the inciting event, for example trauma, infection, or exercise, and given an appropriate triggering signal, a remarkably similar sequence of inflammatory reactions can be reproduced in the affected host. Therefore, physical exercise and training represent an acceptable and good model for the study of limited inflammatory responses in humans.

Key words: trauma, infection, exercise, inflammatory response, cytokines.

Résumé : Une réponse inflammatoire est constituée d'une série de réactions cellulaires et humorales en cascade en réaction à une infection, à une lésion tissulaire et à des agressions apparentées. Une réponse excessive est couramment observée lors de traumatismes, septicémies et brûlures. De plus en plus de données indiquent que la plupart, sinon toutes les caractéristiques d'une réponse inflammatoire classique sont détectables chez un individu faisant de l'exercice; c'est-à-dire mobilisation et activation des granulocytes, des lymphocytes et des monocytes; libération de facteurs inflammatoires et de médiateurs solubles; implication de réactifs de la phase active de l'inflammation; activation du complément et d'autres systèmes de réactions humorales en cascade. On a souvent rapporté et confirmé plusieurs réponses immunitaires induites par l'exercice, mais on connaît peu les mécanismes sous-jacents au déclenchement et à la modulation de ces réponses. Contrairement à la réponse inflammatoire excessive et parfois incontrôlée chez les patients souffrant d'un traumatisme ou de septicémie, qui résulte en morbidité et en mortalité, l'exercice intense et exténuant induit généralement une réponse inflammatoire de nature subclinique qui facilite le processus de réparation d'une lésion tissulaire. Peu importe la cause, que ce soit un traumatisme, une infection ou l'exercice, suite à un signal déclencheur approprié, la séquence de réactions inflammatoires est étonnamment similaire. Donc, l'exercice physique et l'entraînement constituent un bon modèle pour étudier certaines réponses inflammatoires chez les humains.

Mots clés : traumatisme, infection, exercice, réponse inflammatoire, cytokines.

[Traduit par la Rédaction]

Introduction

Strenuous muscular work is known to induce cellular and humoral changes in the body, and some of these changes are readily measurable in the blood (Shephard and Shek 1996). To a large extent, the detectable changes in the circulation appear to be very similar, if not identical to those seen in traumatic injuries and sepsis (Northoff et al. 1995). One or more of the five cardinal signs of inflammation, namely redness, swelling, heat, pain, and loss of function, are evident during and after strenuous activities (Smith 1991). Exercise of sufficient intensity and duration is invariably

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accompanied by activation of different components of a classical acute inflammatory response (Shephard and Shek 1996). While the instigators of the inflammatory response in sepsis have been shown to be bacterial products such as endotoxins (Heumann and Glauser 1994), the inciting agents responsible for triggering the inflammatory cascade in exercise remain elusive.

Although the patient population with inflammatory disorders is a potential source of subjects for research, there have been only limited experimental controlled studies of the inflammatory response in humans, for obvious ethical reasons. Experimental endotoxemia, for example, has been exploited to investigate not only the cellular and humoral changes associated with the induced inflammatory reactions, but also the potential efficacy of therapeutic interventions (Santos and Wilmore 1996). In contrast with the use of toxins as an invasive way to trigger an inflammatory reaction, physical exercise offers a possibly good alternative model to study the inflammatory cascade in a noninvasive manner. This review highlights some of the features of the inflammatory response seen in trauma, sepsis, and exercise. Evidence will also be presented to substantiate the notion that exercise can be used as a model to study limited inflammatory responses in humans.

Basis of inflammation

Inflammation represents a series of reactions occurring in the body in response to tissue damage and infection (Gallin et al. 1988). The main features of the inflammatory responses include vasodilation for increased blood flow to the affected site; increased vascular permeability to facilitate the diffusion of soluble mediators across the endothelial barrier; and cellular infiltration of inflammatory cells at the site of injury (Austin and Wood 1993). The inflammatory focus may contain blood-derived cells such as neutrophils, basophils, eosinophils, and lymphocytes, or tissue-derived cells such as tissue macrophages, mast cells, and tissue fibroblasts (Chrousos 1995). Circulating cells, e.g., lymphocytes and neutrophils, roll on stimulated endothelium before attaching to sites of inflammation or vascular injury (Ahmed and Christou 1996). The cells anchor themselves to the endothelial wall, by the expression of adhesion molecules, notably selectins and integrins, in a process called margination, which facilitates the cells to cross into the nearby tissue site (Mackay and Imhof 1993; Frenette and Wagner 1996). During inflammation, numerous cellular and humoral events are orchestrated by the body in an attempt to restore homeostasis, including leukocytosis and leukocyte activation; infiltration by granulocytes and monocytes or macrophages; activation of the acute-phase response; release of inflammatory mediators; production of free radicals; activation of the complement system; and activation of the coagulation and fibrinolytic cascades (Camus et al. 1993).

Inflammatory mediators: IL-1, IL-6, and TNF

Soluble mediators are intimately involved in mediating and modulating the inflammatory process (Dinarello 1991; Heumann and Glauser 1994). These mediators include those derived by activation of a number of proteolytic cascade systems in the blood plasma, such as the complement, coagulation, kinin, and fibrinolysis systems. Products of arachidonic acid metabolism, such as leukotrienes and prostaglandins, are also mediators of inflammation. Among a long list of mediators, a small group of cytokines, particularly IL-1, IL-6, and TNF, are known to be the key immune mediators in an inflammatory response (Dinarello 1991; Heumann and Glauser 1994). These cytokines are proinflammatory factors, which play an active role in the early phase of the inflammatory sequence (Pyne 1994). They synergize with one another to activate the acute-phase response after tissue injury and microbial insults, resulting in the synthesis and release of acute-phase proteins, which include, for example, some complement components, α1-antitrypsin and haptoglobin. Each of the cytokines mediate pleiotropic effects during the effector phase of inflammation (Bone 1996).

IL-1 is primarily synthesized by cells of the monocyte or macrophage lineage, and its production can be triggered by infection, injury, and different types of immunological stimuli (Dinarello and Wolff 1993). IL-1 can exert multifunctional effects by interacting with numerous cell types (di Giovine and Duff 1990). One of the key functions of IL-1 is in the activation of T cells, resulting in IL-2 production and IL-2 receptor expression on the cell surface (Dinarello 1988). During an inflammatory response, IL-1 induces neutrophils to migrate from the bone marrow to a tissue site via the blood stream by serving as a chemoattractant (Austin and Wood 1993). IL-1 stimulates hepatocytes to produce acute-phase reactants and induces endothelial cells to upregulate their expression of adhesion molecules to increase leukocyte adherence (Dinarello 1988). IL-1 also induces collagenase production in fibroblasts and promotes cartilage and calcium resorption in bones (Dayer et al. 1986; Dinarello 1988). IL-1 acts on macrophages or monocytes during inflammation, inducing its own synthesis as well as the production of TNF and IL-6 (Dinarello 1988; 1991).

IL-6 is another multifunctional cytokine not produced constitutively by normal cells. The production of this cytokine is triggered by infection and tissue injury (Hoch et al. 1993). The pleiotropic effects of IL-6 include the promotion of B cell development; activation of T cells; and induction of the acute-phase response (Van Snick 1990). IL-6 possesses a number of growth factor activities, which promote cell growth and differentiation (Austin and Wood 1993). IL-6 contributes to the body's defence after infection by inducing fever and stimulating the release of adrenocorticotropic hormone (Van Snick 1990; Chrousos 1995). IL-6 is also known to synergize with IL-1 in inducing the cytotoxic T lymphocyte (CTL) response (Austin and Wood 1993). Overall, IL-6 plays an important role in mediating the inflammatory and immune responses initiated by infection and injury.

Tumor necrosis factors (TNF-α and TNF-β) possess a multitude of biological activities in the acute-phase response to infection and injury, and in modulating cell growth and differentiation (Beutler and Cerami 1989; Vassalli 1992). TNF-α, produced primarily by activated macrophages, is also known as cachectin, because it was found to cause wasting or cachexia in animals with chronic infections or malignant growth (Beutler and Cerami 1989). The production of TNF-α is induced by trauma, tissue damage, and

infectious stimuli (Damas et al. 1989; Hoch et al. 1993). TNF-α triggers the synthesis and release of other mediators such as proteases, prostaglandins, and free radicals (Bachwich et al. 1986). This pleiotropic cytokine also promotes macrophages to release inflammatory mediators such as IL-1 and PGE_2, and increases the adhesion of lymphocytes and neutrophils to endothelial cells (Pober and Cotran 1990). TNF-β is produced by activated lymphocytes, but not macrophages. The function of TNF-β is mainly lymphotoxic, and its production can be induced by injury; this cytokine is an important mediator of the delayed-type hypersensitivity inflammatory response (Austin and Wood 1993).

Sepsis, endotoxemia, and proinflammatory cytokines

In Gram-negative sepsis, there is no doubt that the endotoxin or lipopolysaccharide (LPS) of the bacterial cell wall is the primary instigator. Endotoxin is perhaps one of the most potent inducers of the inflammatory response. A number of mediators with specific and interdependent tissue effects are generated. In sepsis, the presence of toxins stimulates the production of a variety of cytokines and inflammatory mediators (Heumann and Glauser 1994; Damas et al. 1992, 1997). Among the proinflammatory mediators, TNF, IL-1, and IL-6 appear in the early part of the inflammatory response, and their appearance at the site of inflammation has been indicated to follow the temporal sequence of TNF appearing first, IL-1 second, and IL-6 last (Chrousos 1995).

Elevations in circulating TNF and IL-6 levels have been shown to occur within 1.5–3 h following the induction of endotoxemia in humans (Santos and Wilmore 1996). IL-1, however, remained undetectable in plasma following endotoxin administration, prompting the authors to hypothesize that IL-1 is "inactive" in human endotoxemia. In contrast with this hyposthesis, IL-1 has been implicated as a crucial mediator of septic shock, because it can cause tachycardia and hypotension as well as synergize with TNF to cause tissue damage and death (Okusawa et al. 1988; Everaerdt et al. 1989). The important role of IL-1 in endotoxin-induced inflammatory reactions is further evidenced by the demonstraton that the administration of a recombinant interleukin-1 receptor antagonist (IL-1ra) effectively reduces the lethality of endotoxin-induced shock in rabbits (Hannum et al. 1990; Ohlsson et al. 1990). Therefore, any failure to detect circulating IL-1 in endotoxemia is insufficient in itself to preclude the contribution of this cytokine to the pathogenesis of septic shock.

In contrast with the generally more elusive detection of circulating IL-1 in endotoxemia and sepsis, the other two proinflammatory cytokines, TNF and IL-6, are readily detectable in experimental and clinical sepsis (Ayala et al. 1992; Ertel et al. 1991; Martich et al. 1991; Wagge et al. 1989; Damas et al. 1989). In a model of chronic sepsis, an increase in TNF-α release was also found to be accompanied by elevated transcriptional activity of the gene encoding the proinflammatory cytokine (Hadjiminas et al. 1994). In normal humans receiving an intravenous injection of endotoxin, peak TNF immunoreactivity occurred at 1.5 h, followed by IL-6 at 2–3 h, with no detectable IL-1β in any treated subject (Martich et al. 1991). In a human model of experimental endotoxemia, Ottaway et al. (1997) also observed that peak circulating TNF occurred about 30 min earlier than that of IL-6. In the same study, a concomitant increase in circulating cortisol levels was also evident, and its appearance was postulated to exert an inhibitory effect on TNF-α and IL-6 synthesis in the inflammatory response, presumably at the transcriptional level (Zanker et al. 1990). In patients with meningococcal septic shock, while the detection of IL-1 was inconsistent, TNF-α and IL-6 were consistently detectable in all patients examined (Waage et al. 1989). Again, peak circulating TNF-α release occurred shortly before IL-6; both cytokines have been implicated as important mediators in septic shock, and an apparent relationship was found between levels of either cytokine and fatal outcome (Cerami and Beutler 1988; Waage et al. 1987, 1989). Based on the analysis of plasma proinflammatory cytokine concentrations in critically ill patients in an intensive care unit, Friedland et al. (1996) also concluded that bioactive TNF in plasma was an independent factor indicating a poor prognosis; their findings are also consistent with the concept that TNF is involved in the early phase of the inflammatory response and that IL-6 is secreted later and for a longer period. In contrast with the predictive value of TNF on outcome in critically ill patients, measurement of TNF-α or IL-6 was not found to be the optimal marker for defining patients with septic shock, in terms of sensitivity, specificity, and predictive values, despite the fact that both cytokines were found to have the highest concentration in patients with acute septic shock (de Werra et al. 1997).

Exercise and proinflammatory cytokines

Cannon and Kluger (1983) first reported the detection of a proinflammatory cytokine with pyrogenic activity in the plasma obtained from human subjects after exercising on a cycle ergormeter for 1 h at 60% VO_{2max}; the active moiety of the exercise-induced mediator was found to be the same as IL-1 (Cannon et al. 1986). Plasma IL-1 activity is maximal a few hours after exercise and returns to basal levels by 24 h (Cannon et al. 1986). More recently, Bury et al. (1995) reported that exercise-induced elevation in plasma IL-1 level was correlated with exercise intensity. Under conditions where subjects exercised at 45, 60, and 75% of their aerobic capacity for 4, 3, and 2 h, respectively, a corresponding progressive increase of their baseline IL-1 value by 60, 97, and 142% was observed at the end of exercise. Following eccentric exercise by running on a 16% inclined treadmill for 45 min, IL-1β was found in the skeletal muscle of exercising subjects for up to 5 days (Cannon et al. 1989). It has been reported that IL-1β not only can augment protease production by fibroblasts and chondrocytes to facilitate the removal of damage tissue in a catabolic capacity (Dayer et al. 1986), it also helps to promote smooth muscle cell growth and augment collagen production in an anabolic manner (Krane et al. 1985; Libby et al. 1988).

Despite reports of circulating and tissue-associated IL-1 in strenuous exercise, the detection of exercise-induced IL-1 release appears inconsistent. For example, no significant changes in cirlulating IL-1β was found in subjects after cycling for 1 h at 60% VO_{2max} (Smith el al. 1992) and in well-trained runners following a 20-km run (Sprenger et al.

Table 1. Circulating TNF-α and IL-6 levels in exercise, endotoxemia, and shock.

(A) Exercise	TNF-α		IL-6		
	pg/mL (mean±SEM)	Change from baseline value	pg/mL (mean±SEM)	Change from baseline value	Reference
2.5-h run	28±7	69% ↑	n.d.	—	Dufaux and Order 1989
2.8- to 4.7-h run	19±2	64% ↑	88±13	79-fold ↑	Camus et al. 1997
250-km cycling	1.5±0.4	130% ↑	41±12	45-fold ↑	Gannon et al. 1997
10-km run	n.d.	n.d.	18 (range 10–29)	8-fold ↑	Camus et al. 1994

(B) Endotoxemia and shock	TNF-α	IL-6	Reference
Experimental endotoxemia pg/mL (mean±SEM)			
Dose: 4 ng/kg	130±23	296±35	Ottaway et al. 1997
Dose: 4 ng/kg	812±331	1026±250	Martich et al. 1991
Clinical endotoxemia pg/mL (range)			
Dose: 1500 ng/kg+	22 – 14 630	590 – 263 510	Da Silva et al. 1993
Septic shock	53–108	85–385	de Werra et al. 1997
Septic shock	100–1000	200–1000*	Waage et al. 1989
Septic shock	78–507	1.2–220*	Damas et al. 1997

Note: +, self-inflicted administration; *, ng/mL; n.d., not determined.

1992). Although elevated IL-1β was not observed in the plasma after the 20-km run, IL-1β was readily detectable in the urine, strongly suggestive of a previous presence of the same cytokine in the circulation. No change in plasma IL-1 concentration was found in a field study where military cadets underwent a 7-day physically demanding ranger training course (Boyum et al. 1996). It is not clear whether the lack of detectable changes in IL-1 may have been due to confounding variables such as caloric deficiency, sleep deprivation, and psychological stress associated with the training course. Thus, it is reasonable to suggest that conflicting reports of IL-1 release in demanding exercise could be due in part to differences in IL-1 assay (bioassay, RIA, Elisa, and immunohistochemcial assay) sensitivity and specificity (Northoff and Berg 1991); its rapid clearance from the circulation (Sprenger et al. 1992); the presence of putative inhibiting factors for IL-1 in whole plasma, which requires fractionation by column chromatography for accurate measurements (Cannon et al. 1986); and confounding experimental variables that may mask IL-1 detection (Boyum et al. 1996). Nevetheless, the involvement of IL-1 in the exercise-induced cytokine cascade is generally recognized (Northoff et al. 1995), and a sequential release of TNF-α, IL-1, IL-6, and IL-1ra in strenuous exercise has been proposed (Pedersen et al. 1997).

Two other proinflammatory cytokines, TNF-α and IL-6, have been found to be elevated after strenuous exertion at various intensities and durations. Circulating TNF-α was increased by approximately 69 and 64% in subjects who completed a 2.5-h and 2.8- to 4.7-h run, respectively (Table 1) (Dufaux and Order 1989; Camus et al. 1997). However, in two studies in which subjects ran for 10 and 20 km, no increase in circulating TNF-α was observed, but urinary TNF-α was found in subjects participating in the 20-km race (Camus et al. 1994; Sprenger et al. 1992). Smith et al. (1992) found no significant changes in plasma TNF-α and IL-6 levels in subjects after completing 1 h of cycling at 60% of maximal oxygen uptake. Following a 250-km competitive cycling race by well-conditioned athletes, plasma TNF-α level was found to increase by 130% (Gannon et al. 1997); the absolute values of their circulating TNF-α level, however, appeared low compared with those reported in other studies (Table 1). Strenuous exercise has also been shown to induce a dramatic increase in plasma IL-6 concentration. A very large elevation (79-fold) in circulating IL-6 was found in a run that required 2.8–4.7 h to finish (Camus et al. 1997), while the completion of a 250-km competitive cycling race in about 6.5 h boosted the IL-6 level by 45-fold (Table 1) (Gannon et al. 1997). By comparison, a 10-km run only triggered an 8-fold increase in plasma IL-6 concentration (Camus et al. 1994). Thus, exercise-induced increase in circulating TNF-α and IL-6 levels appears to have some sort of a relationship to the degree of physical exertion.

Difference in TNF-α and IL-6 concentrations induced by exercise versus septic complications

TNF-α and IL-6 are becoming increasingly used in exercise and clinical studies, where the monitoring of proinflammatory cytokines is required. Under normal and resting conditions, the baseline levels of either cytokine is relatively low, but their circulating concentrations can surge quite readily in strenuous exertion or among critically ill patients with traumatic or septic complications. A consistent pattern of TNF-α and IL-6 response can be reproduced in experimental endotoxemia (Santos and Wilmore 1996; Ottaway et al. 1997). Although the magnitude of the cytokine response varies in between studies, elevated circulating TNF-α and IL-6 concentrations induced in experimental and clinical endotoxemia are in general higher than those observed under strenuous physical activity (Table 1). In clinical conditions in which patients undergo septic shock, the magnitude of TNF-α and IL-6 levels can become

exceedingly high, in the nanogram per millilitre range (Table 1) (Waage et al. 1989; Damas et al. 1997). IL-6 has been reported to be related to mortality, and an IL-6 concentration above 1 ng/mL was found to significantly increase the risk of death (Damas et al. 1992, 1997). Recognizing that performing continuous exercise for about 5 h in a marathon or cycling race can only induce a circulating level of IL-6 to no greater than 100 pg/mL (Table 1), it is extremely unlikely that exercise-induced IL-6 elevation per se could be a life-threatening factor.

Instigators of the inflammatory response

Inflammation is a mannifestation of the response of the body to tissue damage and infection. The instigator of the inflammatory response is obvious in traumatic injury, where tissue damage occurs, and in sepsis, where microbial products such as endotoxins are released (Heumann and Glauser 1994; Northoff et al. 1995). The trigger of inflammation and proinflammatory mediators in exercise, however, is not so obvious. At least two possible mechanisms have been proposed that may account for the activation of the inflammatory response in exercise, namely muscle injury and bacterial translocation from the gut.

Muscle injury

Damage to skeletal muscle fibers occurs after strenuous physical exercise (Fridén et al. 1983). Ultrastructural and morphological changes have been described at the site of muscle injury, where the infiltration of polymorphonuclear leukocytes is a common feature (Fielding et al. 1993). A significant accumulation of intramuscular neutrophils was observed in biopsies obtained 45 min after downhill running, and the neutrophil infiltration persisted for up to 5 days after exercise. Specific immunohistochemical staining also revealed the accumulation of IL-1β at the damaged muscle site. The postexercise neutrophil influx has been suggested to serve to clear tissue damage in preparation for repair and cell growth (Camus et al. 1993). Thus, invading inflammatory cells appear to be the consequence of the damage, in an attempt to remove cellular debris.

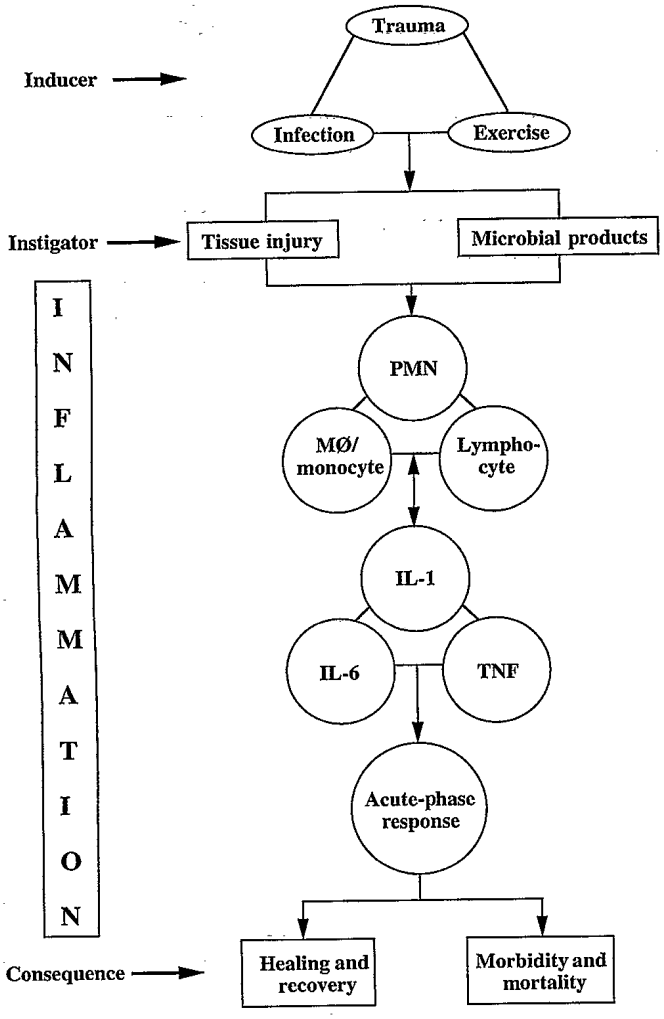
Leukocytosis is a hallmark of exercise-induced cellular changes (McCarthy and Dale 1988), and leukocyte activation is an important part of the inflammatory response (Shephard and Shek 1996). The majority of the leukocyte elevation can be accounted for by granulocytosis, which persists into recovery (Shek et al. 1995; Shephard and Shek 1996). The other elevated leukocyte counts are contributed by a rise in lymphocyte and monocyte counts. The rapid and persistent leukocytosis is believed to be due to the demargination of marginated cells of the noncirculating cell pool (McCarthy and Dale 1988). The demarginated leukocytes are mainly polymorphonuclear (PMN) leukocytes in prolonged exercise such as long-distance running. Since exercise of high intensity and long duration is likely to increase muscle damage, it is conceivable that the continuous release of damaged cell materials could serve as a potent signal to trigger PMN recirculation and activation. Tidball (1995) proposed that a substance released from damaged muscle initiates the inflammatory response, and the activation of resident macrophages or fibroblasts by a "wound hormone" may provide the necessary signals to attract the recruitment of additional inflammatory cells to the injured site. Basic fibroblast growth factor, platelet-derived growth factor, IL-1, and TNF are involved in mediating muscle inflammation and repair. These growth-promoting and repair mediators are known to be released by activated resident macrophages. IL-1, for example, can serve a range of functions in the early stages of inflammation by acting as a chemoattractant for recruiting additional inflammatory cells. TNF-α exerts multiple effects in the inflammatory response, such as inducing IL-1 synthesis (Bachwich et al. 1986) and skeletal muscle proteolysis (Goodman 1991). The biological effects of TNF-α and IL-1 can be further amplified by interferon-γ (Northoff et al. 1995). In summary, exercise and muscle damage increase IL-1 and TNF-α production, and the elevated proinflammatory cytokines contribute to the inflammatory or regererative phases of muscle reponse to injury.

Bacterial translocation from the gut

During strenuous exercise, the redirection of blood flow to the active muscles and skin causes transient hypoperfusion of the gut, resulting in splanchnic ischemia (Moses 1993; Kenney and Ho 1995). Reduced blood supply to the intestine could compromise the barrier function of the gut wall, resulting in the translocation or spillage of bacterial products such as endotoxins to the circulation (Marshall and Nathens 1996). Endotoxins can activate the complement cascade via the alternative pathway, resulting in the production of C3a and C5a, both of which are powerful complement cleavage products, capable of causing vasodilation and increased vascular permeability (Kuby 1994). As an anaphylatoxin, C5a can trigger the degranulation of granulocytes and mast cells, further exacerbating the inflammatory process. Endotoxins are mitogenic and they stimulate lymphocyte proliferation. By activating the Hageman factor (factor XII), endotoxins can also trigger the coagulation and fibrinolytic cascades (Heumann and Glauser 1994). Thus, the release of endotoxins from the gut can significantly amplify the inflammatory response.

Systemic endotoxemia has been documented in athletes after highly demanding physical exertion for a prolonged period (Bosenberg et al. 1988; Brock-Utne et al. 1988; Moore et al. 1995; Camus et al. 1997). Following an ultradistance triathlon competition, the mean LPS concentration was found to be elevated among the competing athletes (Bosenberg et al. 1988). Endotoxemia greater than 100 pg/mL was also observed in exhausted ultramarathoners, who particpated in an 89.4-km race (Brock-Utne et al. 1988), and most of the runners who developed endotoxemia displayed gastrointestinal symptoms. Moore et al. (1995) examined the relationship between endotoxemia and mild postexertional illness in cyclists, who completed a 100-mile road race. While endotoxemia was evident in some cyclists, no causal realtionship to postcompetition illness was found. More recently, Camus et al. (1997) reported that some marathoners, participating in a 2.8- to 4.7-h race, developed moderate, transient endotoxemia, but no correlation between endotoxemia and the magnitude of the inflammatory response was observed.

Fig. 1. A simplified schematic showing the possible inducer, instigator, and consequence of an inflammatory response. Two sets of cellular and humoral mediators, depicted as a "cellular triplet" of polymorphonuclear leukocyte (PMN), macrophage or monocyte, and lymphocyte, and a "cytokine triplet" of IL-1, IL-6, and TNF, in conjunction with the acute-phase response, are key contributors to the inflammatory process.



Thus, although endotoxemia has been repeatedly shown to occur after strenuous exercise, presumably because of endotoxin translocation from the gut, the pathophysiological role of circulating endotoxin in exercise-induced inflammatory response remains obscure.

Despite the detection of endotoxemia in athletes who performed exhaustive endurance exercise, direct evidence substantiating a causal relationship to postexercise illness and inflammatory response is lacking. Endotoxin or LPS binds to CD14 present on the surface of monocytes or macrophages, which then become activated to release a whole host of inflammatory products, including the proinflammatory mediators IL-1, IL-6, and TNF-α (Heumann and Glauser 1994). It is not known what minimal in vivo dose of endotoxin is required to activate phagocytic cells, but it is quite possible that sufficient LPS molecules could have leaked from the gut to trigger the initial events of inflammation, in the absence of detectable endotoxemia. Therefore, failure to detect endotoxemia does not necessarily indicate a lack of involvement of endotoxin in triggering the inflammatory events. More sensitive assays for measuring LPS escaped from the gut and bound to target cells need to be developed, to confirm or refute the hypothesis of bacterial translocation as a possible mechanism in instigating the inflammatory response in exercise.

Cellular and cytokine triplets

Strenuous muscular work can trigger the initiation of an inflammatory cascade, characterized by a series of cellular and humoral changes qualitatively similar to, but quantitatively different from those seen in trauma and sepsis (Shephard and Shek 1996). The underlying mechanisms responsible for the exercise-induced cytokine and cellular inflammatory response is far from clearly understood. A huge collection of studies in trauma, infection, and exercise has identified, at the very least, tissue injury and bacterial products, as the dominant instigators of the ensuing inflammation. The inflammatory response is initiated and propagated by highly complex, but intertwined cellular and humoral mediators. We propose that two sets of cellular and humoral mediators, composed of a "cellular triplet" of PMN, macrophage or monocyte, and lymphocyte and a "cytokine triplet" of IL-1, IL-6, and TNF-α, in conjuction with the acute-phase response, play a major role in mediating and regulating inflammation (Fig. 1). Exercise normally triggers a limited inflammatory response that is beneficial to the host, leading to healing of damaged tissues and full recovery. Trauma, on the other hand, may incite an overwhelming and uncontrollable inflammatory response with serious consequences, resulting in morbidity and mortality. Whether it be beneficial or detrimental, the two sets of triplets serve as the same engine in driving the inflammation in each case.

Concluding remarks

By virtue of their ability to promote the differentiation, maturation, and activation of a variety of cell types, cytokines play an essential role in modulating the inflammatory cascade. Although the published data so far have established the general notion that strenuous exercise can trigger the sequential release of various cytokines, there remains, however, the issue of consistency and reproducibility in cytokine detection and measurement in exercise studies. The determination of circulating cytokine levels is perhaps the most commonly used approach in most studies. This approach, however, suffers from a number of drawbacks such as short cytokine half-lives, neutralizing factors in the circulation, and relatively low concentrations of some cytokines in their free state. Differences in sensitivity and specificity among various assay procedures used for the measurement of the same cytokine also contribute to apparent discrepancies. In view of the technological challenge, a precise cause–effect relationship of cytokine release remains far from being established. With the advent of molecular biology and flow cytometry, some of the shortfalls in plasma cytokine measurements may be circumvented by monitoring

intracelluar cytokine expression at the post-transcriptional level.

The process of inflammation is an innate response of the body to restore "law and order" and re-establish homeostasis, in the face of physical injury and infectious insult. Trauma, infection, and septic complications could drive the inflammatory cascade to such an excessive extent that it can become out of control, with detrimental or even fatal consequences. Shock resulting from sepsis, for example, is associated with uncontrolled, excessive production of proinflammatory mediators (Heumann and Glauser 1994). On the other side of the coin, exercise-induced inflammatory response is normally subclinical in nature and it is "ordered" and "controlled." In this regard, the concerted response is for promoting repair and regrowth, making the response a beneficial one.

Regardless of the inciting event, whether it be trauma, infection, or exercise, and given an appropriate triggering signal, a remarkably similar sequence of inflammatory reactions can be reproduced in the affected host. Although it is debatable whether the triggering mechanisms are the same in each case, the inflammatory cascade itself has undeniable resemblance. Therefore, physical exercise and training represents a good model for the study of limited inflammatory responses in humans.

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