Exercise and Immunity: A Review with Emphasis on the Horse

Melissa Trogdon Hines, Harold C. Schott II, Warwick M. Bayly, and Annette J. Leroux

Exercise has been recognized as a stress, which can significantly alter the host's immune response and, therefore, its susceptibility to disease. Whereas research in this area has previously focused primarily on human subjects and laboratory animals, it has more recently extended to domestic animals, especially the equine athlete. Despite several studies, defining the relationship among exercise, the immune response, and disease has proven difficult due to a number of factors, including the complexity of the immune system and the variable nature of exercise itself. It now appears that exercise has dual effects on the immune system. Suppressive effects, such as a decline in the ratio of $CD4^+$ to $CD8^+$ cells, diminished lymphocyte function, and a decline in the number and cytolytic activity of natural killer cells have been observed in response to brief high-intensity exercise, prolonged exhaustive exercise, and overtraining. In contrast, moderate training generally has beneficial effects on host defense mechanisms. The mechanisms for regulating the dual effects of exercise are complex, involving a network of neuroendocrine hormones and cytokines.
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An association between exercise and disease susceptibility was recognized as early as 1918, when it was reported that pneumonia was more common in human athletes than in sedentary individuals, and that strenuous exercise increased the risk of upper respiratory tract infections progressing to pneumonia.[1] Since that time, several studies have investigated the relationship among exercise, the immune response, and disease, leading to recognition that the stress of exercise has profound but variable effects on the immune system.[2-10] Although comparatively little is known about the specific effects of exercise on immunity in domestic animals, the strenuous exercise that horses and other performance animals routinely engage in makes this subject of importance in veterinary medicine. In this article, we review the literature examining the relationship between exercise and immunity, and its clinical relevance.

Effects of Exercise on the Immune System

Considerable research has investigated the effects of exercise on the immune system, and while it has been established that virtually every aspect of both the nonspecific and specific immune systems can be affected by exercise, the definitive results of these studies often appear conflicting.[2-10] Several factors contribute to the variability among studies, including the complexity of the immune system and differences in experimental design. Function of the immune system depends on a number of cell types, receptor systems, soluble mediators, and their interactions. The effects of exercise on isolated components of the immune system may not reflect a change in the overall immune status. Likewise, because variations in the intensity, duration, or specific type of activity can have significant effects on the response of the immune system, the nature of the exercise being studied needs to be clearly defined. In general, the magnitude of the effects tends to increase as the intensity and duration of exercise increase.[11-13] While intensity is perhaps most objectively assessed in relation to the subject's maximal oxygen consumption ($\dot{V}O_2max$), it can also be defined based on heart rate responses, plasma lactate concentrations, or subjective means. Differences among studies in establishing or defining exercise intensity often make evaluation and comparison of data difficult. It is also important to distinguish among studies investigating the effects of acute exercise, meaning a single exercise bout, and those examining the effects of training, because training can significantly modify both the resting immune status and the response to acute exercise.[12-15]

Other differences in experimental design also contribute to the confusion regarding the effects of exercise on immunity. For example, the methods used to evaluate immune function vary considerably. Also, because many of the responses to acute exercise are transient in nature, a simple variable, like timing of the sampling protocol, can markedly influence results. In addition, exercise is commonly associated with other psychological and environmental stressors that influence immune function and can be difficult to control for. Finally, normal diurnal and seasonal variations in immune function often complicate interpretation of observed changes, as do factors such as genetics and age.[4,5,12]

Despite the large number of confounding variables, a few overall trends regarding the effects of exercise on immunity have been established. In general, acute exercise causes transient immunosuppression, which increases with the intensity and the duration of the exercise (Table 1).[8,11-13,16] In contrast, moderate training is typically associated with enhancement of the immune response and improved resistance to disease (Table 2).[6,11,13-15] Overtraining, on the other hand, may have prolonged suppressive effects.[12,13,15,17,18] To improve understanding of the mechanisms involved in exercise-induced immunomodulation, studies have recently been directed at defining the effects of exercise on specific components of the immune system.

The Effects of Exercise on the Number and Distribution of Leukocytes

In several species, including the horse, exercise produces marked changes in the number and distribution of circulating

From The Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Washington State University, Pullman, WA.
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Reprint requests: Melissa Hines, DVM, PhD, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Washington State University, Pullman, WA 99164-6610.

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Table 1. Effects of High-Intensity Exercise on the Immune System

Cell Type	Cell Number	Function	Species	References
Neutrophils	↑	Microbicidal activity- no change Chemotaxis & respiratory burst- ↓	Human Equine	3, 5, 19, 21, 23-25, 45, 47, 48
Monocytes	↑	Adherence- no change Phagocytosis- ↓	Human	46, 50
Lymphocytes	↑	Proliferation- no change or ↓	Human, lab animals Equine	3, 13, 15, 17, 18, 21, 54, 55
B lymphocytes	↑	In vitro Ab production- ↓ Vaccine response- no change Specific antibody production- ↑	Human Human Lab animals	66, 67, 69
T lymphocytes	CD4: ↓ CD8: no change or ↑	Proliferation- no change or ↓	Human, lab animals	3, 13, 15, 17, 18, 21, 54, 55
Natural killer cells	↓ During exercise ↑ In recovery	Lytic activity- ↑ during exercise, ↓ during recovery	Human, lab animals	16, 41-43, 57, 58
Lymphokine-activated killer cells	Unknown	Lytic activity- ↑ during exericse, ↓ during recovery Lytic activity- ↑ during recovery	Human Equine	54, 62
Alveolar macrophages	No change, ↓	Phagocytic activity- ↓ Respiratory burst- no change or ↓	Equine	48, 73, 77

Abbreviation: Ab, antibody; ↑, increased; ↓, decreased.

leukocytes.[5,19-22] Leukocytosis is among the most consistent responses to exercise, generally occurring after all types of exercise.[3,5,19] The magnitude of the leukocytosis tends to increase with the intensity and duration of exercise, and decrease with the level of conditioning.[19,23] In general, the leukocytosis observed in association with high-intensity exercise is biphasic, with an initial mobilization of lymphocytes followed by mobilization of neutrophils and monocytes[19]; leukocyte numbers typically return to baseline within 24 hours or less. During recovery, lymphocyte numbers return to baseline before the neutrophils, resulting in an increase in the neutrophil-to-lymphocyte ratio. In some cases, the lymphocyte number may decrease below baseline before returning to pre-exercise values. In a study by Wong et al in 4 unconditioned Thoroughbred horses, leukocyte counts at 6, 24, 48, 72, and 120 hours after a single bout of intense exercise were evaluated.[21] The exercise test, performed at a 6% grade on a treadmill, consisted of a 6-minute warm-up followed by 4 minutes at 9 to 11 m/s. As in other species, significant increases in the total leukocyte counts, neutrophil counts, and neutrophil:lymphocyte ratios were observed 6 hours after exercise; lymphocyte counts were stable or slightly increased. Using conditioned Thoroughbreds, Church et al found similar leukocyte responses 4 hours after high-intensity treadmill exercise.[24] Immediately after an actual race or fast training session, Thoroughbred horses had an initial increase in lymphocyte numbers associated with a decline in the neutrophil:lymphocyte ratio, which was followed by an increase in neutrophil numbers and in the neutrophil:lymphocyte ratio during recovery.[25]

Table 2. Effects of Moderate Training on Resting Immune Parameters

Cell Type	Cell Number	Function	Species	References
Neutrophils	No change	Respiratory burst & microbicidal activity- ↓ Killing of phagocytosed yeast- ↓ Respiratory burst- no change	Human Equine Equine	19, 45, 47, 25, 28, 49
Monocytes	No change	Adherence, ↓	Human	19, 45, 46
Lymphocytes	No change	Proliferation- no change, ↑ or ↓ Proliferation- no change	Human, lab animals Equine	11, 13, 18, 56, 49
B lymphocytes	No change	In vitro Ab production- no change or ↓ Specific Ab production – ↓	Human Lab animals	11, 36, 37, 64, 65, 67, 69
T lymphocytes	No change	Proliferation – ↓ or ↑ Proliferation – no change	Human, Lab animals Equine	11, 13, 15, 18, 56, 49
Natural killer cells	↑	Lytic activity – ↑	Human, Lab animals	6, 43, 57, 58
Lymphokine activated killer cells	Unknown	Unknown		
Alveolar macrophages	Transient ↓	Phagocytosis – ↓	Equine	73

Abbreviation: AB, antibody; ↑, increased; ↓, decreased.

As with high-intensity exercise, prolonged, low-intensity exercise in human subjects and laboratory animals is associated with an increase in neutrophil numbers.[5,15,19,23] Although more variable, lymphocyte numbers tend to increase or remain stable at the completion of exercise. However, after endurance riding in horses, the number of neutrophils increases, whereas the number of lymphocytes declines significantly.[26,27] In both horses and human beings, most studies report no significant effects of training on resting leukocyte numbers.[15,19,25,28] Although the mechanisms responsible for the changes in leukocyte numbers after exercise are not well understood, recruitment of cells from other regional pools, such as the spleen and lung, appears to play a major role.[19,29,30]

Considerable interest has recently been given to changes in the distribution of lymphocyte subpopulations in response to exercise. In general, there are 2 major subpopulations of T lymphocytes identified by their cell surface proteins, $CD4^+$ cells and $CD8^+$ cells.[31] While $CD4^+$ cells have been primarily considered T-helper/inducer cells, and $CD8^+$ cells considered T-cytotoxic/suppressor cells, these cells actually have complex roles in initiation and regulation of the immune response. Recently, in a limited study of 3 horses at completion of a 50-mile endurance ride we found a decrease in the number of $CD4^+$ cells with little change in the number of $CD8^+$ cells, resulting in a decrease in the CD4:CD8 ratio.[27] These changes in the distribution of T-lymphocyte subpopulations, which have been associated with immunosuppression, are similar to those in other species after exercise.[11,12,15,17,32-34] Although studies of B cells are somewhat limited, their numbers tend to increase with exercise.[5,11,35]

In general, most studies suggest that training has little or no long-term effect on the distribution of lymphocyte subpopulations.[11,18,36,37] The populations of T-cell subsets and B cells obtained at rest do not differ between athletes and nonathletes.[36] Likewise, there is no difference after training in previously sedentary individuals.[37]

Particular interest has been generated in exercise-induced changes in natural killer (NK) cells, because these cells contribute to the first line of defense against viral infections. Natural killer cells comprise a heterogeneous population of effector cells, which are functionally and phenotypically distinct from B and T lymphocytes.[38-40] Part of the innate immune system, NK cells express spontaneous cytolytic activity against a variety of virally infected and neoplastic cells. In people and laboratory animals, the number of circulating NK cells increases immediately after both acute high-intensity and prolonged low-intensity exercise.[2,41-43] However, their numbers decrease below pre-exercise levels after 1 to 2 hours of recovery. Resting numbers of NK cells may increase in association with endurance training.[14,42,43] Currently, the effects of exercise on numbers of equine NK cells are unknown because identification of these cells in horses is difficult. A monoclonal antibody that binds to a conserved function-associated molecule on NK cells from a variety of species, including the horse, has recently been identified; this antibody may be of use in investigating equine NK cells in the future.[44]

Effects of Exercise on Leukocyte Function

In addition to changes in circulating leukocyte numbers, changes in leukocyte function after exercise have been demonstrated in several species, including the horse. Neutrophil activity appears unchanged in response to brief, high-intensity exercise, but may be enhanced by low- or moderate-intensity exercise in human subjects.[45-47] However, 2 studies in horses showed a decrease in the functional activity of peripheral blood neutrophils after high-intensity treadmill exercise in unconditioned horses.[21,48] In the previously described study by Wong et al,[21] there was a decrease in the chemotactic index and in the respiratory burst activity, as detected by chemiluminescence, 24 hours after acute high-intensity exercise, whereas Adamson et al[48] reported significant inhibition of the respiratory burst activity 30 minutes after high-intensity exercise.

Training may diminish neutrophil function. In conditioned human athletes, the oxidative and microbicidal activity of neutrophils appears to be lower than in nonathletes both at rest and after exercise.[45-47] A study by Buschmann and Baumann, in which 4 3-day-event horses were sampled weekly throughout different phases of training, suggests that the same may be true in horses.[49] Killing of phagocytosed yeast cells by peripheral blood neutrophils was decreased during 4 to 7 weeks of intensive training, compared with the killing rate observed prior to training and during light training. However, the respiratory burst activity remained unchanged.

Thus far, relatively few studies have examined the effects of exercise on the activity of peripheral blood monocytes.[45,46,50] Lewicki et al found that high-intensity exercise had no effect on monocyte adherence in either trained or untrained human subjects.[46] However, trained subjects manifested significantly lower baseline adherence capacities than their untrained counterparts. Another study of monocytes by Bieger et al reported depressed phagocytic activity in response to high-intensity exercise in untrained human subjects.[50] In contrast, studies examining the effects of high-intensity exercise on differentiated tissue macrophages have documented increased metabolic, chemotactic, and phagocytic activity.[51-53]

Lymphocyte function in response to exercise has most often been assessed by measuring the proliferative response of these cells to mitogens and antigens. After exercise, peripheral blood lymphocytes from human subjects and laboratory animals, and splenic lymphocytes from the latter, have decreased proliferation in response to mitogens; the extent of suppression generally increases with the exercise intensity and duration.[3,13,15,17,18] Because the distribution of lymphocyte subpopulations changes in response to exercise, it is not clear whether this finding reflects a true functional change or is a consequence of changes in cell numbers. The results of studies investigating the effects of acute, high-intensity exercise in horses have been variable. In the study by Wong et al[21] of 4 unconditioned horses, there was no change in lymphocyte responsiveness to the mitogens phytohemagglutinin (PHA), concanavalin A (ConA), or pokeweed (PWM). In contrast, in a study of 6 unconditioned horses, Keadle et al found a decrease in the lymphocyte proliferative response to PWM and to influenza virus.[54] Studying 4 conditioned horses, Kurcz et al also found suppression of lymphocyte responsiveness, using the mitogens ConA and PHA.[55] The varying results among these studies may be related to differences in the intensity of exercise, the exact level of subject fitness, or the experimental protocol. For example, only Keadle et al sampled horses immediately on completion of exercise, and exercise-induced changes in lymphocyte function are often transient in other species.[3,13,15,17,18,54] Also, the relatively small numbers of horses sampled makes the results of these studies difficult to interpret.

Studies investigating the effects of training on lymphocyte function have produced variable results.[13,18,49,56] Several studies have indicated that resting lymphocyte function, as assessed by proliferation, decreases in response to training.[18,56] In contrast, in a study of human subjects comparing sedentary and moderately or highly trained individuals, the resting function was found to be lowest in the sedentary subjects.[13] In addition, a consistent decrease in lymphocyte proliferation was observed during acute, high-intensity exercise irrespective of the level of training. In 3-day-event horses, Buschmann and Baumann found no change in baseline lymphocyte responsiveness as a result of intensive training.[49]

Natural killer cell lytic activity has also been shown to be influenced by exercise.[16,41-43] In some cases, the changes are not associated with commensurate fluctuations in NK cell numbers, suggesting an actual difference in function.[57,58] Lytic activity of peripheral blood NK cells typically increases during exercise and is subsequently suppressed for several hours during recovery, generally returning to resting levels within 24 hours.[14,16,58] Because the spontaneous cytolytic activity of NK cells is important in the early control of viral infections, the decline in this activity during recovery from acute exercise may reflect impaired immune surveillance and resistance to infection. In contrast to the suppressive effects of acute exercise, moderate exercise training has been shown to enhance resting NK cell activity.[8,43,58,59] This response may play a role in the decreased severity of upper respiratory tract infections observed after moderate training in human subjects.[8,59] Unfortunately, because of the difficulty in consistently evaluating equine NK cell function, the effects of exercise on this cell type in horses have not yet been established.

Recently, exercise-induced modulations of lymphokine-activated killer (LAK) cell activity have been investigated.[60-62] A functionally defined cell type, LAK cells exhibit enhanced cytotoxicity as a result of incubation with interleukin-2 (IL-2) and are capable of lysing some non-NK–sensitive targets.[60] Whereas LAK cell activity in horses appears to be mediated by T cells, in other species it appears to be predominantly mediated by activated NK cells, with some contribution by T cells.[60,61] In human volunteers exercising on a bicycle ergometer, LAK cell activity increased during exercise at 25%, 50%, and 75% of $\dot{V}O_2max$, and it was suppressed below resting values only after exercise at 75% of $\dot{V}O_2max$.[62] In unconditioned horses, LAK cell activity increased on completion and 20 minutes after high-intensity treadmill exercise, with a decline toward resting values within 2 hours.[54]

Effects of Exercise on Humoral Immunity

Antibodies are important effectors of host resistance to disease. Although studies are conflicting, there is evidence in several species, including horses, which suggests that intense exercise does not significantly alter serum immunoglobulin (Ig) concentrations when changes in plasma volume are taken into account.[21,63-65] However, after an ultramarathon, serum Ig concentrations in runners were depressed for 2 days.[65] With regard to the effects of training, there was no difference in resting antibody concentrations between human athletes and sedentary individuals.[64]

Studies investigating production of antibody by B cells after exercise have also yielded conflicting results.[5,66,67] Using lymphocytes collected from human subjects, Hedfors et al[66] showed suppression of antibody synthesis during acute exercise, despite an increase in the number of B cells.[66] However, Eskola et al[68] found that runners immunized with tetanus toxoid immediately after a marathon had no impairment of their abilities to produce specific antibody, compared with nonathletes immunized at the same time.[68] Verde et al[69] investigated the effects of acute treadmill exercise at 80% of $\dot{V}O_2max$ in elite human athletes undergoing either baseline or heavy training. There was no change in the in vitro production of IgG or IgM at 5 minutes after exercise in either group, but at 30 minutes, synthesis of both IgG and IgM was enhanced in individuals undergoing heavy training.[69] There was also a trend for lymphocytes from athletes in heavy training to have a diminished baseline ability to produce antibody in vitro. In an experimental animal model, mice trained on a treadmill showed significantly higher specific antibody to *Salmonella typhi* after immunization than did nontrained control mice immunized at the same time.[67] Further investigation of this area is clearly needed to help make vaccination recommendations for horses in training.

Effects of Exercise on Respiratory Tract Immunity

The most prevalent disease syndrome in both human and equine athletes appears to be respiratory tract infection, yet relatively little is known about the effects of exercise on local immunity. A number of factors probably contribute to the development of respiratory tract disease in athletes. It has been proposed that high ventilatory flow rates during exercise may result in local damage to the mucosal surfaces of the upper respiratory tract.[9] Also, IgA, which is the predominant Ig in mucosal secretions, and plays an important role in preventing respiratory tract infections, may be affected by exercise. Resting concentrations of IgA have been shown to be decreased in salivary and nasal washes of human athletes.[63,70-72] In addition, the concentrations and flow rate of salivary IgA and IgM generally decrease after intense exercise in both trained and untrained subjects, whereas the concentration of IgG remains unchanged, suggesting a specific effect on mucosal Igs.[71] Interestingly, a temporal relationship between the decline in IgA concentration and the appearance of upper respiratory tract infection has been shown in 2 groups of elite human athletes.[72] Several studies have investigated pulmonary immunity in horses by analyzing bronchoalveolar lavage fluid, which represents the lower respiratory tract.[48,73-77] In equine studies by Huston et al, concentrations of IgA and IgG in bronchoalveolar lavage fluid remained unchanged after either a single bout of high-intensity exercise or a 6-week period of interval training.[73,74]

Cellular immunity, particularly alveolar macrophage function, is also of importance in preventing respiratory tract infections. While the results of studies in horses vary, they suggest that pulmonary cellular immunity may be impaired after brief high-intensity exercise.[48,73,77] For example, in 5 unconditioned horses, Huston et al documented a decrease in both total numbers and phagocytic activity of pulmonary alveolar macrophages after high-intensity exercise.[73] A similar study by Wong et al found that the metabolic activity of alveolar macrophages, as assessed by chemiluminescence, was suppressed, but there was no change in the cellular composition of the fluid.[75] In a study by Adamson and Slocombe,[48] also in unconditioned horses, the alveolar macrophage population remained unchanged in size, granularity, and respiratory burst activity after high-intensity exercise. Studies evaluating the effects of training on local cellular immunity have also yielded variable results. During 6 weeks of interval training, Huston[74] reported a decrease in total numbers of aveolar macrophages during weeks 3 and 4, which then returned to pretraining levels[74]; the phagocytic capacity of these cells was decreased throughout the 6-week period of interval training. An investigation of 10 Thoroughbreds trained on a treadmill for 8 weeks found an increase in the total nucleated cell count at the end of the training period, coinciding with the highest speeds and greatest distances, suggesting that only high-intensity training affects bronchoalveolar lavage cytology.[76] A recent study of bronchoalveolar lavage cytology in 62 Thoroughbred racehorses in training reported a neutrophilia and increased macrophage activity, as assessed by morphology, in horses exercising at higher intensities.[77]

Mechanisms of Exercise-Induced Changes in the Immune System

Neuroendocrine Hormones

The mechanisms responsible for changes in leukocyte numbers and function in response to exercise are complex; however, neuroendocrine hormones are believed to play a primary role. Exercise induces significant increases in plasma concentrations of cortisol and catecholamines, the magnitude of the changes being influenced by the intensity and duration of exercise, and by the level of training of the individual.[19,78,79] Hormonal responses in exercising horses are generally consistent with those seen in other species.[24,80,81] Particular attention has been given to cortisol concentrations, which are increased both in the circulation and bronchoalveolar lavage fluid after acute high-intensity exercise.[21,24,54,55,73,80] Likewise, rises in plasma cortisol concentrations similar to those seen after brief, high-intensity exercise have been documented at completion and 30 minutes after an 80-km endurance ride.[81] In addition, significant increases in plasma concentrations of both epinephrine and norepinephrine have been demonstrated after exercise in Thoroughbreds; these increases are directly related to both exercise intensity and duration.[82] Epinephrine and norepinephrine concentrations were also increased immediately after endurance exercise, although not to the extent seen after high-intensity exercise.[81]

Although increases in neuroendocrine hormone concentrations have been measured in association with alterations in immune function in several species, a direct causal relationship has not been established. The general consensus is that increased plasma catecholamine concentrations mediate the leukocytosis during exercise, whereas increased plasma cortisol concentration may mediate increased leukocyte counts during the recovery phase.[5,19] In addition to affecting changes in leukocyte numbers, it appears that these substances significantly alter cellular function. It is well established that glucocorticoids can be immunosuppressive at certain concentrations through inhibition of macrophage function, IL-2 secretion, $CD4^+$ cell activation, and NK cell lytic activity.[5,83-86] Catecholamines may also diminish immune function, since they increase intracellular cyclic adenosine monophosphate activity, thus inhibiting both B- and T-cell responses to mitogens.[5,87] Also, epinephrine release during physical exercise contributes to alterations in NK cell function.[88]

Cytokines

Cytokines are soluble mediators that play an essential role in initiating and regulating the immune response. To date, studies have consisted of quantifying circulating concentrations of these mediators in response to exercise.[89-93] After acute exercise, concentrations of the macrophage products IL-1, IL-6, interferon α, and tumor necrosis factor (TNF) α are increased.[89-93] In contrast, plasma concentration of IL-2, a T-cell product, decreases after exercise, a finding that may be associated with increased expression of the IL-2 receptor on lymphocytes.[90,91] With regard to the effects of training, one study found that resting concentrations of IL-1 are higher in runners than in nonathletes.[94] However, Smith et al found no influence of training on baseline plasma concentrations of IL-1 β, IL-6, or TNF.[95]

The mechanisms responsible for exercise-induced alterations in plasma cytokines are unknown. Some cytokines may be secreted by macrophages in response to exercise-induced tissue damage.[95] Both human athletes and racehorses have increases in plasma concentrations of endotoxin after strenuous exercise, which could contribute to the release of TNF.[96,97]

In most studies, the changes in plasma cytokine concentrations have thus far been small, and their concentrations generally do not exceed normal ranges. However, some studies have found significant increases in cytokine concentrations in urine samples, suggesting that failure to detect changes in plasma concentrations may result from the rapid clearance of cytokines from the circulation.[98] Furthermore, it is likely that circulating concentrations of cytokines represent only a fraction of the amount released in the tissues.[93,95] Also, cytokines can be effective at low concentrations, and small increases in a combination of cytokines may have marked effects. Although the specifics of their role are currently unclear, it is likely that cytokines are important mediators of exercise-induced changes in immunity, because they influence virtually every aspect of immune function.

Other Mediators

A variety of other substances, such as arachidonic acid metabolites, growth hormone, prolactin, and endogenous opioids, may also be involved in the modification of immune function by exercise.[5,86,89,99,100] Prostaglandins may play an important role in mediating the effects of exercise. Not only may they suppress macrophage function, but cortisol and prostaglandin E_2 are additive inhibitors of NK cell activity.[5,100] Furthermore, postexercise suppression of NK cell activity can be abolished by prior administration of the nonsteroidal anti-inflammatory drug, indomethacin, suggesting that prostaglandins are involved in the inhibition.[101] Next, the ability of the opiod antagonist, naloxone, to attenuate the rise in NK activity observed during and immediately after exercise suggests that β endorphin is an important mediator of NK activation during physical exercise.[99] Clearly, a number of substances that modulate the immune system are released during exercise.

Clinical Relevance

Improved understanding of the relationship between exercise and immune function will aid in the prevention and control of certain diseases. While most attention has been focused on the role of exercise in susceptibility to infectious disease, in human medicine recent interest has been generated in the benefits of exercise in patients with immunodeficiency disorders, such as aging, alcoholism, and acquired immunodeficiency syndrome (AIDS). Although the variability in responses to exercise makes it difficult to make specific recommendations, preliminary evidence suggests that exercise may be used to effectively modulate the immune response.

Infectious Diseases

The variable nature of exercise and the diverse, complex interactions between pathogens and host have led to conflicting conclusions concerning the relationship between exercise and resistance to infection. Several epidemiological studies in human subjects suggest that susceptibility to disease is decreased by moderate physical activity, but increased by strenuous exercise.[6-10,59] For example, in a study of 36 women, those involved in moderate exercise training had significantly less severe upper respiratory infection symptomatology compared with the sedentary control group.[8] In contrast, a prospective study by Peters and Bateman showed a significantly higher incidence of upper respiratory infection in marathon runners than in controls, with a correlation between the frequency of infection and the running speed.[9] Nieman et al further demonstrated that athletes who participated in an actual race, increasing the level of exercise and stress, were 5 times more likely to develop illness than those only in training.[6,7] Experimental studies of induced infectious illness in laboratory animals found that the increased susceptibility to disease associated with strenuous exercise is pathogen-specific.[10,102]

Although there is little documentation in veterinary medicine, it is widely accepted that the stress experienced by animals training or actively racing contributes to an increased risk of developing disease. Experiments performed in calves exercised on a treadmill suggested the presence of a serum factor released during exercise which markedly enhanced the in vitro replication of infectious bovine rhinotracheitis virus.[103] In horses, it is well recognized clinically that stress such as exercise or transport is a risk factor for pleuropneumonia.[104] A recent epidemiological investigation of influenza in racehorses found that age was the major risk factor; however, training and racing schedules were only analyzed in the convalescent period, making it difficult to assess their effects on the occurrence of illness.[105]

The assumption that immunosuppression is a factor in infectious disease of horses has led to widespread use of agents designed to augment immune responses. These immunomodulators are often used despite the fact that the status of the immune system in treated animals and the precise actions of the agent are poorly understood. Among the most recently marketed immunostimulants are bacterial cell-wall products reported to have a variety of effects on the immune system, such as enhancement of lymphocyte proliferation and NK cell lytic activity.[106-108] Therefore, these agents could theoretically diminish suppressive effects of exercise on immune function. However, their use has also been associated with adverse effects, such as the development of interstitial pneumonia.[109] Further information concerning both the effects of exercise on the immune status of horses and the mechanisms of immunomodulators is needed before the use of these agents can be recommended for equine athletes.

It is well recognized that nutritional factors affect the immune response, and recent studies in human athletes and laboratory animals have investigated the relationship between nutrition and exercise-induced immunosuppression. In exercising rats, adequate dietary protein was essential for maintenance of the normal immune response, and additional supplementation with vitamins A and E enhanced function of alveolar macrophages.[110] The amino acid glutamine, the major source of which is skeletal muscle, is utilized at a high rate by cells of the immune system. In human athletes, concentrations of glutamine have been shown to be decreased in plasma from runners after a marathon race, and in athletes suffering from the overtraining syndrome, which is characterized by poor performance, fatigue, depression, and increased susceptibility to infection.[111] It has been hypothesized that the decreased plasma concentration of glutamine contributes to immunosuppression in these athletes. Preliminary evidence in swimmers suggests that supplementation with branched chain amino acids, including glutamine, may increase the CD4:CD8 ratio and the plasma concentrations of IgA.[112] In Thoroughbred horses, Snow et al reported that there was a trend for the plasma ascorbic acid concentration to decrease at the beginning of hard training.[113] Although the significance of ascorbic acid remains controversial, it has been suggested that it is important in withstanding stress, and that it enhances neutrophil chemotaxis and overall immune function.[113,114] With further study, it may be possible to document whether the multitude of nutritional supplements currently administered to horses have a beneficial effect on the immune system.

Other Clinical Applications

Exercise might also have a role in the treatment of diseases that are characterized by immunosuppression. For example, in humans, exercise may have an impact on the management of AIDS, an immunodeficiency disorder characterized by decreases in the number of $CD4^+$ cells and in the CD4:CD8 ratio. A recent study utilizing an aerobic exercise training program in patients with AIDS demonstrated a significant increase in the number of T-helper cells.[115] The increases were comparable to those observed in some studies using the drug azidothymidine (AZT) but were without the accompanying adverse effects of drug therapy. In addition to enhancing critical components of cellular immunity, aerobic training appears to provide the added beneficial effects of diminishing anxiety and depression in patients infected with human immunodeficiency virus.[116] Also, long-term survivors generally engage in physical fitness programs.[117] At this time, it is unknown whether routine moderate exercise could diminish some of the immunosuppressive effects of viral infections in animal patients.

Recent epidemiological studies have shown a decreased incidence of cancer in physically active subjects.[93,118,119] In addition, in human patients with cancer, moderate exercise appears to improve both their physiological and psychological condition.[118] Similarly, several studies in animals have demonstrated that exercise can inhibit the growth and metastasis of a variety of experimentally induced tumors.[118,120,121] The mechanisms by which exercise influences resistance to tumor growth and spread are complex, but increased numbers and activity of macrophages and NK cells may play a role.[93,118,120,121] Neoplasms are an important cause of morbidity and mortality in animals, and understanding the relationship between exercise and tumor immunity may lead to improved means of control.

Impaired immune function may contribute to the increased incidence and severity of disease, which is recognized in elderly patients in both human and veterinary medicine.[122] Although the potential benefits of exercise in reducing coronary heart disease and osteoporosis in human patients are well recognized, it now appears that exercise may also diminish the immunosuppressive effects of aging.[59,117] In a study of elderly human subjects, Nieman et al found that exercise improved both NK-cell activity and lymphocyte proliferative responses.[59] The incidence of upper respiratory infections was also lower in the conditioned individuals.

Summary

A complex relationship exists among exercise, the immune system, and susceptibility to disease. Despite the large number of variables complicating studies in this area, it is apparent that the stress of exercise can have dual effects on the immune system, causing either enhancement or suppression. Although not yet well documented, exercise-induced immunosuppression may contribute to the increased incidence and severity of disease observed in racehorses and other performance animals. Thus, further defining the effects of exercise on the immune system may lead to the development of means to enhance the immune response and ultimately aid in the prevention and control of disease. For example, recommendations for training programs and vaccination protocols may be altered. In addition, specific therapeutic regimens designed to maintain function of the immune system may be developed. While most attention has been focused on the role of exercise in increasing susceptibility to disease, exercise can also have beneficial effects on the immune system, which may potentially aid in the treatment of patients with immunodeficiency disorders. Improved understanding of the relationship between exercise and immunity has implications for the control of disease in multiple species.

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