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COMMENTARY

Acknowledging Dr. Roy Shephard's Contributions to Our Understanding of Inflammation: A Physical Training Model

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Abstract

Dr. Roy Shephard has contributed substantially to the development of the field of exercise immunology. Through his understanding of the physiological and immunological changes that occur in response to strenuous exercise, Dr. Shephard was one of the first to propose the idea that exercise could serve as a model to study the inflammatory process. Together with his graduate students, Dr. Shephard tested the efficacy of such a model. This was done by investigating the inflammatory changes that occur in response to various types of exercise, performed alone or in combination with additional stressors. Through these investigations, Dr. Shephard was able to conclude that if exercise was to serve as a model to study inflammation, it should be prolonged, strenuous exercise that is performed in combination with additional stressors (e.g., psychological, thermal or nutritional).

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Introduction

Over the years, Dr. Shephard has contributed substantially to the development of the field of exercise immunology. Although the first hint that exercise could modulate host defense was introduced in the early 1900's (Abbott and Gildersleeve, 1910). Dr. Shephard and his colleague, Dr. Pang Shek went as far as to propose the idea that physical exercise could be used as a model to study inflammation. During his tenure at the Department of National Defence, Dr. Shephard explored this idea with his graduate students. His work laid the foundation for other researchers to subsequently investigate ways to ameliorate the inflammatory process and immune changes that occur in response to physical stress such as trauma and strenuous exercise.

Inflammation

Inflammation is the body's response to tissue injury and/or infection (Shek and Shephard, 1998). It is identified by the presence of one or more of the cardinal signs (redness, swelling, heat and/or pain at the site of injury) (Sherwood and Kell, 2010) brought about by cellular and molecular adaptations and include an increase in white cell counts (a rise in neutrophil and monocyte counts), a reduction in the CD4:CD8 ratio and an

increase in inflammatory molecules (e.g.,. interleukin-6 [IL-6] and C-reactive protein [CRP]) (Yao et al., 2011). It was understood that tissue injury and sepsis were associated with an inflammatory response, but debate arose on how exercise (something that was supposed to be good for you) could induce inflammation? Dr. Shephard recognized that strenuous physical activity was associated with exercise-induced muscle injury and there was growing evidence that there possibly could be some bacterial translocation from the gut (Shek and Shephard, 1998). Both of these processes could induce an inflammatory response.

Experimental Models of Inflammation

Dr. Shephard also was aware of the limitations imposed by the various experimental models of inflammation that had been used. Although major experimental manipulations could be done using an animal model, the findings of such studies were difficult to extrapolate to humans due to interspecies differences (Shek and Shephard, 1998). It was also known that the majority of human studies were limited either to the study of sepsis or to the immune response to severe trauma (e.g., burns). One type of experimental human model involved the injection of a small dose of endotoxin into healthy participants, followed by an examination of the physiological and immunological responses that occurred. However, involvement in such a study posed risks to the participants.

There was mounting evidence that strenuous, physical activity (e.g., marathon running) could cause sub-clinical injury and initiate an inflammatory response and immunosuppression (Northoff et al., 1995). These changes were similar to those observed in clinical sepsis. Based upon these reports, Dr. Shephard proposed that physical activity and training could potentially be used as a tool to examine the immune response to inflammation and trauma. There was such an interest in this area, that in 1997, Dr. Shephard and Dr. Shek hosted a symposium entitled "Immune Responses to Inflammation and Trauma: A Physical Training Model" at the Defence and Civil Institute of Environmental Medicine (now known as Defence Research and Development Canada [DRDC]) bringing researchers from around the world to discuss this topic.

Testing the Physical Training Model

Dr. Shephard designed several studies to determine which would be the best exercise model to use to study inflammation. These included an examination of the effects of (a) various types of exercise on components of the inflammatory response, (b) intense military training on general health of military recruits and (c) exercise in environmental extremes (heat or cold) on immune function. All of these studies, directed through Dr. Shephard's laboratory, demonstrated parallels between exercise and clinical sepsis, although the magnitude of change in exercise was much less than that which occurred during sepsis.

(a) Various types of exercise. In one study, Dr. Shephard and his graduate students (Brenner, et al., 1999; Natale, et al., 2003) compared the immune responses to a brief, all-out (near maximal) effort with that of prolonged exercise and resistance exercise. All of the exercises were performed at the highest intensity that could be tolerated by the healthy participants. It was

hypothesized that exercise-induced muscle injury would be greatest following a standard circuit training routine. However, both all-out exercise (5-min of cycle ergometer exercise performed at 90% of maximal aerobic power) as well as prolonged sub-maximal exercise (2 hours at 60% of maximal aerobic power) yielded similar cellular responses, each of which were greater than those that occurred with resistance training. Only prolonged exercise was associated with a rise in pro-inflammatory markers (IL-6 and tumour necrosis factor-alpha [TNF-α]).

(b) Intense military training. Dr. Shephard also conducted field tests with the Canadian Military in order to examine the impact of basic infantry training on the immune function of Canadian Forces recruits (Brenner et al., 2000). It was hypothesized that the combination of rigorous exercise together with the psychological stress of a new environment would lead to an increase in the incidence of infections (reflective of an inflammatory state). Although there was a reduction in levels of immunoglobulin A (IgA) in some of the recruits (some recruits had quit smoking), phytohaemagglutinin-stimulated lymphocyte proliferation and natural killer (NK) cell activity were significantly increased after 18.5 weeks of training. Dr. Shephard thus acknowledged that more intensive training or exposure to prolonged, strenuous exercise in combination with other stressors (environmental, psychological and/or nutritional) was necessary if one was to model the inflammatory response.

(c) Exercise in environmental extremes. In collaboration with DRDC and the U.S. Army Research Institute of Environmental Medicine (USARIEM), Dr. Shephard and his graduate students conducted a series of studies that examined the effects of exercise in combination with thermal stress. These studies demonstrated that certain components of the exercise-induced immune response could be modulated by exposure to different environmental conditions and that some of these changes (albeit smaller) were similar to that observed in clinical sepsis (Shephard, 2001).

For example, a combination of repeated bouts of moderate-intensity exercise and heat stress augmented the exercise-induced leucocytosis and the drop in CD4:CD8 ratio know to occur (Severs et al., 1996). In addition, prolonged exercise (6-hour, 250 km road race) performed in warm weather induced an increase in total leukocyte, granulocyte, lymphocytes and monocyte counts as well as in certain inflammatory markers (IL-6, TNF-α) 2.5 hours following (Gannon et al., 1997). However, 7-days of exhausting exercise (consisting of aerobic, anaerobic and resistive exercises) performed in combination with cold-wet exposures demonstrated that cold exposure could differentially modulate cytokine expression. Exercise-induced increases in some inflammatory markers (IL-1B and TNF-α) were actually blunted when cold exposure followed an intense bout of exercise (Rhind, et al., 2001).

Conclusions

Overall, the results of these studies have led Dr. Shephard to conclude that prolonged, strenuous exercise performed under environmental extremes or in combination with other stressors (e.g., psychological or nutritional stressors) held the most promise to be used as a model to study inflammation. Together with his graduate students, Dr. Shephard's work has laid the foundation for other investigators to follow. Researchers have subsequently moved on to investigate the possible mechanisms that could contribute to the inflammatory changes that occur in response to strenuous exercise (Rhind, et al., 2004) whereas others have been examining ways to treat or minimize the inflammatory response that occurs during exercise (Nieman, 1999; Nieman, et al., 2006).

Qualifications

The author's qualifications are as follows: Ingrid Brenner, R.N., Ph.D.

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