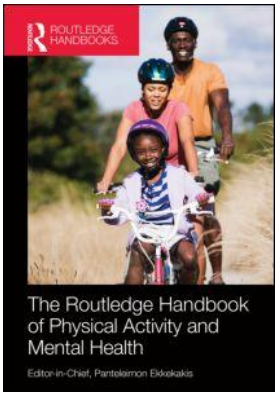

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PHYSICAL ACTIVITY, STRESS, AND IMMUNE FUNCTION

Kate M. Edwards and Paul J. Mills

The mind–body connection links many psychological processes and physiological systems. While connections between the mind and the immune system specifically have been recognized for well over a century, the mechanisms involved are only more recently being elucidated, and ways that we can utilize this interaction for clinical benefit are still being explored.

Examining the functions of the immune system can take several forms. The enumerative method simply records the numbers of cells, separating different cell types (e.g., monocytes, neutrophils, natural killer cells, T cells, B cells), differentiation stages (e.g., naïve, cytotoxic), and homing potential (e.g., chemokine receptor expression, adhesion molecule expression). Changes in cell numbers across short- or long-term situations/experiences give us a limited amount of information about cell mobilization, and differentiation. *In vitro* tests such as natural killer cell cytotoxicity and T-cell cytokine production are often combined with enumerative methods to provide information on the functioning capacity of cells during the time of study. Finally, *in vivo* tests such as wound healing and vaccination allow us to examine the function of the system as a whole rather than in separate portions. In and of themselves these latter tests lack the ability to provide detail on mechanisms of change but are the most clinically relevant assessment of the capacity of the immune system to respond to a challenge.

It is critical to understand that an *in vivo* immune response involves much more than just immune cells. The interactions of the autonomic nervous system and the endocrine system, in particular the hypothalamic-pituitary-adrenal axis, with immune function are well known, but the complexity of the interaction means they are less well understood. In discussion of behavioral influences on immune function we must recognize the impacts of such behaviors on these intricately linked systems. Stimuli such as stress and exercise activate and alter the functioning of these regulatory systems and thus alter control of immune responses, but the precise mechanisms of action remain to be firmly established.

In this chapter we will describe the use of the vaccination response as an *in vivo* method of assessing immune function. Vaccination is a fascinating tool for understanding the impact of stress and behavior on the function of the immune system, but also in the wider context of its clinical implications. Arguably the greatest medical intervention, alterations in vaccine responses, have enormous public health importance. We begin with a brief discussion of the immunological steps that together form the vaccine response, and the different ways it is possible to quantify this response. Then we review evidence for the negative effects of psychological stress on vaccination

responses and finally detail various behavioral interventions that have been investigated as methods of boosting the vaccination response.

Vaccination response

Vaccination is a complex process that includes many possible points that may be susceptible to alteration by stress or physical activity. The first step of the immune response is antigen encounter, internalization and presentation performed by specialized antigen-presenting cells, including macrophages and the highly efficient dendritic cells. Antigens are presented on the cell membrane by the major histocompatibility complex (MHC) and are recognized and bound to by the rare naïve antigen-specific CD4+ T lymphocytes. After activation comes proliferation and maturation into T-helper (T_H) cells, which help direct the response. Antigen-specific naïve B cells, similarly recognize native antigen, internalize, and, using MHC molecules, present it for cognate interaction with T-helper cells, providing activation and co-stimulatory signals. Activated B lymphocytes mature and differentiate into plasma cells, the antibody secreting cells, or to long-lived memory B cells. In the case of a response to a polysaccharide antigen (called T-independent, compared to the T-dependent response to a protein antigen), the antibody response is not dependent on the cognate interaction between T_H lymphocytes and the B lymphocyte. In this situation, co-stimulation is provided by direct interaction with the native antigen; however, for efficient B-cell proliferation to plasma and memory cells and antibody (Ig) class switching, T_H-derived cytokines are needed. The maintenance of the response to vaccination is dependent on the memory lymphocyte pools and antibody production by plasma cells, which continues without a secondary antigen exposure, but slowly declines over time (for further details of the generation of the immune response, see Goldsby, Kindt, & Osborne, 2000).

The quantification of the response to an antigen through vaccination can be achieved in two main ways: antibody production and memory lymphocyte response. The plasma cells' production of antibody is quantifiable simply by measurement of serum IgG (antibody titre) change from pre-vaccination antibody titre to a point post-vaccination, most often 4–8 weeks post for peak responses and 6–12 months for sustained responses. The memory lymphocyte response can be measured *ex vivo*, without re-exposing the participant to the antigen. *In vitro* stimulation of peripheral blood mononucleocytes with the antigen causes stimulation of the memory T lymphocytes; subsequent quantification of cytokine released can therefore measure the cell-mediated capacity of the immune response to vaccination.

Measuring the response to vaccination through antibody production or cell-mediated response allows the quantification of the response, but, given the overarching aims of vaccination, it is important to consider the clinical implications of these outcomes. In fact, there is strong evidence that the size of the antibody response is related to protection against infection (Hannoun, Megas, & Piercy, 2004; Schuerman, Prymula, Henckaerts, & Poolman, 2007). Indeed, a 4-fold increase in antibody titre is the consensus for 'seroconversion', deemed protective, after vaccination. Thus, these measures of response strength have direct clinical implications.

Effects of chronic psychological stress on vaccination responses

The detrimental effects of chronic psychological stress on the body are well established. The vaccination model provides us with many examples that immune function is negatively affected in situations of chronic stress. Studies have primarily taken two different approaches to characterize stress, either comparing 'stressed' and 'non-stressed' groups (particular situations of chronic psychological stress such as caregiving for a relative with Alzheimer's disease or a child

with disabilities, or patients with post-traumatic stress (PTSD) compared with age and sex-matched control groups), or cross-sectional analyses determining numbers of life-events and perceived stress. While many different populations have been examined, the two most commonly studied have been the elderly and young, healthy adults.

The strong justification for a focus on elderly patients is found in immunosenescence, the detrimental effects on immune function of age. The reduction in functional capacity through dysregulation of the immune system is seen in the increased rates of infectious disease and associated mortality in the elderly (Bender, 2003). Indeed, the public health impact of immunosenescence is compounded by the double hit, that vaccination, our most effective tool for preventing infectious disease, is less effective in the aged population, the response affected by the same immunosenescent changes.

Several extensive reviews have concluded that chronic psychological stress can impair the immune response to immunization (Burns, Carroll, Ring, & Drayson, 2003; Cohen, Miller, & Rabin, 2001; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998). Glaser et al. (1998) concluded that the elderly or other at-risk populations show the greatest stress-related immunological impairment and, as such, suffer the most potent adverse health consequences of infection, disease, and mortality. Cohen et al. (2001) agreed with this conclusion and suggested that the small to medium effects of stress are seen most easily when the immune response has the greatest variability. Therefore, stress-related effects are most likely to emerge in populations with poor immune function, such as the elderly, or in responses to antigens that do not elicit robust responses. Burns et al. (2003) extended the discussion and highlighted that the most convincing evidence for stress-induced immunosuppression emerges from secondary, rather than primary, responses to T-dependent vaccinations, and that these effects are most apparent some time after the vaccination (6–12 months), rather than during the peak immune response 4–6 weeks later. These reviews suggest that both the type of vaccine and the time scale of the immune response should be considered when investigating stress-related effects.

In 2009 a meta-analysis reviewed 15 studies to assess the overall reported effect of chronic psychosocial stress on influenza vaccination responses (the most commonly used vaccine). A significant adverse effect of stress was confirmed, and using a 4-fold increase in antibody titre to signify protection, the size of the effect was 41% protected and 59% unprotected in stressed individuals, and 59% protected, 41% unprotected in unstressed individuals. Interestingly, the effect of immunosenescence (reduction of immune function with age) did appear to interact with stress, with the association of stress with reduced vaccination responses greater in older adults (over 43 years counted as 'older'; 37.5% protected older stressed, 62.5% protected older unstressed; Pedersen, Zachariae, & Bovbjerg, 2009).

Most recently, Powell, Allen, Hufnagle, Sheridan, and Bailey (2011) reviewed evidence for psychosocial stress effects on vaccination responses, including examination of potential mechanisms. Given the paucity of human studies, they included animal studies and concluded that the primary mediator is likely to be cortisol (product of hypothalamic-pituitary-adrenal (HPA) activation) in particular through its effects on dendritic cell functions of processing and presenting antigen (Powell et al., 2011).

Interventions

The loss of immune function capacity through disease, age, or chronic stress has great implications for population morbidity and mortality. Unsurprisingly then, identifying factors and interventions that promote stronger responses are of great interest and public health importance. Traditionally this has involved the search for exogenous adjuvants to add to vaccine formulations and

development of vaccines with greater immunogenicity, a search that pharmaceutical companies are continuously engaged in. The use of behavioral interventions, however, has many advantages over this exogenous approach and has shown good success. Thus, these interventions are of potential clinical interest as well as academic interest in terms of how immune function is modulated in response to such interventions. In this section, summarized in Figure 23.1, we will describe the studies that are advancing our understanding of modulation of immune function through behavior and thus enhancement of vaccine responses.

Psychological component interventions: meditation and stress management

There are now several examples of intervention studies based around psychological components such as meditation and stress management. For example, a group of healthy adults who were randomized to receive mindfulness meditation training for 8 weeks showed greater antibody responses to influenza vaccination compared with a waitlist control group (Davidson et al., 2003). Similarly an 8-week cognitive behavioral stress management intervention in elderly caregivers was associated with better protection rates after influenza vaccination compared to non-intervention caregivers (Vedhara et al., 2003).

The traditional Chinese wellness practices of Tai Chi (also called Taiji) and Qigong involve a combination of 'three regulations': body focus, breath focus, and mind focus. Both involve physical movements (slow, meditative, dance-like movements), meditation postures, and gentle or vigorous body shaking (Jahnke, Larkey, Rogers, Etnier, & Lin, 2010). The practice of Tai Chi or Qigong has been associated with many health benefits, and although there is an exercise portion to the practice, the emphasis on meditation has led to inclusion in this section. There are two randomized controlled trials examining the effects of Tai Chi or Qigong on response to vaccination, with both reporting benefits for immune function. Yang et al. (2007) conducted a

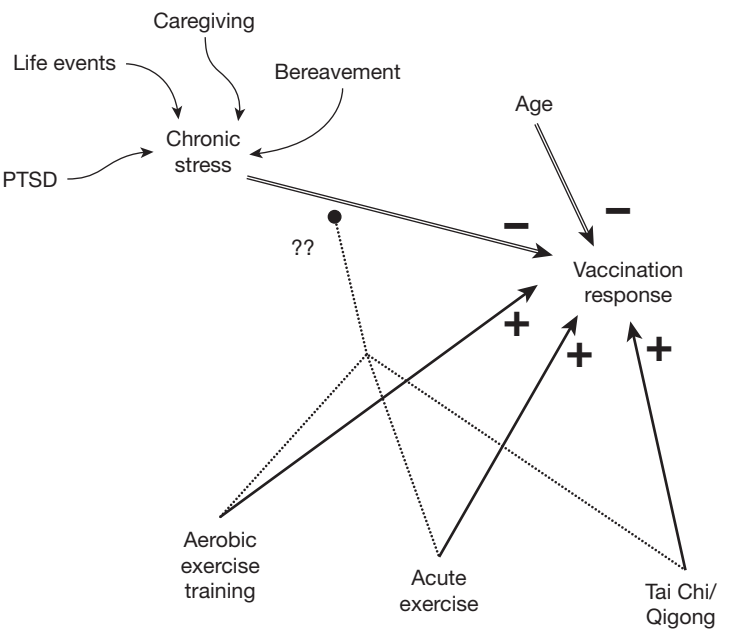

Figure 23.1 The effects of behaviors and stressors on vaccination responses.

5-month training of combined Taiji and Qigong practice in older adults, with three sessions per week (N = 27), and a parallel waitlist control group (N = 23). All subjects received the influenza vaccine and antibody responses were assessed at 3, 6, and 20 weeks post-vaccination. The Taiji and Qigong group showed a significant increase in magnitude and duration of antibody response compared to control group participants, and when analyzed for seroconversion, the percentage of participants showing a protective antibody titre post-vaccination was greater in the Taiji and Qigong group. In a larger (N = 112) study, Irwin and colleagues found that after a 16-week Tai Chi intervention, compared to health education control training, elderly adults similarly showed improved responses to Varicella zoster virus vaccination (Irwin, Olmstead, & Oxman, 2007).

Effects of chronic physical activity on vaccination responses

The effects of chronic physical activity, or exercise training, on vaccination response have been investigated primarily in elderly populations. Several cross-sectional studies as well as recent longitudinal studies have addressed the question of the impact of chronic physical activity or exercise training on vaccine responses. Kohut and colleagues (Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002) categorized older adults according to habitual physical activity. They found that those who participated in vigorous exercise three or more times per week had a higher influenza antibody titre than those who exercised at a lower intensity or not at all. Similar results were found by Smith, Kennedy, and Fleshner (2004) who compared physically active and sedentary older and young adults in their response to vaccination with a novel antigen KLH (keyhole-limpit hemocyanin, a benign protein). Again, the positive effects of physical activity were found in the older group, with greater antibody responses. However, in the younger cohort, all of whom showed the expected stronger responses compared to the elderly cohort, the effects of chronic physical activity were not apparent in antibody responses. Finally, Keylock et al. (2007) in a small study compared high- and low-fit older adults' responses to influenza and tetanus vaccine responses, but found very few differences among groups.

In addition to these cross-sectional studies, there are now several examples of well-designed randomized controlled trials that examined exercise training effects on vaccine responses. The first and smallest of these studies was by Kohut et al. (2004), who conducted a 10-month, three sessions per week, aerobic training program in 14 older adults, while a control group of 13 older adults continued their usual activities of low-level exercise or no exercise. All participants received the annual influenza vaccine prior to commencing the intervention, and showed similar responses, with marginally smaller responses in the exercise group. After the 10-month intervention, participants received the influenza vaccine for the following annual vaccine. In the post-intervention data, the exercise group showed significantly stronger responses to two of the three strains contained in the vaccine, with no difference in the third strain. This initial study has been followed by two further examinations, both of which show confirmatory results. Grant et al. (2008) compared an 8-month aerobic exercise program with a flexibility and balance program and assessed immunization with keyhole-limpit hemocyanin. In the primary response to this novel antigen, the aerobic training group showed greater antibody responses than the flexibility group. Finally, Woods et al. (2009), in the largest study to date (N = 144), compared the response to influenza vaccine in elderly adults after a 4-month cardiovascular aerobic training program (3 days per week) with a flexibility and balance control group. The cardiovascular training group showed a longer-lasting seroprotective response in a greater percentage of participants than the flexibility group, extending the protection afforded by vaccination.

In contrast to the beneficial effects of moderate exercise training, intensive exercise training has been associated with increased risk of upper respiratory tract infections and suppression of

various immune parameters (e.g., Heath, Macera, & Nieman, 1992; Brenner, Shek, & Shephard, 1994). However, in a study comparing the antibody responses to the polysaccharide pneumococcal vaccine in elite swimmers at the end of an intensive 12-week training program, at 14 days post-vaccination no differences in antibody responses were found between swimmers and age-matched controls (Gleeson et al., 1996).

In sum, there is good evidence that moderate chronic levels of physical activity or exercise training lead to better immune function as measured by response to vaccination. The effect is apparent after relatively short periods of training (4–10 months) and is indicated to have the largest and thus most beneficial effects in the elderly.

Effects of acute exercise on vaccination responses

It is reasonably intuitive that chronic stress might harm immune function, while moderate chronic exercise would benefit it, but to understand how acute exercise has come to be considered a way to boost immune function we must first think about the immune responses elicited by a single acute exercise bout. One of the best-known effects of acute exercise (indeed, or psychological stress) is lymphocytosis, a rapid increase in the numbers of circulating immune cells (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996). This increase is roughly proportional to the length and intensity of the exercise bout and is controlled by the neuroendocrine response to stress, i.e., the rapid release of epinephrine along with the increased shear stress of blood flow causing a mobilization of cells into the circulation. At the cessation of acute exercise the number of circulating lymphocytes decreases, and often is seen to reduce to below pre-exercise levels. This reduction represents the next stage of the response – the distribution of cells to sites of potential need. Dhabhar and McEwen elegantly demonstrated this effect by measurement of lymphocyte influx to an implanted surgical sponge in the skin, and found that the number of cells infiltrating the 'wound' was increased after acute stress (Viswanathan & Dhabhar, 2005). Subsequently, they used military metaphors to describe the meaning of the response (Dhabhar & McEwen, 1997). At rest, cells are found in the 'barracks', such as the spleen. On a signal for action (exercise or stress), they enter the circulation, the 'boulevards' to patrol, and from there they traffic towards sites of danger or potential danger, the skin or gut endothelial tissue, the 'battle stations' (Dhabhar & McEwen, 2001). This mobilization to 'patrol for danger' and move to 'sites of battle' has been identified as a possible method to enhance immune responses; if the system has been primed by exercise, its readiness to respond might result in better responses to challenge at this time compared to at rest. Figure 23.2 illustrates the response using the same metaphors described by Dhabhar and McEwen, including the suggestion of vaccination timed with exercise to harness the effects of the redistribution of cells.

In fact the lymphocytosis of exercise is only part of the hypothesis of how exercise might help the immune system respond to a vaccine. Other variables such as increased blood flow, greater capillary permeability, cytokine and chemokine release from exercising muscles, and increased lymph flow might all be involved in changing the response. These will all be described in more detail in the later mechanisms section.

Although we will not describe them here, there are many examples in the animal literature that show enhancing effects of acute stress on the immune response to antigen (Millan et al., 1996; Persoons, Berkenbosch, Schornagel, Thepen, & Kraal, 1995; Silberman, Wald, & Genaro, 2003); our focus is to describe the evidence in humans. Historically there are two papers that seem to address the question of acute exercise effects on vaccine response. In fact they were designed according to the 'open window hypothesis' that suggested a period of immune suppression and vulnerability to infection after a single bout of strenuous and prolonged exercise.

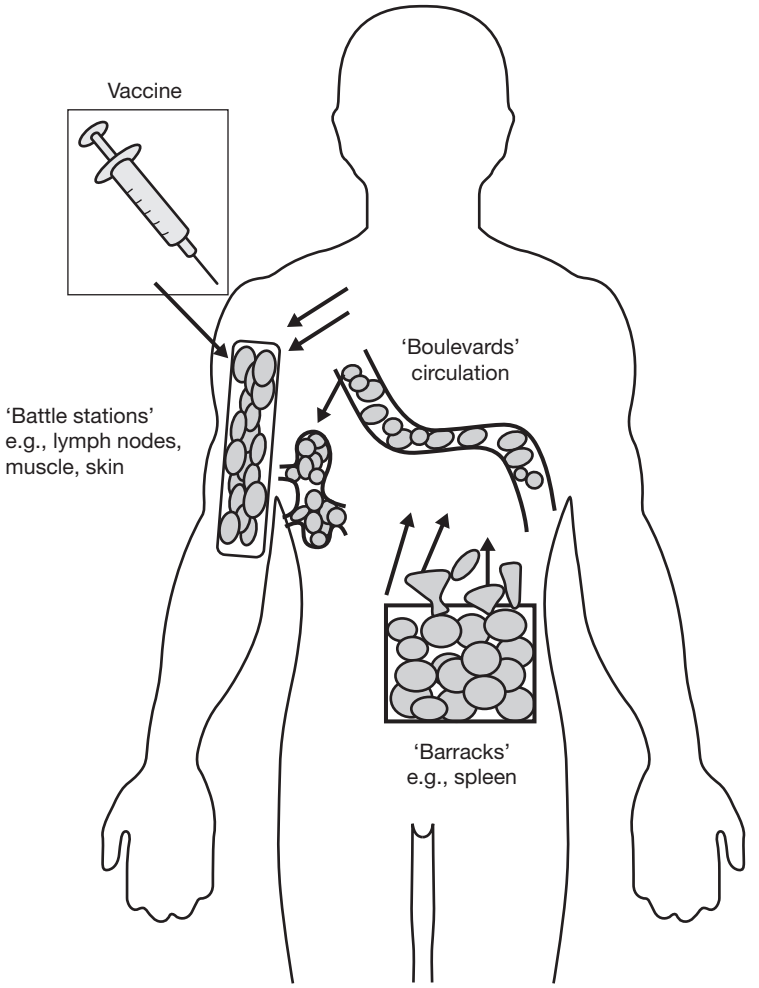

Figure 23.2 Military metaphors model of acute stress-induced redistribution of lymphocytes.

In contrast to the open window hypothesis, but in keeping with the acute stress-induced enhancement hypothesis, Eskola and colleagues found that the antibody response to tetanus toxoid vaccination was higher in a group who had completed a marathon prior to inoculation, compared with a non-runner control group (Eskola et al., 1978). A similar study by Bruunsgaard and colleagues did not, however, find differences in antibody responses to diphtheria, tetanus toxoid, and six pneumococcal serotypes between triathletes who had just completed a half-ironman competition prior to vaccination compared with either resting triathletes or sedentary controls (Bruunsgaard et al., 1997). The design of these studies used extreme bouts of prolonged, intense exercise, the sample sizes were relatively small, and neither controlled for the exact duration and relative intensity of exercise in each participant. Despite these limitations in both investigations, it is important to note that neither study supported the hypothesis that exercise suppresses antibody response to vaccination; indeed, they provide pilot data for the acute stress-induced immunoenhancement hypothesis.

Recently, several studies have begun to examine the acute stress-induced immunoenhancement hypothesis in humans in more detail, and show good evidence for a beneficial effect on vaccination response. In the first of these studies, the effects of either resting control, acute dynamic (cycling) exercise, or psychological stress on the response to two vaccines (influenza and meningococcal A+C) were assessed (Edwards et al., 2008, 2006). Two vaccines were used to represent thymus-dependent (influenza) and thymus-independent (meningococcal) vaccines, and thus discern the importance of the role played by T cells in altering the response. Sixty young adult participants all completed one 45-minute task; the exercise group completed a moderate-intensity cycling task, those in the psychological stress group completed a time-pressured mental arithmetic test, and those in a non-stress control group rested quietly. Immediately following their allotted task, participants received the two vaccines into contralateral arms. Results indicated task-induced immune response enhancements to both vaccines, but only in the situation of a weaker control response. For the influenza vaccine, women in both the exercise group and psychological stress groups showed enhanced antibody responses to the A/Panama influenza strain at 4 and 20 weeks post-vaccination, in comparison to the resting control group (Edwards et al., 2006). This strain elicited particularly poor antibody responses in the female control group, while in contrast, men displayed robust responses to all strains, and no effects of exercise or stress were observed. In response to the meningococcal vaccine, both exercise and psychological stress groups improved the antibody response to meningococcal A in men compared with controls (Edwards et al., 2008). In agreement with influenza findings, augmentation was observed where the control group response was poor; on this occasion, men, rather than women, in the control group had weaker responses to this particular strain. These results confirmed that the adjuvant effects of exercise and psychological stress are not limited to thymus-dependent (e.g., influenza) or thymus-independent (e.g., meningococcal) vaccines, and thus do not seem to be dependent on T-cell interactions.

The follow-up study was very similar in design, but changed the task used based on the hypothesis of potential mechanisms (Edwards et al., 2007). A resistance-based, eccentric exercise protocol was developed, designed to initiate a local inflammatory response in the biceps brachialis and deltoid muscles of the arm into which the influenza vaccine would be injected. The hypothesis described a response initiated in the tissue where the vaccine would be received to provide the most efficient way of stimulating the immune response. Sixty healthy young adults were randomly allocated to either an exercise group or a control group. The 25-minute exercise task involved the eccentric portion of exercise only; 50 repetitions each of the bicep curl and lateral raise exercises being performed with the non-dominant arm using a weight 85% of the single repetition maximum (1RM). The control group rested quietly for the same time. A 6-hour delay was included prior to vaccination (to allow for the cytokine response to the exercise to develop) after which participants received an influenza vaccine into the non-dominant (exercised) arm. Results indicated that women in the exercise group showed greater antibody responses to two of the influenza strains at 6 and 20 weeks post-vaccination. Again, an enhancement effect was found in strains with a weaker control response. The two strains producing relatively weak antibody responses in women in the control group were enhanced by exercise; however, men showed more robust responses to all strains and no effects of exercise were found.

These two initial studies provided evidence that acute exercise might benefit responses to vaccination in a setting of less robust control responses. There followed two larger studies, which provide somewhat mixed findings, but taken together, extended the evidence for the acute stress-induced immunoenhancement hypothesis. These two studies investigated the effects of exercise timing and intensity, with a view to elucidating the most efficacious protocol, and were again

in a population of young, healthy adults. Interestingly, in the timing study (Campbell et al., 2010) a full-dose influenza vaccine was used, while the intensity study (Edwards et al., 2010) used a reduced dose (0.5 of recommended dose) influenza vaccine, examining the importance of strength of response to the enhancing capacity of exercise.

Campbell, Edwards, and colleagues first examined the timing of exercise (Campbell et al., 2010) in 156 healthy young adults. Three timings were compared to a purely resting control, with all three exercise groups completing the same eccentric exercise task as previously described (85% 1RM) (Edwards et al., 2007). In keeping with the first eccentric exercise study, a time point 6 hours prior to vaccination was employed based on reported kinetics of the cytokine interleukin-6 (IL-6) response to eccentric exercise (Edwards et al., 2007; MacIntyre, Sorichter, Mair, Berg, & McKenzie, 2001). However, the first study had employed a task immediately prior to vaccination according to the observation that many of the exercise-induced physiological and immunological changes peak at exercise cessation and return to baseline, thus a group was including exercising immediately before vaccination. Finally, a group performed the task 48 hours prior to vaccination. This time point was included to capture the peak of the muscle damage response, which at 48 hours post-exercise is shown to include a peak in accumulated inflammatory infiltrate, including neutrophils, mononuclear cells, cytokines, and heat shock proteins (Fielding et al., 1993; J. M. Peake et al., 2005). A full-dose influenza vaccine was administered and all three strains produced robust responses in both men and women (23-, 10-, and 14-fold changes from baseline to 28 days), which were not different between exercise and control groups, nor among exercise groups. Physiological indices demonstrated that exercise timing did alter the profiles of muscle damage (pain and plasma creatine kinase) among the groups at the time of vaccination, but contrary to expectation IL-6 was highest in the 48-hour and immediately prior exercise groups, indicating that the kinetics did not follow the same inflammatory response as previously reported (MacIntyre et al., 2001; Paulsen et al., 2005). Although this null finding was unexpected, it was not entirely surprising given the strong responses to all strains of virus contained in the seasonal influenza vaccine.

Edwards, Campbell, and colleagues also set out to examine the influence of exercise intensity (Edwards et al., 2010). In a similar design, the effects of three different exercise intensities were compared with a resting control group. This, the largest of the studies in the literature, included 160 healthy young adults randomized to one of four groups. Exercise intensities of 60%, 85% (as had been used in prior studies), and 110% of 1RM were used. The importance of intensity on the adjuvant effect is of particular interest, not only to determine a task with maximum efficacy, but also for clinical application, i.e., if intensity shows no effect, a modest bout of exercise could still be prescribed for a beneficial effect on protection afforded by vaccination. In this cohort, a reduced-dose (50% of recommended dose) influenza vaccination was used, based on the previous finding that, in a similar population, a full-dose seasonal influenza vaccine produced robust responses in all three strains, without any exercise-induced enhancement. Administering a reduced dose modeled poorer responses, which might be elicited by a less immunogenic antigen exposure or an immune-compromised population. As expected, smaller-fold changes were seen, with two strains showing responses of 5- and 6-fold changes, while the final strain still showed a robust 19-fold response. As hypothesized, exercise enhanced the antibody response in both of the strains that demonstrated a weaker response in the control group. There were no differences among the three exercise groups in antibody responses, despite physiological differences such as dose-dependent changes in arm circumference and reported pain, and the creatine kinase response.

Most recently, the speculation that exercise elicits enhancing effects on weaker, but not stronger, responses was directly addressed (Edwards et al., 2012). In a study of 133 healthy young

adults, the effects of a 15-minute resistance band-based exercise task versus resting control prior to receiving the pneumococcal vaccine was evaluated, with half of the cohort receiving the full dose of vaccine and half receiving a reduced dose (50%) of vaccine. The findings demonstrated an overall effect of exercise groups showing stronger responses than control groups to the 11 pneumococcal strains measured. Importantly, when examining the effect of dose, within groups receiving the full dose there was no significant difference between exercise and control participants' responses. However, in the groups that received the reduced dose, the exercise group showed significantly stronger responses than the control group. These data add to the hypothesis that acute exercise enhances poorer responses and encourages investigation of the potential to use adjuvant vaccine responses in populations known to suffer vaccine failure and poor response rates.

Potential mechanisms

We began this section describing the lymphocytosis response to acute stress and illustrating how this might relate to enhanced immune responses to challenge at the time of acute stress. This is one likely potential mechanism of acute stress-induced enhancement. The rapid increase in cell numbers observed in the circulation includes increases in monocytes and dendritic cells (Ho et al., 2001; Hong & Mills, 2008), which are responsible for antigen recognition, uptake, and presentation. Thus, acute exercise initiates leukocyte mobilization and subsequent extravasation into tissues, guided by chemoattractants of the transient inflammatory response in the exercised muscles. In this way, acute exercise would induce leukocyte mobilization and localization in exercised muscles, the intra-muscular administration of antigen further attracts leukocytes, and the immune response develops, theoretically enhanced by the exercise-induced magnification of accumulation of leukocytes.

There are also several other related and linked mechanisms that may also contribute to acute stress-induced immunoenhancement, which are summarized in Figure 23.3. Firstly, the 'danger signal' response of cells to stress such as exercise. This response is especially true in exercise that includes eccentric (muscle applies force as it lengthens) components, which causes damage to the internal structure of the muscle fibers, and results in oedema, muscle pain, muscle weakness, leakage of muscle and cellular proteins, and cellular infiltration (Peake, Nosaka, & Suzuki, 2005; Peake et al., 2005). This damage is greater than that observed with concentric (shortening) muscle contractions (Sorichter, Puschendorf, & Mair, 1999) and is greatest when the exercise is unaccustomed (Sorichter et al., 2006). The range of danger signals released includes IL-6, uric acid, Heat Shock Protein (HSP) 60, and HSP70, which are thought to play a role in orchestrating inflammation and repair of the surrounding tissues (Hirose et al., 2004; Matzinger, 2002). They may also result in increased leukocyte homing to the site of vaccine administration and/or enhanced antigen uptake and processing, making the initial phase of the immune response more efficient and subsequently enhancing the antibody response. In support of this hypothesis, the extent of the self-reported pain and the change in upper arm limb circumference following eccentric exercise, both indirect indicators of muscle damage, have been significantly positively correlated with the subsequent cell-mediated immune response to the vaccination (Edwards et al., 2007).

Within the danger signals described, we must in particular describe the role of cytokines, such as IL-6, which have been specifically implicated in enhancing vaccine responses (Krakauer, 1995; Lee, Youn, Seong, & Sung, 1999). For example, higher levels of circulating IL-6 have been found in patients with good antibody responses than in patients who do not respond to vaccination (Krakauer, 1995). Further, the co-administration of IL-6 gene with vaccine completely protects mice from a lethal challenge with influenza virus (Lee et al., 1999). Given these findings,

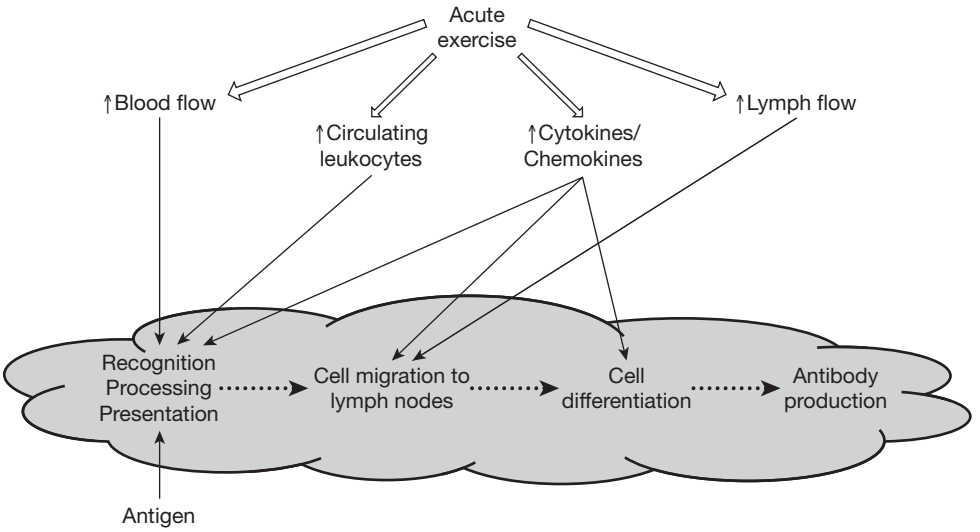

Figure 23.3 Potential pathways for acute stress-induced responses involvement in vaccination response.

it has been hypothesized that increased levels of IL-6 in the systemic circulation as part of the acute stress response may play a role in augmenting the immune response to vaccination. Indeed, the extent of the IL-6 response to a bout of acute exercise has been associated with the antibody response at 6 weeks post-vaccination (Edwards et al., 2006). However, no associations have been observed between the IL-6 response 24 hours post-exercise and the antibody response to vaccination (Campbell et al., 2010; Edwards et al., 2010). Given differences in task and timing of measurements, it is difficult to discern the true role of the IL-6 exercise response and the enhancement of vaccine responses, especially as circulating levels of IL-6 do not always accurately represent intra-muscular signaling following eccentric exercise (Tomiya, Aizawa, Nagatomi, Sensui, & Kokubun, 2004). Thus, it is likely that local milieu rather than systemic measurements are needed for mechanistic understanding.

A final mechanistic pathway to be considered is the increase in lymph drainage. There is evidence to suggest that muscular contractions are associated with a temporary increase in lymph drainage around the site of exercised muscle tissue (Havas et al., 1997). Thus, exercise contractions would lead to enhanced immune cell transport from the site of antigen administration into exercised muscles via the altered lymph fluid dynamics. Therefore, it is be hypothesized that performing exercise could enhance antigenic transport to the lymph nodes where recognition by lymphocytes takes place and thus make the response more efficient. However, this is yet to be directly measured in vaccination studies and thus remains speculation.

Summary: stress and exercise effects on immune function

It is widely acknowledged that chronic psychological stress has a negative impact on immune function while, conversely, exercise training and physical activity confer benefits to immune function over sedentary behavior. Both of these findings mirror much of the literature regarding health risks and therefore emphasize the importance of prescription of moderate exercise, perhaps especially in the setting of immunocompromise such as advanced age. The recent evidence that acute exercise enhances vaccination responses might seem less intuitive, but offers an opportunity to understand acute physiological changes and their impact on immune response to challenge.

In addition, the public health relevance of both acute and chronic exercise in improving the response to, and thus protection afforded by, vaccination indicates that this line of research may lead to clinical benefit. It is not clear how behavioral interventions including acute and chronic exercise or meditative practices like Tai Chi will interact with the immune dysregulation effects of chronic stress, age, or even disease, although it appears that positive effects may be most pronounced in these settings. These answers will help inform the best practice for maintaining or improving immune function when impacted by deleterious factors.

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