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Stressor-Induced Alterations of Adaptive Immunity to Vaccination and Viral Pathogens

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KEYWORDS

• Psychoneuroimmunology • Stress • Influenza vaccine
• Antibody response

Scientists and physicians who are asked about significant achievements in public health often rank the development of vaccines at the top of the list. In fact, the Centers for Disease Control have listed vaccination as one of the 10 greatest health achievements in recorded history.[1] This fact is not surprising, given that once devastating diseases, such as polio, rubella, and smallpox (to name a few) have been largely contained or eliminated. Protective immunity, however, does not always develop on vaccination, and it is now known that genetic, environmental, and psychosocial factors can influence the development of protective immunity. The purpose of this review is to describe basic mechanisms involved in vaccination, to describe clinical studies linking psychosocial stressor to protective immunity induced by vaccines, and finally to describe animal studies that have attempted to define mechanisms linking the stress response to alterations in adaptive immunity.

VACCINES

Active vaccination is the process in which immunogenic material from a pathogenic microbe is administered to individuals to induce protective immunity against a disease. The first documented use of vaccination occurred in the late 1700s when Edward

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Immunol Allergy Clin N Am 31 (2011) 69–79
doi:10.1016/j.iac.2010.09.002 **immunology.theclinics.com**
0889-8561/11/$ – see front matter

Jenner observed that resistance to smallpox could be induced by exposure to cowpox. To prove this concept, Jenner administered the pus from a cowpox lesion to an 8-year-old boy. Six weeks later, Jenner inoculated the boy's arm with smallpox, and as expected, the young boy did not develop any symptoms of the smallpox.[2] This seminal observation helped trigger the development of immunology, and was the first evidence that protective immunity could be induced through vaccinations.[2]

Over the next century, vaccines were developed to protect against other devastating diseases (most notably rabies vaccines by Louis Pasteur), triggering a quest to determine the scientific basis of vaccination. It is now recognized that vaccines work by inducing the development of adaptive immunity (both cellular and humoral components) to the microbe being vaccinated against. Although immunity to the cowpox virus was sufficiently similar to the smallpox (ie, variola) virus to elicit protective immunity without inducing any symptoms of either the cowpox or the smallpox, this is by no means the norm. Thus, the challenge for vaccine development and effective immunization is to develop a vaccine that has the necessary immunogenic potential to stimulate a robust adaptive immune response and yet does not cause disease.

Vaccine Types

At present, there are 3 strategies for vaccine preparation that elicit the desired immune response.[2] Live attenuated vaccines are composed of intact microbes that have been attenuated by treating the viruses in a way that reduces their virulence disease while maintaining immunogenicity. Examples of live attenuated vaccines include measles/mumps/rubella (MMR), nasally administered influenza vaccine, and oral polio vaccine. This type of vaccine is advantageous because it causes a mild, often asymptomatic infection that stimulates both innate and adaptive immune responses, leading to significant antiviral protection. Some microbes, however, easily revert to their virulent form from this induced attenuated form. Thus, only microbes with low reversion rates can be used as live attenuated vaccines.

If attenuation is not possible, an alternative form of the microbe that will still induce a strong immune response is a killed or inactivated microbe vaccine. In this case, the microbe is killed or inactivated so that it cannot replicate and cause disease. The microbe can either be left intact (eg, whole virus vaccines) or can be dissociated, such as with a detergent (eg, split-virus vaccines). Split-virus vaccines contain all of the dissociated viral particles. The most commonly used killed vaccine is the influenza vaccine, which is a split-virus trivalent vaccine comprised of viral components from 3 different types of influenza virus. While safer than live, attenuated vaccines, the immune response to killed vaccines is often effective for shorter periods of time and induces more limited protection.

A third vaccine form is the subunit vaccine. Subunit vaccines contain only the portions of the pathogen that the immune system recognizes and reacts to. For example, immune system recognition of the capsular antigens of *Neisseria meningitides* results in protective immunity.[3] Thus, meningococcal vaccines are subunit vaccines that contain *N meningitides* capsular antigens.[3] Other commonly used capsular vaccines include the DTaP vaccine to protect against diphtheria, tetanus, and pertussis, as well as the pneumococcal vaccines to protect against *Streptococcus pneumoniae*, the *Haemophilus influenzae* type B vaccine (Hib), and vaccines against hepatitis A and B. Although this type of vaccine eliminates all safety concerns and is easily stored and stable for long periods of time, subunit and conjugate vaccines do not often induce the development of antigen-specific T lymphocytes.[4] As a result, cell-mediated immunity is not strongly activated.

Vaccine-Induced Immunization

Protective immunity involves the effective development of adaptive immunity. While neutralizing antibodies produced by B cells are commonly viewed as the crucial component of protective immunity, T-cell responses are also essential.[4] Because many studies assessing the impact of psychosocial factors on the immune response to vaccines have involved influenza vaccination, the immune response to influenza and the influenza vaccine is outlined here. It should be noted, however, that the immune response is similar to other types of inactivated vaccines.

Respiratory epithelial cells are the primary target for influenza virus.[5,6] On infection, these cells produce chemokines and cytokines to recruit and activate cells of the innate immune system. The innate immune cells, primarily macrophages and dendritic cells (DCs), are then responsible for initiating the adaptive immune response. This response occurs when the macrophages and DCs phagocytose and degrade the virus so that viral antigen can be expressed along with major histocompatibility complex class I (MHCI) or MHCII. The macrophages and DCs migrate to draining lymph nodes where they come into contact with T cells. Viral antigen presentation in the context of MHC, along with recognition of costimulatory cues, causes virus-specific CD4+ and CD8+ T cells to clonally expand in the lymph nodes. These antigen-specific T cells can then leave the lymph node and traffic back to the site of infection to eradicate virally infected cells. Although most of these effector T cells will undergo apoptosis when the virus is eradicated, a fraction of these cells become long-lived memory cells.[5] On reinfection, the virus-specific memory T cells that were generated from the primary infection will begin to reactivate. Effector memory T cells, which are characterized by their shortened telomeres and lack of CD62L, CD27, and CCR7, are the first responders to antigen.[7,8] T cells can quickly enter nonlymphoid tissue and begin responding to the viral infection. Central memory T cells, on the other hand, do express the adhesion molecules CD62L, CD27, and CCR7 on their surface, and as a result are able to quickly move to lymphoid tissues where their specific antigen is present.[7,8] Here they undergo clonal expansion before migrating to the infected peripheral tissue.

Not all of the antigen-specific CD4+ T cells will migrate to the infected tissue. Activated CD4+ T cells enhance B-cell activation and are necessary for antibody responses to protein antigens.[9,10] B cells receive their first activation signals by follicular DCs or free antigen within the lymphoid follicle.[9,11] On receiving this activation signal, they migrate to the T-cell zone of the lymph node where they come into contact with CD4+ T cells. The T and B cells interact, and the B cells are stimulated by CD40L on the CD4+ T cells and by cytokines. The B cells then migrate back to the germinal center of the lymphoid follicle where they develop into long-lived antibody-producing cells, called plasma cells, or into memory B cells. The plasma and memory forms of B cells are responsible for the protective antibody response that is induced by vaccines, due to their prolonged production of neutralizing antibodies. These antibodies are typically of the IgG isotype.[9,11] Ultimately, it is the level of protective antibody within circulation that determines resistance or susceptibility to the target microbe. As a result, studies assessing the impact of psychosocial stress on vaccination have primarily focused on circulating levels of protective antibodies.

Psychosocial Stressors and Impact on Immunization

One of the central questions regarding psychoneuroimmunology (PNI) is whether exposure to stressors, or certain emotional characteristics or states like anxiety or

depression, influence susceptibility and resistance to infectious pathogens. While not feasible for many researchers, experimental infection with live, replicating pathogens can provide important information regarding the impact of emotions on the functioning of the immune system. Studies conducted by Dr Sheldon Cohen and his colleagues have assessed immune responses to viral infection in healthy humans. Subjects were intranasally challenged with different types of respiratory viruses, including rhinovirus, respiratory syncytial virus, corona virus, and influenza A virus.[12] Overall, the studies indicated that symptom severity and the duration of illness tends to be strongest in individuals with higher levels of perceived stress. For example, persons with higher levels of perceived stress produced more nasal mucus after the experimental infection and had higher levels of interleukin (IL)-6 in the nasal secretions, which would reflect a more severe infection.[12] Of note, this effect was dependent on social modifiers. Individuals that were more socially integrated were less likely to develop symptoms from the experimental viral challenge than were individuals that were less socially integrated.[12]

While much can be learned from this type of study, this approach is not feasible for many investigators in PNI, and determining links with subtle psychosocial factors are difficult because of the limited number of subjects that can be challenged with infectious virus. As a result, investigators have begun studying the immune response to different types of vaccines to ultimately understand how psychosocial factors can influence the development of adaptive immunity to microbial challenge.

Designing vaccine-based studies of stress in adults can be difficult because in developed countries, such as the United States, most vaccines are given during childhood. Thus, most participants in laboratory studies already have preexisting immunity to available vaccines, which makes experimental design and data interpretation difficult. Some vaccines, however, have only recently been recommended for children, such as the hepatitis B vaccine. Other vaccines, such as the influenza virus vaccine, vary from year to year based on the analysis of the latest antigenic characteristics of the virus determined by the Centers for Disease Control.[13,14] As a result, many healthy adults are seronegative for hepatitis B and have not generated antigen-specific immunity to the current year's influenza virus vaccines. Thus, these vaccines are useful in assessing how psychosocial factors can influence the development of protective immunity.

Clinical Studies of Stressor Exposure and Vaccination

One of the first studies to demonstrate that exposure to stressful situations would affect the antibody response to vaccines was conducted in medical students who were vaccinated with the recombinant hepatitis B vaccine series.[15] For this vaccine, repeated injections are normally needed to develop protective immunity. In the medical students, approximately 21% developed a protective antibody response after the first vaccine injection, whereas the remaining students developed a protective antibody response after the second injection. Of note, the 21% of the students that seroconverted 1 month after the primary exposure had lower Profile of Mood State anxiety scores than did the students that needed a booster injection to develop protective antibody.[15] This study suggested that mood could significantly change responsiveness to vaccination. Subsequent studies focused more closely on populations experiencing long-term stressful situations.

One such stressful situation is caring for a spouse with a chronic, debilitating illness such as Alzheimer disease. Thus, studies have investigated whether caregivers of spouses with Alzheimer disease develop protective immunity to the influenza vaccine.[16] In comparison with healthy age-matched control subjects, caregivers

had lower levels of total and neutralizing antibody to influenza A virus vaccine. This effect could be due to a lack of CD4+ T-cell help, because IL-2 production, which serves to simulate T-cell proliferation, was significantly reduced in the caregivers.[16] The effects of caregiving are not limited to immune responsiveness to an influenza vaccine, because similar results were found using the pneumococcal vaccine.[17]

The effects of caregiving on immune reactivity to the influenza vaccine appear to be strongest in the elderly, as studies in younger adults have been mixed. One study assessing antibody responses to influenza vaccine in nonelderly caregivers of spouses with multiple sclerosis failed to find any decrement in protective antibody responses.[18] In a different study, however, parents caring for children with a developmental disability had lower antibody responses to pneumococcal vaccine than did appropriately matched controls.[19] While it is tempting to speculate that the more consistent results in the elderly are caused by an age-related decrement in immunity, it is also possible that the results reflect differences in stress perception by the participants. For example, older spousal caregivers of dementia patients report greater distress than do younger caregivers of spouses with multiple sclerosis.[18] Moreover, psychosocial factors, such as loneliness and depression, may be important variables in influencing the immune response to vaccines because older caregivers report high levels of depression,[20] whereas loneliness and low social integration appears to be associated with lower antibody responses in medical students [15] as well as university freshmen.[21]

Whereas prolonged stressors have consistently been found to reduce antibody responses to vaccination,[22] short-lasting stressors have been found to enhance the antibody response to vaccination. For example, acute mental stress in the form of a paced mental arithmetic task prior to vaccination with the influenza vaccine resulted in higher antibody titers in women, but not in men, when compared with appropriately matched controls.[23] It is not clear why such effects were found only in women, but it is possible that the results reflect differences in cardiovascular responses to the mental arithmetic. For example, participants who had higher blood pressure during the mental arithmetic and delayed diastolic blood pressure recovery were found to have higher antibody levels to influenza vaccine.[24] Similar results have been found with acute exercise in healthy adults, which has been shown to enhance antibody responses to influenza vaccine in women, and measures of cell-mediated immunity to vaccination in men.[25] This finding has led some to propose exercise as an appropriate behavioral adjuvant to vaccination,[26] which may be particularly important for older individuals. For example, studies have shown that exercise in previously sedentary older individuals significantly increased influenza antibody titers on vaccination.[27] This effect is likely caused by the stimulatory effects of exercise on cell-mediated and humoral immunity, which are often decreased in older individuals.[28,29]

Clinical studies involving human subjects have clearly indicated that psychosocial factors influence the immune response to vaccination. However, these studies have not provided insight into the mechanisms by which psychosocial stressors affect adaptive immunity. The use of animal models has broadened and deepened our understanding of the behavioral and biologic mechanisms by which psychosocial factors affect the immune response. It is somewhat ironic that although most clinical studies of stress and vaccination have assessed neutralizing antibodies to the vaccines, much more is known about stressor-induced modulation of CD8+ T-cell responses in mice. This fact potentially has significant implications for the design of new vaccines, because many current human vaccines do not elicit strong CD8+ T-cell responses. Thus, revealing the underlying stressor-induced mechanisms that alter antiviral CD8+ T-cell responses can lead to the improvement of cell-mediated

vaccination strategies. The following discussion highlights some of the important findings in rodent models that provide insight into the mechanisms of neuroendocrine-mediated regulation of antiviral immune function and vaccine efficacy.

Animal Studies Involving Stressor Exposure and Adaptive Immunity

Although not strongly enhanced by many current vaccines, the primary effector cell responsible for eradicating virally infected cells is the cytotoxic CD8+ T cell. The main effector mechanism of CD8+ T cells during a viral infection is the secretion of cytotoxic factors, including cytokines, perforin, and granzymes, that directly mediate the lysis and apoptosis of virally infected cells.[30–33] In addition to the generation of effector responses, successful activation of primary CD8+ T cells in response to antigenic challenge leads to the development of antigen (Ag)-specific memory CD8+ T cells. This process is not only important for the development of memory during an infection but also important for the development of memory responses elicited by vaccination.[34–36] To mount a successful primary adaptive immune response to viral infection, CD8+ T cells must recognize their cognate antigen in the context of MHCI. Antigen-presenting cells, particularly DCs, play a critical role in driving adaptive immune responses, as they both present antigen and present important regulatory signals (eg, costimulatory molecules and cytokines) to T cells during antigen presentation.[37] Both CD8+ T cells and DCs contain receptors for neuroendocrine hormones,[38] therefore neuroendocrine mediators may directly affect CD8+ T cells or may indirectly affect the CD8+ T-cell response by influencing the capability of DCs to take up, process, and present antigen to the T cell.

These mechanisms have been explored in several studies of mice exposed to a prolonged restraint stressor during viral infection with influenza A virus or herpes simplex virus-1 (HSV-1) infection. Restraint is a commonly used murine stressor that induces a consistent and prolonged endocrine stress response, and studies using prolonged restraint found that stressor-induced adrenal glucocorticoid hormones can impair CD8+ T-cell responses to HSV-1.[39–44] Glucocorticoids, namely corticosterone (CORT) in mice and cortisol in humans, are known to decrease nuclear factor-κB activation.[45] This decrease results in the reduction of inflammatory cytokine production and subsequently leads to significant functional consequences in affected cell subsets. Both primary CD8+ T-cell responses as well as the generation of CD8+ T-cell memory responses following vaccination were diminished after exposure to endogenous or exogenous CORT.[41,42] Of importance, the frequency of HSV-specific CD8+ T cells in secondary lymphoid tissues and at the site of HSV infection was significantly reduced; HSV viral titers were increased, and viral clearance was reduced as a consequence of stressor exposure.[39,40] In addition, CD8+ T cells in lymphoid tissue had a reduction in functional capacity as secretion of interferon-γ and granzymes were diminished in stressed mice after HSV infection.[39,40,43,44] This decreased functional capacity translated to weakened protective immunologic memory.[46]

The effects of the stressor on antiviral CD8+ T-cell responses to viral infection were found to be mediated by CORT; administration of the GC receptor antagonist RU486 before and during the stressor restored the number of CD8+ T cells in the lymph nodes of stressor exposed mice.[47] The effects on T cells, however, appear to be indirect, because a study using mice that lack functional GC receptors in their T cells still found that stressor exposure decreased CD8+ T-cell number and function.[43] This result suggested the CORT was not directly inhibiting the CD8+ T cells and suggested that other mechanisms, such as disruption of DC function or reduced CD4+ T-cell help, were at play. Consistent with this view, DC function was found to be significantly impaired by CORT, which was associated with a decrease in antigen-specific CD8+

T-cell proliferation.[43] In vitro, it was shown that CORT disrupts the ability of DCs to process and present viral antigens to T cells,[48,49] ultimately suggesting that stressor-induced CORT decreases the ability of DCs to present antigen and stimulate CD8+ T-cell function. Although these studies were focused on CD8+ T cells, because DCs also activate CD4+ T cells and B cells,[37] CORT-induced suppression of DC function likely affects CD4+ T-cell activity and B-cell antibody production.

Other neuroendocrine mediators have been shown to play an important role in immune regulation during the stress response. In mice exposed to the prolonged restraint stressor and subsequently infected with influenza A, it was evident that blocking GC receptors alone did not restore all of the stress-induced changes of the immune system.[50–53] While blocking GC receptors reversed the stress-induced decrease in leukocyte trafficking into lymphoid tissues and the lungs, the function of these cells was not restored.[51] Of note, blocking the effects of stressor-induced catecholamines (ie, epinephrine and norepinephrine) by antagonizing β-adrenergic receptors during stress restored the activation of CD8+ T lymphocytes in stressor-exposed mice challenged with influenza virus.[51] In several studies a chemical sympathectomy with 6-hydroxydopamine prior to infection resulted in alteration in primary and memory CD8+ T-cell responses.[54,55] These studies in rodents, as well as many other laboratory animal studies, demonstrate the many, and complex, ways through which psychological stressors affect the immune response.

Human clinical studies assessing the impact of stressor exposure on the immune response to vaccines show that while some stressors, such as caregiving, tend to decrease the adaptive immune response, acute stressors tend to enhance adaptive immunity. Similar differences are evident with animal stressors, and a study by Powell and colleagues[56] showed that DCs from mice exposed to a repeated social stressor have an increase in costimulatory molecules important for CD8+ T-cell activation (eg, CD80, MHCI, CD44) on their cell surface and secrete an increased amount of inflammatory cytokines in response to in vitro stimulation of Toll-like receptors. Repeated exposure to social stress has also been shown to enhance the adaptive response to influenza virus infection, by increasing the number of antigen-specific memory CD8+ T cells that are critical for establishing virus-specific immunologic memory.[57] Together, these studies suggest that the stressor enhanced the ability of the DCs to process antigen and stimulate adaptive immunity. Although it is not completely clear why this stressor would enhance, rather than suppress, DC activity, it was shown that exposure to the social stressor caused the DC to be resistant to the suppressive effects of CORT.[56] These studies indicate that when determining the impact of stressor-induced hormones on adaptive immunity, a crucial mediating factor is the impact that the hormones have on antigen-presenting cells. Whether stressors enhance or suppress antigen-presenting cell activity likely determines whether stressor exposure will enhance or suppress the immune response to vaccination.

SUMMARY

There is now ample evidence that psychosocial factors affect the immune response to vaccination. For the most part, studies have found that prolonged, life-altering stressors, such as caring for a spouse with a chronic and debilitating illness, decrease the antibody response to vaccination. Although less well studied, this effect is likely caused by stress perception and available coping resources, because factors such as perceived burden, loneliness, and social support have been found to be associated with the altered immune response. The impact of stressor exposure on immune responses to vaccines can also be enhancive, but in this case the stressor tends to

be in the form of an acute, short-lasting stressor. Exercise in previously sedentary adults has also been shown to boost the immune response, making it an intriguing possible adjuvant to vaccination.

While human studies continue to define stressor characteristics and psychosocial variables that lead to immunosuppression versus immunoenhancement, very little is known regarding the biologic mechanisms through which stressors affect the immune response to vaccines. Studies in laboratory animals, however, have found that stressor-induced hormones affect the ability of antigen-presenting cells, primarily DCs, to process and present viral antigen. The primary mediating hormone appears to be CORT. Stressors that cause a prolonged increase in CORT, such as prolonged restraint, suppress the ability of DCs to process and present antigen, and stressors that induce DC resistance to CORT, such as social stress, increase the ability of DCs to process and present antigen. These effects on the DC significantly affect the development of antigen-specific memory T cells, and although less well studied, are also likely to affect the antibody response to vaccines. As research progresses in both humans and laboratory animals, the complete set of psychological and physiological factors by which stressor exposure affects the immune response to vaccines will become more clearly defined.

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