Published in final edited form as:
Immunol Allergy Clin North Am. 2011 February ; 31(1): 133–140. doi:10.1016/j.iac.2010.09.013.

The Adverse Effects of Psychological Stress on Immunoregulatory Balance: Applications to Human Inflammatory Diseases

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Summary

Psychological stress has known effects on the immune system that include impact on effector as well as regulatory components. This results in increased susceptibility to various infections such as the common cold as well as latent virus reactivation and impact on immunoregulatory circuits. This may be at least one of the mechanisms that explains the known adverse associations between stress and inflammatory disease activity and, perhaps, etiology as well. One of the great challenges in this area of translational research is defining the risks associated with stress in specific patient populations and, ideally, individuals. Future studies must include identification and validation of biomarkers that can categorize patient risk for adverse immune effects from various forms and degrees of psychological stress and how this impacts the course of their inflammatory disease.

Keywords

stress; immunoregulation; single nucleotide polymorphisms; inflammation

Introduction

Psychoneuroimmunology (PNI) research has long been concerned with the relationships between excessive psychological stress and health risks. Ancient medical authorities recognized the relationships between stress and health (1), and the negative impact on inflammatory processes was the presumed basis for the increased incidence of infections seen in high-stress populations (2). Only relatively recently have the medical and scientific communities come to appreciate that psychological stress can not only increase susceptibility to infection but also impair wound healing and enhance hypersensitivity inflammatory states such as allergy, asthma, and various autoimmune conditions (3)

Two great pioneers of PNI research, Ader and Cohen, began their work when the technology of immunology research was in its relative infancy. Accordingly, the idea that stress was largely immunosuppressive prevailed as most of the animal models were designed to show

increased susceptibility to infection with exposure to specific stressors. Yet there emerged an interest, beginning in the older medical literature that described relationships linking stress with various inflammatory diseases (4).

As technology for more accurately and definitively assessing various components of the immune response has developed, research has confirmed that high levels of stress have effects far beyond merely suppressing immune function, including altering immunoregulatory networks and causing increased risk for allergic and autoimmune diseases in both young and older individuals. In the past 30 years, PNI research has established that the brain and the immune system are inextricably linked through a variety of pathways that include the hypophyseal-pituitary-adrenal axis and other endocrine organs including thyroid, gonadal and adrenomedullary, as well as autonomic nervous system components (5). Though their neuroendocrine pathways are not identical, both anxiety and depression states are associated with similar effects on both regulatory and effector immune components (6). This has been confirmed through observational studies; people with inflammatory diseases such as asthma and autoimmunity have increased prevalence of anxiety and depressive states (7). Conversely, people with anxiety and depressive disorders are at increased risk for various inflammatory diseases (8).

Further research has shown that certain therapeutic agents that impact neuroendocrine and/or autonomic pathways can also affect how individuals respond to stress-induced changes in immune function (9). All of these findings have been firmly established in animal models, normal human volunteers, and even some patient populations with certain inflammatory disease states. In addition, investigator have shown that demographic parameters such as gender, race, body mass index, age, and socioeconomic status have an impact on the prevalence and severity of conditions such as cardiovascular disease (10), hypertension (11) and diabetes (12). Individual differences based upon these demographic parameters are also likely modifiers of stress-related immune effects.

This brief review will provide an overview of the major immune mechanisms reported to be most adversely affected by stress and a brief discussion of current research, clinical and policy issues that need to be addressed in order to more effectively implement specific stress reduction/management strategies for individual patients with inflammatory diseases.

Normal Immune Responses

In normal humans, presentation of antigen for a specific protective immune response elicits a complex series of events that results in a mixed cellular and humoral protective response, the intensity and nature of which depends upon the specific inciting antigen (13). Generally speaking, extracellular pathogens (i.e., bacteria) incite primarily a humoral response, while intracellular pathogens (e.g., virus, fungi, mycobacteria) elicit a cell-mediated response. Antiviral immunity is particularly complex because both mechanisms are necessary for host resistance: cellular immunity, to eliminate the virus-infected host cells, and humoral immunity, which produces antiviral neutralizing antibodies to prevent reinfection. The host immune response has a variety of mechanisms to direct the immune response into the humoral vs. cellular direction, including the nature of antigen presenting cells, major histocompatibility complex restriction, and availability of specific T and B cell components; however, the central control of the cellular vs. humoral response to an antigenic challenge appears to be via production of specific cytokines.

A central source of these cytokines comes from CD4+ helper T cell subpopulations, often referred to as Th1 and Th2 cells (14). Human Th1 cells secrete a number of different cytokines with the seminal Th1 cytokine being interferon gamma (IFNγ). These cytokines are important factors in the generation of cellular immune responses, including antigen-

specific cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. Additionally, IFNγ in particular has an antagonistic activity against Th2 cytokines. Interleukin-12 (IL-12) and IL-18, produced primarily by activated macrophages, play a central role in upregulating IFNγ production. In contrast, Th2 cells secrete various other cytokines including IL-4, IL-5, IL-9, IL-10 and IL-13, which are involved in isotype switching of B cells as well as proliferation and differentiation into antibody-secreting plasma cells. In particular, IL-4 and IL-13 are involved in the isotype switch from IgM to IgE, the antibody responsible for classical allergic disease. IL-4 and IL-10 are also regulatory cytokines, antagonizing the activities of Th1 cytokines.

Immune Deviation vs. Immune Regulation

In the normal host response, as described above, specificity, intensity, and duration are all essential components of normal host immunity. When any or all of these components become dysfunctional, immune-based diseases can be expected to develop. Normal regulatory mechanisms occur to keep type, duration, and intensity of immune responses within normal homeostatic boundaries. Specificity involves both epitope recognition on a molecular level and host defense against intracellular vs. extracellular pathogens on an organismic level. The pathogen discrimination is called *immune deviation* and is mediated by Th1 (for intracellular pathogen defense) and Th2 cytokines (for extracellular pathogen defense). Additionally, the intensity and duration of these responses must be regulated as well. Recent studies have indicated the presence of T cell subpopulations that can regulate intensity and duration of various immune responses. Various names have been used to describe these cells, including suppressor T cells, Th3 cells, Tr1 cells and, most recently, regulatory T cells (T_{REG}). There appear to be at least two types of CD4+ T_{REGS} in normal humans characterized by their surface markers CD4 and CD25 as well as intracellular expression of Fox P3, a DNA-binding transcription factor which is highly expressed in T_{REGS} (15).

Impact of Psychological Stress on Immunoregulation

Stress is best thought of as a psychophysiological process, usually experienced as a negative emotional state, which is the appraisal of situational and psychological factors. Stressors, defined as events posing threat, harm, or challenge, are judged in the context of dispositional and environmental factors and, if appraised as menacing or challenging, produce specific responses directed at reducing the stress. A common clinical observation is the adverse relationship between stress and human disease. Indeed, various sources have estimated that up to 75 percent of all visits to physicians' offices are stress-related. This appears to be particularly true in relationship to clinical conditions characterized by immune-based dysfunctions such as increased susceptibility to infections (16), allergic diseases, and asthma (17). Stress is also suspected to play a role in morbidity and mortality in other immune-based diseases such as cancer (18), HIV disease (19), inflammatory bowel diseases (20), and even immune senescence (21). Stress may also cause persistent increases in sympathetic nervous system activity, including increased blood pressure (22), heart rate, and catecholamine secretion (23) as well as platelet aggregation. This may explain, at least in part, the known association between stress, immune alterations, and cardiovascular disease (24). Although stress-induced immune dysfunctions were once thought of primarily as immunosuppressive, more recent data have suggested that immunoregulatory dysfunctions may play a more central role in stress-induced immune alterations. Thus, because of an inappropriate, rather than deficient, immune response, otherwise healthy individuals may, at times of significant stress, have increased incidence, severity and/or duration of multiple distinct conditions (25). This could be expected to significantly affect the performance, stamina, and/or durability of these individuals.

The psychological and behavioral consequences of stress may have additional, albeit indirect, effects on health by increasing incidence and/or severity of negative affects, increases in health-impairing behaviors (e.g., poor diet, lack of exercise, substance abuse), poor sleep, and decreased quality of life (26). These research studies suggest that stress-induced changes in psychological, behavioral, and/or physiological functioning can be harmful and may result in negative health consequences through both direct and indirect mechanisms. The clinical significance of these sympathetic nervous system and immune system changes must still be defined for specific patient populations. It is reasonable to conclude, however, that such stress-induced changes would adversely affect health in many individuals particularly those with underlying inflammatory diseases.

Effects of stress on immunoregulatory balance

As PNI developed, early studies suggested that stress was primarily immunosuppressive in action since the models were focused on increased susceptibility to infections and decreased vaccine responses (27). Our group and others provided evidence that stress could alter the Th1/Th2 cytokine balance with strong deviation toward the Th2 component which could not only increase susceptibility to certain infections but increase activity of various hypersensitivity diseases (28–30). More recent work is showing that stress, both acute and chronic, can alter the balance in fashions that may increase risk for (and thus susceptibility to) factually developing clinical conditions such as asthma, coronary artery disease, and/or diabetes (31).

Although there are a number of studies that report that chronic clinical stress and *in vitro* presence of stress hormones such as corticosteroids and catecholamines can significantly alter the Th1/Th2 balance, very little has been published examining the effects of psychological stress on T_{REG} expression (32). Of those studies that have been published, methodological differences make interpretation and conclusions difficult. Yet many of the inflammatory diseases reported to be adversely affected by stress have distinct Th1 or Th2 predominance as part of their pathophysiology (33). What is common to many inflammatory diseases is a defect in number and/or function of various immunoregulatory components. This indicates a significant need for more intensive studies into the effects of stress on immunoregulatory circuits in normal host as well as those with diverse inflammatory states. It is encouraging to observe that the body of work presented by others in this volume establishes beyond reasonable doubt that chronic (and in some instances acute) stress is associated with adverse health outcomes for a variety of infectious, malignant and inflammatory diseases.

Which Test Reveals Which Dysfunction for Which Illness?

As in all areas of biomedical research, PNI has an abundance of different instruments and methodologies that measure levels of stress and stress perception, anxiety, depression, anger, loneliness and other emotional states that have been validated in various research settings. Similar patterns exist for endocrine, immune and molecular effects of experimental or naturalistic stress. The data are robust and compelling *on a population* (or subpopulation) basis. However, the major limitation to clinical utility of stress research data for assessment and treatment of individual patients is the expected variability in population data. This can significantly limit the ability to identify the most stress susceptible patients for individual, customized therapeutic interventions.

A critical challenge for PNI researchers in addition to the excellent ongoing mechanism-based studies is to find stable biomarkers that will allow individuals to be assigned to various risk categories in terms of intrinsic as well as situational risk. When one considers the various pathways put forth to explain the impact of psychological stress on immune

function (34), there are multiple points along the pathways for variability – from diversity in the individual perception of a given stressor to differences in levels of stress hormone production, hormone receptor expression and density on specific immune cellular elements to disparity in numbers of immune cells, effector/regulatory ratios, cytokine receptors and cytokine levels - all of which may have differing clinical consequences.

When searching for stable biomarkers, genetic approaches are often attractive because of the relatively straightforward methodology and the relative stability of genetic biomarkers. Combining the understanding from previous PNI work, looking for specific gene expression and/or variability in well characterized stress models can offer opportunities to find stable biomarkers for stress responses. For example, gene microarrays can be useful as a screening tool to compare and contrast individual responses to the same stressor. Single nucleotide polymorphisms (SNP) are an increasingly popular approach to biomarker identification in disease associational research and can be useful in PNI studies as well. Categorizing subpopulation of research participants in terms of SNPs for stress hormone receptors, cytokine receptors, hormone and cytokine promoters may hold promise, particularly in combination.

Other approaches to identifying biomarkers include the use of surrogate markers – that is, an assay that identifies a substance that changes with stress but is not directly involved in the mechanistic pathway. An example is α amylase analyzed in the saliva as a surrogate measure of blood catecholamine levels. The amylase is produced and secreted into the saliva as blood catecholamines (epinephrine and norepinephrine) bind to their receptors on the salivary acinar cells, activating them to produce amylase (35). These potential biomarkers must have certain characteristics to have any significant clinical utility - (a) they should be a marker that will increase with specific stressful situations and decrease with effective resolution of the stressful situation; (b) they should be stable enough to be obtained at various times and clinical situations (hospital, outpatient clinic); (c) they should be reflective of a defined pathway affected by the stress – for example, serum IgE has been noted to be elevated in certain stressful situations (36). Given the knowledge that IgE increases with increased IL-4 (Th2) production and stressful situations can change the Th1/Th2 balance toward Th2 (37), it is reasonable to suggest that a clinical lab test like serum IgE could have value in assessment of the clinical impact of a life stressors on the underlying immune system of the host that could identify risk for inflammatory disease; and (d) ideally, the lab test biomarker should correlate with the intensity and duration of the stressful experience. There are other lab tests that can provide chronic information in other clinical settings – such as the Hemoglobin A1C test which correlates with overall glucose control for the previous 3 months in a diabetic patient. Such “stress susceptibility” tests could, at least in theory, be useful to assess the impact of chronic (or perhaps severe acute) stress on host immunity.

Future Directions

PNI researchers are actively responding to the call for translational research in the field in order to identify specific risk factors and develop scientifically sound rationales for interventions in specific disease states as well as to provide prophylactic stress management strategies to aid in healthy aging lifestyles. We are rapidly entering the next phase of translational studies that will further define modifiers of individual stress perceptions including cultural influences, learned behavior, socioeconomic conditions and general healthy living behaviors such as exercise regimens, body habitus, and use of various substances including alcohol, recreational psychoactive drugs and tobacco. Such modifiers must be accounted for when studying degrees of stress-induced immune dysfunction. The search for biomarkers that can identify stress susceptibility in individuals should focus on

those that correlate well with ultimate clinical outcomes thus allowing rapid assessment of specific interventional strategies in specific patient populations.

Although the modern "mainstream" western medical community has, until recently, largely minimized or even ignored the potential effects of stress as a confounder for therapeutic response or even a risk factor for immune-based inflammatory diseases, research opportunities are now abundant. Over the past decade, the field has advanced to the point where sophisticated cellular and molecular immunology techniques are being used to identify effects of stress on various components of host immunity from toll-like receptors (38) to regulatory networks involving cytokines and regulatory T cells (39).

Significant challenges face researchers striving to close the knowledge gaps that currently hinder the development of effective modes of diagnosing and developing appropriate therapies for stress-exacerbated conditions. These come from both immunological and psychological perspectives. There are known immune differences between populations based upon gender, race, age, body mass index, and even co-morbidities such as whether or not pharmaceutical agents are being taken. From a psychological perspective, an individual's *perception* of stress—rather than the specific stressor—has gained increasing importance in naturalistic research studies (40) . Duplicating such perceptions in the laboratory, especially in human studies, will be daunting.

If PNI is to advance as a meaningful discipline in clinical medicine, the above-mentioned challenges must be overcome. It is no longer tenable to utilize statistical methodology based solely on population analysis that may have a meaningful p-value, but offers little if any direct application to patients. The solution will clearly involve defining criteria, such as biomarkers, that can identify stress-susceptible *individuals* in the long term and higher-risk *subpopulations* in the short term. Such techniques must be able to identify whether stress susceptibility is permanent (genetic), temporary (environmental), or both (e.g., moderate genetic susceptibility under severe environmental conditions), as well as make clear the duration of these changes. Just as individual risk for the adverse effects are known to vary, so too can we expect individual responses to specific stress management therapies to vary in effectiveness unless/until we become more effective in our classification of individual stress risk.

Acknowledgments

Supported in part by grants 1 CPI MP061018-02, 5 R21 AT002938-02 and 1 R21 HL96086-01 from the National Institutes of Health

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