Psychoneuroimmunology

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Psychoneuroimmunology refers to the study of the interactions among behavioral, neural and endocrine, and immune functions. It is, perhaps, the most recent convergence of disciplines that has evolved to achieve a more complete understanding of adaptive processes. Until recently, the immune system was considered an independent agency of defense that protected the organism against foreign material (i.e., proteins that were not part of one's "self"). Indeed, the immune system is capable of considerable self-regulation. However, converging data from the behavioral and brain sciences now indicate that the brain plays a critical role in the regulation or modulation of immunity. This new research indicates that the nervous and immune systems, the two most complex systems that have evolved for the maintenance of homeostasis, represent an integrated mechanism for the adaptation of the individual and the species. Thus, psychoneuroimmunology emphasizes the study of the functional significance of the relationship between these systems—not in place of, but in addition to the more traditional analysis of the mechanisms governing the functions within a single system—and the significance of these interactions for health and disease.

BRAIN-IMMUNE SYSTEM INTERACTIONS

Evidence for nervous system-immne system interactions exist at several different biological levels. Primary (thymus, bone marrow) and secondary (spleen, lymph nodes, gut-associated lymphoid tissues) lymphoid organs are innervated by the sympathetic nervous system, and lymphoid cells bear receptors for many hormones and neurotransmitters. These substances, secreted by the pituitary gland, are thus able to influence lymphocyte function. Moreover, lymphocytes, themselves, can produce neuropeptide substances. Cytokines produced by macrophages and activated lymphocytes (and by cells of the central nervous system) are critical elements in the cascade of immune responses to antigenic stimulation and also serve to energize the hypothalmic-pituitary-adrenal axis. Thus, there are anatomical and neurochemical channels of communication that provide a structural foundation for the several observations of functional relationships between the nervous and immune systems. Lesions or electrical stimulation of the hypothalamus, for example, can alter antibody- and cell-mediated immune responses, and elicitation of an immune response results in an increase in the firing rate of neurons within the ventromedial hypothalamus at the time of peak antibody production. Changes in hormonal states can influence immunologic reactivity and, conversely, the immune response to antigenic challenges includes the release of cytokines which influence the neural regulation of psychophysiological processes and is also associated with changes in circulating levels of hormones and neurotransmitter substances.

STRESS AND IMMUNITY

Data suggesting a link between behavior and immune function include the experimental and clinical observations of a relationship between psychosocial factors, including "stress," and susceptibility to or progression of disease processes that involve immunologic mechanisms. There are, now, abundant data documenting an association between stressful life experiences and changes in imunologic reactivity. The death of a family member, for example, is rated highly on scales of stressful life events and, depending on gender and age, is associated with depression and an increased morbidity and mortality. Bereavement and/or depression are also associated with changes in some features of immunologic reactivity such as reduced lymphoproliferative responses (a general measure of the physiological status of T (thymus-derived) and B (bone marrow-derived) lymphocytes and impaired natural killer cell activity, lymphocytes capable of destroying cancer and virally-infected cells without having had prior contact with the foreign material. Changes in immunity are also associated with the affective responses to other "losses" such as marital separation and divorce. Other, less severe, naturally occurring stressful experiences such as taking examinations result in transient impairments in several parameters of immune function in medical students. In students that are seropositive for Epstein-Barr virus (EBV), for ex-

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ample, there are elevated EBV titers, interpreted as a poorer cellular immune response control over the latent virus, during examination than control periods. It should be emphasized, however, that the association between stressful life experiences and disease and the association between stressful life experiences and changes in immune function do not, in themselves, establish a causal link between "stress," immune function, and disease.

In animals, a variety of stressors can, under appropriate experimental circumstances, influence a variety of immune responses in a variety of species - in a variety of ways. Stressful circumstances can also alter the host's defense mechanisms allowing an otherwise inconsequential exposure to a pathogen to develop into clinical disease. Our understanding of the interactions between neuroendocrine and immune function under normal and stressful conditions, however, is incomplete. Glucocorticoids secreted by the adrenal cortex, a common endocrine feature of the stress response, are, in general, immunosuppressive and there are numerous examples of stress-induced, adrenocortically-mediated changes in immunity. However, there are numerous other observations of stress-induced changes in immunity that are independent of adrenocortical activation. It is evident from the available literature that the immunologic consequences of stressful experiences involve complex neural, endocrine, and immune response interactions. Since immune responses are, themselves, capable of altering levels of circulating hormones and neurotransmitters, these interactions probably include complex feedback and feedforward mechanisms, as well.

In sum, the direction, magnitude, and duration of stress-induced alterations of immunity are influenced by: (a) the quality and quantity of stressful stimulation; (b) the capacity of the individual to cope effectively with stressful events; (c) the quality and quantity of immunogenic stimulation; (d) the temporal relationship between stressful stimulation and immunogenic stimulation; (e) sampling times and the particular aspect of immune function chosen for measurement; (f) the experiential history of the individual and the existing social and environmental conditions upon which stressful and immunogenic stimulation are superimposed; (g) a variety of host factors such as species, strain, age, sex, and nutritional state; and (h) interactions among these several variables.

CONDITIONING

Central nervous system involvement in the modulation of immunity is dramatically illustrated by the classical (Pavovian) conditioning of the acquisition and extinction of suppressed and enhanced antibody- and cell-mediated immune responses. Using a one-trial taste aversion conditioning situation, a distinctively flavored drinking solution, the conditioned stimulus (CS), was paired with an injection of the immunosuppressive drug, cyclophosphamide, the unconditioned stimulus (UCS). When subsequently immunized with sheep red blood cells, conditioned animals reexposed to the CS showed a reduced antibody response compared to nonconditioned animals and conditioned animals that were not reexposed to the CS.

The acquisition and the extinction (elimination of the conditioned response by exposures to the CS without the UCS) of the conditioned enhancement and suppression of both antibody- and cell-mediated immune responses—and nonimmunologically specific host defense responses, as well—have now been demonstrated under a variety of experimental conditions. For example, the immunological effects of "stress" have been conditioned, and still other studies have demonstrated conditioning effects using antigen, itself, as the unconditioned stimulus. The hypothesis that conditioned alterations of immunity are merely a reflection of stress responses, notably, adrenocortical secretions, is not supported by the available data. In keeping with the bidirectional nature of nervous and immune system interactions, it is also possible to condition the physiological effects elicited by the products of an activated immune system.

The biological impact of conditioned alterations in immunity is illustrated by experiments in which conditioning operations were applied in the pharmacotherapy of spontaneously developing systemic lupus erythematosus in New Zealand mice. In conditioned animals, substituting CSs for active drug on some of the scheduled treatment days delays the onset of autoimmune disease using a cumulative amount of immunosuppressive drug that is ineffective by itself in altering the progression of disease. Similarly, reexposure to a CS previously paired with immunosuppressive drug treatment prolongs the survival of foreign tissue grafted onto mice. These dramatic results address the clinical implications of the behavioral component of research in psychoneuroimmunology, but they have yet to be experimentally verified in human subjects or patients.

Again, in keeping with the reciprocal nature of the relationship between neural and endocrine and immune responses, there are data indicating that immune status influences behavior. For example, emotional and cognitive changes are associated with lupus in human patients and there are changes in the behavior of animals that accompany the progression of their autoimmune disease.

PROSPECTS

We cannot yet describe the mechanisms underlying the functional relationships between the nervous system and the immune system illustrated by conditioned and stressor-induced modulations of immune functions. It is assumed that different conditioning and stressful experiences induce different patterns of neuroendocrine changes that define the milieu within which immunologic reactions occur. This milieu is influenced by neural and endocrine signals to the immune system and signals from the immune system that initiate further neural and endocrine changes—and by regulatory feedback loops between as well as within these "systems." An elaboration of the integrative

nature of neural, endocrine and immune processes and the mechanisms underlying behaviorally-induced alterations of immune function is likely to have important clinical and therapeutic implications that will not be fully appreciated until more is known about the extent of these interrelationships in normal and pathophysiological states.

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Floor Space Needs for Laboratory Mice: C57BL/6 Males in Solid-bottom Cages with Bedding

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INTRODUCTION

The welfare of laboratory animals remains a concern to the general public and to laboratory animal users. Furthermore, scientists hope to use animal housing systems that do not impose any unforeseen stress. Floor space is provided for laboratory animals based on concerns about animal well-being, animal performance, and economics—rather than by a rational examination of scientific data.

An examination of the scientific literature that forms the basis of current recommendations for space for laboratory mice reveals that the floor space recommendations are not based on controlled investigations. Indeed, we found a paucity of information on space needs for mice.

Many of the early studies of "crowding" in mice were conducted with the idea of studying the physiological basis of stress but not of establishing a minimum space requirement. Investigators commonly induced crowding and used a speculative control treatment that provided enough space to not cause the stress response to crowding. In other instances, many studies confounded space per animal with group size (mice per cage). For example, Christian (1955) used cages of 935.5 cm^2 to house laboratory mice in groups of 1, 4, 8, 16, and 32 and wild mice in groups of 1, 3, 4, 6, 8, 9, and 17 mice per cage. The crowding effect was composed of the confounded effects of less floor space per mouse plus the combined group-size effects that the increasing social pressures precipitated to create the experience of crowding. Many authors (Barnard and others 1994; Christian and others 1961; Gammallo and others 1986; Hull and others 1976; Jean-Faucher and others 1981; Ortiz and others 1985; Peng and others 1989) directly confounded the effects of floor space per mouse and group size in similar models to study crowding. Defining the floor space that induced the stress response was not an objective of the early work; instead, mice were added to cages until the desired response was achieved. The investigators were concerned more with the physiological mechanisms involved during crowding than in recommending a floor area that was not stressful to mice.

We know that many factors will potentially interact with the establishment of minimum floor space needs for mice and other animals. We are especially concerned about important effects of cage type, floor surface (bedded or wire), genetic line, gender, and cage changing frequency. Thus, in this study, we sought to investigate the floor space needs of mice of only 1 strain (C57BL/6) of male mice in 1 cage type (solid floor with bedding). To assess mouse welfare, we used measures of growth, survival, adrenal hormones, and immune status. We also recorded extensive video tapes so behavioral measures may be collected in the future. The specific objective of this study was to determine the growth and endocrine and immunological responses of C57BL/6

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[1]Abbreviations used in this paper: NK, natural killer; PHA, phytohemmaglutinin.