

06 - 1.6 Immune System and Central Nervous System

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1.6 Immune System and Central Nervous System Interactions Interactions between the immune system and the central nervous system (CNS) play a critical role in the maintenance of bodily homeostasis and the development of diseases, including psychiatric disease. Alterations in CNS function brought about by a variety of stressors have been shown to influence both the immune system as well as diseases that involve the immune system. Moreover, many of the relevant hormonal and neurotransmitter pathways that mediate these effects have been elucidated. Of considerable interest is accumulating data that cytokines, which derive from immune cells and microglia, have profound effects on the CNS. The relative role of cytokines and their signaling pathways in the various psychiatric diseases is an area of active investigation, as is

the role of infectious and autoimmune diseases in the pathophysiology of psychiatric disorders. Taken together, these findings highlight the importance of interdisciplinary efforts involving the neurosciences and immunology for gaining new insights into the etiology of psychiatric disorders.

OVERVIEW OF THE IMMUNE SYSTEM The immune system has the capacity to protect the body from the invasion of foreign pathogens, such as viruses, bacteria, fungi, and parasites. In addition, the immune system can detect and eliminate cells that have become neoplastically transformed. These functions are accomplished through highly specific receptors on immune cells for

molecules derived from invading organisms and a rich intercellular communication network that involves direct cell-to-cell interactions and signaling between cells of the immune system by soluble factors called cytokines. The body's absolute dependence on the efficient functioning of the immune system is illustrated by the less than 1-year survival rate of untreated infants born with severe combined immunodeficiency disease and the devastating opportunistic infections and cancers that arise during untreated acquired immunodeficiency syndrome (AIDS).

BEHAVIORAL CONDITIONING The fact that learning processes are capable of influencing immunological function is an example of interactions between the immune system and the nervous system. Several classical conditioning paradigms have been associated with suppression or enhancement of the immune response in various experimental designs. The conditioning of immunological reactivity provides further evidence that the CNS can have significant immunomodulatory effects. Some of the first evidence for immunological conditioning was derived from the serendipitous observation that animals undergoing extinction in a taste-aversion paradigm with cyclophosphamide, an immunosuppressive agent, had unexpected mortality. In that taste-aversion paradigm, animals were simultaneously exposed to an oral saccharin solution (the conditioned stimulus) and an intraperitoneal injection of cyclophosphamide (unconditioned stimulus). Because the animals experienced considerable physical discomfort from the cyclophosphamide injection, through the process of conditioning they began to associate the ill effects of cyclophosphamide with the taste of the oral saccharin solution. If given a choice, the animals avoided the saccharin solution (taste aversion). Conditioned avoidance can be eliminated or extinguished if the saccharin is repeatedly presented in the absence of cyclophosphamide. However, it was observed that animals undergoing extinction of cyclophosphamide-induced taste aversion unexpectedly died, leading to the speculation that the oral saccharin solution had a specific conditioned association with the immunosuppressive effects of cyclophosphamide. Repeated exposure to the saccharin-associated conditioned immunosuppression during extinction might explain the unexpected death of animals. To test that hypothesis researchers conditioned the animals with saccharin (conditioned stimulus) and intraperitoneal cyclophosphamide (unconditioned stimulus) and then immunized them with sheep red blood cells. At different times after immunization the conditioned animals were re-exposed to saccharin (conditioned stimulus) and examined. The conditioned animals exhibited a significant decrease in mean antibody titers to sheep red blood cells when compared to the control animals. Thus, the evidence demonstrated that immunosuppression of humoral immunity was occurring in response to the conditioned stimulus of saccharin alone.

STRESS AND THE IMMUNE RESPONSE Interest in the effects of stress on the immune system grew out of a series of animal and human studies suggesting that stressful stimuli can influence the development of immune-related disorders, including infectious diseases, cancer, and autoimmune disorders. Although stress has been historically associated with suppression of immune function, recent data indicate that such a conclusion oversimplifies the complexities of the mammalian immune response to environmental perturbation and that stress may also activate certain aspects of the

immune system, particularly the innate immune

response. Stress and Illness Experiments conducted on laboratory animals in the late 1950s and the early 1960s indicated that a wide variety of stressors—including isolation, rotation, crowding, exposure to a predator, and electric shock—increased morbidity and mortality in response to several types of tumors and infectious diseases caused by viruses and parasites. However, as research progressed it became increasingly clear that “stress” is too variegated a concept to have singular effects on immunity and that, in fact, the effects of stress on immunity depend on a number of factors. Chief among these factors is whether a stressor is acute or chronic. Other critical variables include stressor severity and type, as well as the timing of stressor application and the type of tumor or infectious agent investigated. For example, mice subjected to electric grid shock 1 to 3 days before the infection of Maloney murine sarcoma virus-induced tumor cells exhibited decreased tumor size and incidence. In contrast, mice exposed to grid shock 2 days after tumor cell injection exhibited an increase in tumor size and number. The relevance of the effects of stress on immune-related health outcomes in humans has been demonstrated in studies that have shown an association between chronic stress and increased susceptibility to the common cold, reduced antibody responses to vaccination, and delayed wound healing. In addition, stress, as well as depression, through their effects on inflammation have been linked to increased morbidity and mortality in infectious diseases, such as HIV infection, autoimmune disorders, neoplastic diseases, as well as diabetes and cardiovascular disorders, which are increasingly being recognized as diseases in which the immune system, inflammation in particular, plays a pivotal role (Fig. 1.6-1).

FIGURE 1.6-1 Inflammation and disease. IL, interleukin; TNF, tumor necrosis factor; NF-κB, nuclear factor κB; CRP, C-reactive protein. (From Cowles MK, Miller AH. Stress cytokines and depressive illness. In: Squire LR, ed. *The New Encyclopedia of Neuroscience*. Academic Press; 2009:521, with permission.) Effects of Chronic Stress When challenged with a medical illness or chronic psychological stressor, complex interactions between the immune and nervous systems promote a constellation of immune-induced behavioral changes, alternatively referred to as “sickness syndrome” or “sickness behavior.” These behavioral changes include dysphoria, anhedonia, fatigue, social withdrawal, hyperalgesia, anorexia, altered sleep-wake patterns, and cognitive dysfunction. Although seen in response to infection, the full syndrome can be reproduced in humans and laboratory animals by administration of innate immune cytokines. Blocking cytokine activity diminishes or prevents the development of sickness behavior in laboratory animals, even when such behavior develops as a result of psychological stress. Evidence that cytokine-induced behavioral toxicity is related to major depression comes in part from studies showing that in humans and laboratory animals, antidepressants are able to abolish or attenuate the development of sickness behavior in response to cytokine administration.

RELEVANCE OF IMMUNE SYSTEM-CNS INTERACTIONS TO PSYCHIATRIC DISORDERS Major Depression The neuropsychiatric disorder that has been best characterized in terms of the influence of the brain on the immune system and vice versa is major depression. For many years major depression was seen as the quintessential example of how stress-related disorders may decrease immunocompetence. More recently, however, it has become evident that stress also activates inflammatory pathways, even while suppressing measures of acquired immunity. Not surprisingly, studies now indicate that, in addition to immunosuppression, major depression is also frequently associated with inflammatory activation. Recent research showing that proinflammatory

cytokines are capable of suppressing many of the immune measures examined in major depression may provide a mechanism to account for how chronic stress-induced inflammatory activity may give rise to depression-related suppression of in vitro functional assays, such as lymphocyte proliferation. Bipolar Disorder Patients with bipolar disorder evince many of the immune alterations frequently observed in the context of unipolar depression. Several studies have observed that bipolar patients, especially when manic, demonstrate increased plasma concentrations of inflammatory cytokines. Other studies indicate that treatments for mania, such as lithium, lower plasma concentrations of a number of cytokines. Of interest, the available literature seems to suggest that patients in the manic phase of the disorder may be more likely than depressed patients to demonstrate increased inflammatory markers. It should not be surprising that mania—which seems the phenomenological opposite of depression—should be associated with increased inflammation, given that mania and depression have also been reported to show identical neuroendocrine and autonomic abnormalities, such as dexamethasone nonsuppression and increased sympathetic activity, both of which would be expected to promote inflammatory activity. Schizophrenia There has been growing interest in the idea that infectious agents, particularly viruses, may underlie at least some cases of schizophrenia. Although it is well established that viral encephalitis can present clinically as psychosis, the primary focus of the “viral hypothesis” for schizophrenia has been on infections during neurodevelopment given its congruence with the emerging consensus that prenatal or early postnatal insult is implicated in the causality of schizophrenia. Several lines of indirect evidence suggest that viral infection during CNS development may be involved in the pathogenesis of schizophrenia. The data include: (1) an excess number of patient births in the late

winter and early spring, suggesting possible exposure to viral infection in utero during the fall and winter peak of viral illnesses, (2) an association between exposure to viral epidemics in utero and the later development of schizophrenia, (3) a higher prevalence of schizophrenia in crowded urban areas, which have conditions that are particularly conducive to the transmission of viral pathogens, and (4) seroepidemiological studies indicating a higher infection rate for certain viruses in schizophrenia patients or their mothers. In addition, schizophrenia has been associated with indices of immune activation, including elevations in cytokines. Although these immune findings in patients with schizophrenia may indicate evidence of immune system activation secondary to infection, it should be noted that they might also indicate that an autoimmune process is involved in the disorder. Despite the plethora of studies pointing to abnormalities in cellular and humoral immunity in schizophrenia, the data have not been uniform or conclusive, and there is a need for more studies that account for confounding variables such as medication status and tobacco use. Moreover, attempts to isolate infectious agents from schizophrenic brain tissue or to detect viral nucleic acids in the CNS or peripheral blood of patients with schizophrenia have generally yielded negative results. Because the initial neuronal abnormalities in schizophrenia have been proposed to arise during neurodevelopment, a perinatal viral infection could insidiously disrupt development and then be cleared by the immune system prior to clinical diagnosis. In such a scenario, host factors such as cytokines could be responsible for causing the developmental abnormality by interacting with growth factors or adhesion molecules. Recent animal models have identified that maternal immune activation with resultant production of interleukin 6 (IL-6) critically affects behavioral and transcriptional changes in offspring. Behavioral changes, including deficits in prepulse inhibition and latent inhibition, are consistent with behavioral abnormalities in animal models of both schizophrenia and autism. Various animal models using influenza virus, Borna

disease virus, or lymphocytic choriomeningitis virus in rodents have demonstrated that prenatal or postnatal viral infections can lead to neuroanatomical or behavioral alterations that are somewhat reminiscent of schizophrenia in humans. As mentioned earlier, epidemiological studies also support the link between infection with a teratogenic virus and the development of psychotic disorders later in life. Associations have been observed between maternal infection with rubella or influenza during gestation and the development of a schizophrenia spectrum disorder in the offspring. Similarly, maternal antibodies to herpes simplex virus that develop during pregnancy are correlated with increased rates of psychosis during adulthood in the offspring. Non-HIV retroviruses might also play a role in the pathogenesis of schizophrenia. Retroviruses integrate into host deoxyribonucleic acid (DNA) and can disrupt the function of adjacent genes. Moreover, the genomes of all humans contain sequences of “endogenous retroviruses” that hold the capacity to alter the transcriptional regulation of host genes. If genes controlling the development or function of the brain undergo transcriptional disruption by retroviral effects, then this might lead to a cascade of biochemical abnormalities eventually giving rise to schizophrenia. Autism

Although a convincing case can be made for a significant immune component in autism, the relationship of immune abnormalities to the neurobehavioral symptoms of the disease remains controversial. The claim that autism is triggered by childhood vaccines has not been substantiated by recent epidemiological studies, and immune-based therapies for autism have not been reliably effective. Thus, although it is tempting to speculate that the immune system holds a clue to a cure for autism, there is currently not enough data to determine whether immune anomalies cause autism, are caused by autism, or are just adventitiously associated with the disease.

Alzheimer’s Disease Although Alzheimer’s disease is not considered primarily an inflammatory disease, emerging evidence indicates that the immune system may contribute to its pathogenesis. The discovery that amyloid plaques are associated with acute-phase proteins, such as complement proteins and C-reactive protein, suggests the possibility of an ongoing immune response. The idea that inflammatory processes are involved in Alzheimer’s disease has been bolstered by recent studies showing that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is negatively correlated with the development of Alzheimer’s disease.

HIV AIDS AIDS is an immunological disease associated with a variety of neurological manifestations, including dementia. HIV encephalitis results in synaptic abnormalities and loss of neurons in the limbic system, basal ganglia, and neocortex.

Multiple Sclerosis Multiple sclerosis (MS) is a demyelinating disease characterized by disseminated inflammatory lesions of white matter. Considerable progress has been made in elucidating the immunopathology of myelin destruction that occurs in MS and in the animal model for the disease, experimental allergic encephalomyelitis. Although the initial step in lesion formation has not been determined, disruption of the blood-brain barrier and infiltration of T cells, B cells, plasma cells, and macrophages appear to be associated with lesion formation.

Other Disorders Finally, several disorders are seen in which neural-immune interactions are suspected but not well documented. Chronic fatigue syndrome is an illness with a controversial etiology and pathogenesis. In addition to persistent fatigue, symptoms frequently include depression and sleep disturbances. Tests of immune function have found indications of both immune activation and immunosuppression. Neuroendocrine assessments indicate that patients with chronic fatigue syndrome may be hypocortisolemic because of impaired activation of the hypothalamic-pituitary-adrenal

axis. Although an acute viral infection frequently precedes the onset of chronic fatigue syndrome, no infectious agent has been causally associated with it. In contrast, Lyme disease, in which sleep

disturbances and depression are also common, is clearly caused by infection with the tick-borne spirochete *Borrelia burgdorferi*, which can invade the CNS and cause encephalitis and neurological symptoms. Lyme disease is remarkable because it appears to produce a spectrum of neuropsychiatric disorders, including anxiety, irritability, obsessions, compulsions, hallucinations, and cognitive deficits. Immunopathology of the CNS may be involved, because symptoms can persist or reappear even after a lengthy course of antibiotic treatment, and the spirochete is frequently difficult to isolate from the brain. Gulf War syndrome is a controversial condition with inflammatory and neuropsychiatric features. The condition has been attributed variously to combat stress, chemical weapons (e.g., cholinesterase inhibitors), infections, and vaccines. Given the impact of stress on neurochemistry and immune responses, these pathogenic mechanisms are not mutually exclusive.

THERAPEUTIC IMPLICATIONS The bidirectional nature of CNS-immune system interactions implies the therapeutic possibility that agents known to positively alter stress system activity might benefit immune functioning and, conversely, that agents that modulate immune functioning may be of potential benefit in the treatment of neuropsychiatric disturbance, especially in the context of medical illness. Increasing evidence supports both hypotheses.

Antidepressants and the Immune System Emerging data indicate that in animals and humans, antidepressants attenuate or abolish behavioral symptoms induced by inflammatory cytokine exposure. For example, pretreatment of rats with either imipramine or fluoxetine (a tricyclic antidepressant and selective serotonin reuptake inhibitor, respectively) for 5 weeks prior to endotoxin administration significantly attenuated endotoxin-induced decrements in saccharine preference (commonly accepted as a measure for anhedonia), as well as weight loss, anorexia, and reduced exploratory, locomotor, and social behavior. Similarly, several studies in humans suggest that antidepressants can ameliorate mood disturbances in the context of chronic cytokine therapies, especially if given prophylactically before cytokine exposure. For example, the selective serotonin reuptake inhibitor paroxetine significantly decreased the development of major depression in patients receiving high doses of interferon- α (IFN- α) for malignant melanoma.

Behavioral Interventions and Immunity It has been known for years that psychosocial factors can mitigate or worsen the effects of stress, not only on immune functioning but also on the long-term outcomes of medical conditions in which the immune system is known to play a role. Therefore, behavioral interventions aimed at maximizing protective psychosocial factors might be predicted to

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