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Review

Neuroimmunologic influences in neuropsychiatric and psychophysiologic disorders[1]

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ABSTRACT

Top down central nervous system (CNS) influences on the immune system and bottom up immune system influences on the CNS take part in a complex feedforward and feedback loop which may be responsible for initiating events and perpetuating circumstances in the course of neuropsychiatric as well as immune system diseases. In this paper the authors examine the neuroendocrine-neuroimmune stress response system, the concept of autoimmunoregulation, and recent studies of immune and pharmacological dysregulation in neuropsychiatric and psychosomatic illnesses. The authors review the recent English-language literature on these subjects. Support for the hypothesis that macrophages play an important role in neurodevelopment and in the pathophysiology of various neuropsychiatric conditions is found. The interplay between neurologic and immune systems may help to uncover the pathophysiologies of certain neuropsychiatric systems. This may provide new strategies for pharmacologic anti-inflammatory treatments. The monocyte/macrophage, which crosses the blood-brain barrier is an essential candidate cell in the study of psychoneuroimmunology.

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INTRODUCTION

All living organisms seek to maintain their survival in the presence of both extrinsic and intrinsic stressors. When successful, these organisms can be said to be in homeostasis — an harmonious state born of an extremely complexified equilibrium. The harmony achieved is constantly challenged often to the point of threat[1]. Survival through successful adaptation is maintained by adaptational responses balancing an huge array of biological, psychological and sociological behaviors. The broad spectrum of stimuli capable of engaging the stress-response neuroendocrine system reflects how well integrated our perceptions of the physical and psychological worlds needs to be[2]. In this context clinically significant stress can be understood as a state of disharmony or threatened homeostasis[2]. Biochemical, physiological, and behavioral concomitants of stress may co-mediate a disease response based on what is called "allostatic loading" which overwhelms allostasis-relative stability in the face of change[3].

There is now ample evidence of bi-directional communication during the stress response between the chemical messengers (neurotransmitters, neuropeptides, neurohormones, and gases) of the CNS and the chemical messengers (cytokines, gases) of the immune system[4,5]. Bidirectionality has been a stimulus for a variety of studies seeking to establish a link between the CNS and the immune system in such varied syndromes as depression, schizophrenia, autoimmune disease, and chronic fatigue syndrome.

In another example of bidirectionality mammalian glial cells, such as astrocytes and macrophage-derived microglia, mediate various CNS immune responses and also may be involved in neuronal growth and maintenance activities[6,7]. The macrophage may play a pivotal role

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in immune-nervous system bi-directional communication responding to both cytokine and neuropeptide signals. Macrophage-microglia cells thus may be important factors not only in the onset of certain neurological diseases, but also in the development of neuropsychiatric and psychosomatic disorders under certain circumstances[8].

THE STRESS RESPONSE SYSTEMS

The two major stress response components are the limbic-hypothalamic-pituitary-adrenal (HPA) axis including the corticotrophin-releasing hormone (CRH) system with neurons projecting from lateral paraventricular nuclei (PVN) and the sympathetic nervous system (SNS) with norepinephrine (NE) containing catecholaminergic fibres arising in the locus coeruleus (LC) in the brainstem. There is evidence of commonality of effect and communication between the PVN-CRH and LC-NE systems.

It has been postulated that immune activation may cause an increase in HPA axis output. Glucocorticoid elevations frequently are seen during immune responses and interleukin-1 (IL-1) release may be responsible for this HPA hyper-responsivity[9]. IL-1 is known to increase CRH and ACTH release and to stimulate adrenal steroid production[10,11]. IL-1 may also stimulate noradrenergic and serotonergic turnover in the midst of an immune response, and this may in turn excite the CRH-PVN system[12,13]. Maes *et al* speculate that CRH-PVN hyperactivity related to IL-1 may cause a feedback inhibition on monocyte cytokine-induced immune functioning[14]. There is also an immunoendocrine interaction during stress when immunocytes produce ACTH from propiomelanocortin (POMC) in a quantity sufficient to produce hypercortisolism[15].

An intricate association of the stress systems with areas of the brain integral to emotional tone and behavior and to cognition and planning exists[2]. Stress activates limbic system structures including the amygdala and hippocampus. The LC-NE SNS stimulation of the amygdala is important for the recovery of affect-laden information and its emotional analysis. Stress hormones released during emotional periods stimulate the basolateral nucleus of the amygdala (BLA) resulting in memory consolidation of the associated events. This effect involves activation of β-adrenoreceptors in the BLA modulating long term potentiation memory processes in the hippocampus through stria terminalis efferents[16]. In the context of an emotional stress the amygdala is important for the activation in turn of the PVN-CRH and LC-NE systems. The hippocampus performs an inhibitory function, dampening amygdala activity and the PVN-CRH system. The function of corticotropin-receptors in the hippocampus and their regulation during stress serves as another link[17].

Stress linked hypersecretion of glucocorticoids as occurs in subtypes of major depressive disorder can even lead to overt neuronal loss in the hippocampus[18]. We now know that neurogenesis does take place in human hippocampus[19]. Hippocampal cell growth appears to benefit from an enriched environment low in stress[20,21]. Antidepressants and electroconvulsive therapy also increase neurogenesis in rat models[22]. Hippocampal glucorticoid receptor disruption may serve as a site of HPA axis feedback dysregulation in depression[23].

The mesolimbic dopamine system, with a key role played by the nucleus accumbens, is thought to be integral to the interaction between emotional motivation and movement (via the mesostriatal system), and in reinforcement and reward[24]. The activity of the stress systems, which is under mesolimbic control, is meant to be a temporary acute phenomenon in relation to a threat to homeostasis. The typical catabolic and immunosuppressant effects of PVN-CRH and LC-NE activation confers survival advantage under conditions of challenge or threat[2]. However, if this physiology persists in a protracted dysregulated fashion, there will be consequences in the form of disease. Prolonged and elevated CRH production as a result of limbic hypothalamic overdrive may explain the pathogenesis of this common stress syndrome.

NEUROIMMUNE MODULATION

In terms of the immune system, CRH secretion stimulates ACTH which stimulates glucocorticoid release with effects on inflammatory processes mediated by cytokines such as IL-1, interleukin-6 (IL-6), and tumor necrosing factor (TNF), which themselves modulate immunocyte behavior and function, and feedback to the hypothalamus and pituitary[1,25]. CRH will also, as a part of arcuate POMC-stimulation, promote the release of ACTH and α-MSH along with β-endorphin, which have also been shown to have direct modulatory effects on immunocyte behavior and function[26].

Thus the CNS can help regulate the immune system in a number of ways[27]. Physical and emotional stress, circadian rhythms, and environmental stimuli will be perceived and appraised in the thalamo-limbic and thalamocortical circuits influenced by the brainstem. The

mesocortical-mesolimbic systems and the extended amygdala-hippocampal complex will have reciprocal connections with each other and with the CRH-PVN and NE-LC[2].

It is of interest that Licinio and his colleagues at NIMH have proposed that CRH may also affect disease susceptibility by promoting the production of POMC transcription factors which may then bind to contingent intracellular targets such as a viral genome thus predisposing to infection; an oncogene thus predisposing to neoplasm; or an inflammatory mediator gene thus predisposing to an inflammatory disease[28].

The CNS also modulates the immune system through the other arm of the stress system — the sympathetic nervous system. Catecholamines released at autonomic nerve terminals and from the adrenal medulla can result in leukocytosis, lymphopenia via sequestration and natural killer cell deactivation[29]. It should be noted that adrenal cortical glucocorticoids also contribute to stress-induced changes in blood leukocyte distribution involving increases in numbers and percentages of neutrophils and decreases in numbers and percentages of lymphocytes[30]. Sympathetic nerves are plentiful in important immune system organs such as lymph nodes, thymus, spleen, bone morrow, intestinal Peyer's patches, and thoracic duct[31,32].

Opioid neuropeptides such as β-endorphin or met-enkephalin have overall stimulatory effects on immune cell activity[33]. Opiate alkaloids such as morphine, unlike opioid neuropeptides, inactivate human monocytes and granulocytes[34]. Immunomodulation of cellular activation has been shown to be mediated directly by nitric oxide (NO) release. This NO release is triggered when morphine stimulates a novel μ_3 opiate alkaloid specific, opioid neuropeptide non-reactive receptor located on the surface of macrophages, granulocytes, endothelial cells, Kupffer cells and invertebrate and mammalian microglia[33]. The question of a functional relationship between the immune system and endogenous opiates can be raised in light of the demonstration of the latter material in the circulation[35].

The presence of opiate alkaloids in the circulation and of special opiate receptors on immunocytes, enables these compounds to participate directly in inhibiting autoimmunoregulatory activities. An indirect pathway for the suppression of immune processes by morphine can also be postulated, occurring via the HPA axis[36,37]. In this case immunosuppression may be initiated by a stimulatory signal from morphine, furnished in the brain, to CRH-producing neurons of the hypothalamus. This concept is supported by the immunocytochemical demonstration of a morphine-like compound in the rat hypothalamus[38].

The direct and indirect downregulating activities attributable to endogenous morphine should be considered in the context of other chemical mediators known to act in the same capacity. One of these inhibitory molecules is the cytokine IL-10, which is released by macrophages to counteract excessive immuno-stimulation caused by other cytokines[39]. Another inhibitory signal-molecule produced by immunocytes is ACTH which, like IL-10, participates in autoimmunoregulatory activities[26].

Under what circumstances would the immunosuppressive activity of endogenous morphine be called into action? Stimulatory signals need to be stopped as soon as they are no longer required, in order to prepare the organism for a subsequent challenge. Also as we have seen, a prolonged excessive immune response can be pathogenic. An endogenous opiate would seem to be an appropriate candidate to complete compensatory immunosuppression. For example, during major surgical interventions, the immunsuppressive effect of ACTH and IL-10 produced by immunocytes may not suffice to lower the hyperstimulation of granulocytes and macrophages attributable to their release of IL-1 and TNF due to this trauma. Under these circumstances, morphine may be called on to downregulate the process in order to restore the normal level of activity[40]. The validity of this proposal is supported by tests carried out with blood samples taken from patients during cardiopulmonary bypass (CPB) operations. In preparations exposed to morphine, signs of cellular activity were less pronounced than in untreated samples[32].

The results of another experiment in an invertebrate are indicative of the down regulating capacity of endogenous morphine under conditions of stress. The sequence of activities generated by subjecting the mollusk *Mytilus* to stressful interventions (electrical shock and prevention of valve movements) was studied[41]. The immediate stress response was activation of the animal's defense system, as judged by conformational changes in its immunocytes, and interpreted to emerge upon the release of endogenous opioids and additional stimulatory molecules. When the state of alertness had subsided 24 h later the return of the immunoactive hemocytes to a more "inactive" conformation was found to concur with a temporary but significant rise in the opiate content of nervous tissue and

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hemolymph[40,41]. The immunocyte conformation at this time resembled that of unstressed animals exposed to exogenous morphine.

Comparable studies in vertebrates have shown an increase in morphine concentration in the spinal cord of rats suffering from chronic pain elicited by experimental arthritis[42]. The same was true for animals subjected to prolonged food deprivation in which the morphine content of brains was higher than in controls.

These studies of various traumatic situations suggest that in the hierarchy of available downregulating mechanisms, morphine operates as a strong backup system. The observations that this secondary system goes into effect after a latency period during which endogenous opiate levels rise, is in line with the fact that the μ_3 opiate receptor has an affinity constant in the range of 1 mmol/L.

From an evolutionary viewpoint, having a network of immunostimulatory agents has provided great survival value for vertebrates and invertebrates alike. The need for the operation of more than one immunosuppressive mechanism is obvious. One of endogenous morphine's important tasks may be to meet this vital demand. An immunologic balance is essential if health is to be maintained.

THE CONCEPT OF IMMUNOLOGIC DISSONANCE

Recently Bone wrote an exceptional review article examining the potential etiologies for the "systemic inflammatory response syndrome" (SIRS) and the "multiple organ dysfunction syndrome" (MODS). Today MODS affect about 40 % of the critically ill and it is the major cause of intensive care unit mortality[42]. There are five stages in the development of MODS. In Stage 1, stimulatory immunomodulators are released at the site of local injury or infection in order to promote wound healing and to fight foreign antigens. If the patient is healthy and the initial threat is small, homeostasis will be quickly restored when inhibitory immunomodulators are released to downregulate the inflammatory response. In Stage 2, local mechanisms are insufficient resulting in the need for the release of stimulatory immunodulators into the systemic circulation. This leads to the recruitment of more immune cells to the local site. These will follow the systemic release of inhibitory immunomodulators which will restore homeostasis by reducing the inflammatory response. In Stage 3, there is a huge outpouring of stimulatory immunomodulators into the systemic circulation or there is an insufficient systemic release of inhibitory immunomodulators which will restore homeostasis by reducing the inflammatory response. Downregulation is therefore unsuccessful setting the stage for patients to experience the symptoms of SIRS (hypotension, temperature abnormalities, tachycardia, endothelial disruption leading to transudation, ischemia, intravascular coagulation, vasodilatation, and shock) and perhaps the first signs of MODS. In Stage 4, excessive concentrations in the systemic circulation of inhibitory immunomodulators are produced in response to the huge outpouring of stimulatory molecules in Stage 3 or without provocation. These patients will develop "compensatory anti-inflammatory response syndrome" or CARS in which they will become immuno-suppressed hosts prone to infection. Patient survival in Stage 3 or 4 depends on whether immunologic balance and homeostasis can be restored. In Stage 5, the patient has reached the advanced level of MODS. This is the stage of "immunologic dissonance." There is no balance between stimulatory and inhibitory immunomodulators. While some patients suffer from overwhelming persistent inflammation, others suffer from ongoing immunosuppression and recurrent infections. There are even some patients who experience an oscillation between stages of inflammation and immunosuppression.

Stimulatory immunomodulators include macrophage products such as TNF, IL-1, IL-6, and IL-8; neutrophils and their products; lymphocytes and their products, platelets and their surface coagulation factors; and mast cells and their products among many others. Inhibitory immunomodulators include IL-4, IL-10, IL-11; soluble TNF receptors; IL-1 receptor antagonists (IL-1ra), transforming growth factors and others not yet described. Endogenous opiates may in this context be an important inhibitory immunomodulator in the prevention of SIRS and MODS.

Adult respiratory distress syndrome (ARDS) is an example of SIRS. There is recent evidence that low concentrations of the anti-inflammatory cytokines IL-10 and IL-1ra obtained early on from the bronchoalveolar lavage fluid of ARDS patients are well correlated with more severe eventual organ damage and worse prognosis[43]. It has also been suggested that ARDS is actually a disorder produced when an alarm reaction (a severe stress response) in the CNS is engendered in the context of trauma provoking endothelial dysfunction and hypercoagulation in cerebral microvessels particularly in and around the

hypothalamus leading to microthrombotic hypoxic cell damage. This may result in the secondary development of a systemic immune system imbalance based on a stress response system fixated in an abnormal state[44]. In an effort to test the CNS origin of ARDS, deOliveira and colleagues pretreated Wistar rats, about to be traumatized into an ARDS-like state, with neurodepressant agents such as morphine, pentobarbital, haloperidol, diazepam, and chlorpromazine. All of these agents provided some protection against the subsequent development of ARDS from a peripheral scald burn and from an anterior hypothalamic electrolytic lesion. The authors suggest that early on, the ICU patient, at risk for ARDS, might benefit from the institution of what they call a "prophylactic pharmacological hibernation." This may produce a desirable CNS metabolic and electrical depression reducing the likelihood of inappropriately heightened and persistent CNS stress responses that unless checked, might kindle a SIRS and a MODS.

Endogenous opiates might be important natural "prophylactic pharmacological hibernation" agents that can contribute to an anti-flammatory response both indirectly through actions at the level of the hypothalamus and directly through inhibitory immunomodulator effects on immune cell surfaces mediated by μ_3 receptors.

There is evidence that morphine and other opiates exist endogenously in the mammalian enzymatic systems for the conversion of thebaine to codeine to morphine. Recently Bianchi *et al* detected codeine-and morphine like substances in mammalian brain by immunocytochemistry[38]. They reported the presence of these compounds inside the cell bodies, fibers and terminals of neurons in certain brain areas of the cortex, limbic system, hypothalamus, and mid-brain that are known to be rich in mu receptor concentration. It is thought that endogenous morphine is stored in the brain as a conjugate compound called the 3-ethereal sulfate which has high intrinsic activity for mu-receptors[32]. Neurons in the brain areas where morphine and codeine were localizable were able to store and accumulate tritiated morphine infused into the cerebral ventricles[38]. The implication of these findings is that endogenous codeine and morphine may play significant roles as intrinsic ligands for brain mu receptors[38,37].

Future research into whether immunologic dissonance is partly related to defects in an endogenous opiate system would appear to be warranted. We have recently postulated that endogenous morphine, through a naloxone antagonizable and constituitive nitric oxide synthase (cNOS) mediated process, can perform a general physiological downregulating function. In the immune system, morphine, by stimulating intracellular calcium transients, can activate cNOS, increase NO, stabilize the IκBα inhibitor complex associated with NF-κB thereby decreasing its binding with the DNA promotor region responsible for proinflammatory cytokine production[45]. Proinflammatory cytokines play an important role in inducing the bradykinin B1 receptor ($B\kappa B_1$). Glucocorticoid (GC) reduction of inflammation induced upregulation of $B\kappa B_1$ occurs at least partly because GCs can directly inhibit activated NF-κB. GCs can also increase transcription and expression of IκBα in some cells[46].

THE NEUROENDOCRINE-NEUROIMMUNE STRESS RESPONSE SYSTEM

Depending on the sensitivity of the stress response systems, a hypo- or a hyper-immune state might be expected as an outcome. If a hypersensitive stress response system initiated by CRH is postulated in melancholic depression, then we might expect to see a reduction in some measures of immune function, and there is some evidence of this[1]. In a hyposensitive stress system, as has now been suggested in such disorders as chronic fatigue syndrome, there might be a hyperimmune outcome[47].

Chrousos and Gold discuss an animal model of autoimmune inflammatory disease, the Lewis rat. There is a generalized CRH neuron gene defect in Lewis rats making them CRH hyporesponsive not only to inflammatory stimuli but also to biochemical and environmental triggers as well[48]. These rats, therefore, show the behavioral hypoarousal and hyperimmune syndromal profile consistent with decreased CRH synthesis and release leading to defective counterregulation, and autoimmune inflammatory phenomena[1].

Evans and his colleagues suggest an interesting disease causal model in which biological and environmental factors may result in psychiatric illness or mood disorders in relation to endocrine dysregulation which in turn mediates immune system changes that could then have clinical prognostic significance in development or persistence of physical illness[49].

Research in neuroimmunology has also focused on possible immune mediated causes of psychiatric disorder as well as on possible immune system exacerbation of psychiatric distress.

The top down scenario incorporates the fact that in-

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teroceptive experiential appraisal by the mind taking place in the mesocortical-mesolimbic brain will modulate the hypothalamic-pituitary-adrenal axis as well as the autonomic nervous system, both sympathetic and parasympathetic. Internal and external events perceived as stressful will be transmitted through these stress response systems to viscera and muscle. Outcome in the periphery will provide "somatic markers" of the experience which in turn become integrated as descriptors of it[30].

An end organ in the periphery that receives top down input is the immune system[27]. The monocyte-macrophage is a key constituent of the immune cascade and a prime recipient of stress related information. The monocyte-macrophage initiates the quick non-specific cell mediated response as well as the delayed specific humoral response[11]. Stress hormones will have an impact on macrophage (Mϕ) function. For example, glucocorticoids (GC), adreno-corticotrophic hormone (ACTH) and, melanocyte stimulating hormone (MSH) tend to inhibit Mϕ function while opioid neuropeptides tend to stimulate them.

When the Mϕ sets in motion the acute phase response (APR), there are often central nervous system consequences to pay. In the APR a wide array of insults, including infection, ischemia, trauma, endotoxin, burn, malignancy, inflammation and even strenuous exercise and agitation, engage the immune system in a cascade of events for the purpose of destroying foreign agents, removing damaged tissues, and repairing organ damage. It is now known that cytokines can deliver messages to important brain regions producing fever and behavioral effects. Cytokines affect vagal paraganglia receptors resulting in nucleus tractus solitarious changes which then produce neurobehavioral effects[31]. There is also a likelihood that cytokines and secondary endothelial products such as nitric oxide are traversing the blood-brain barrier through fenestrated endothelium in circumventricular regions of the brain including the median eminence, sub-fornical organ, organism vasculosum, and pineal gland. Under certain conditions, immune cells may themselves attach to endothelium and extravasate into the brain undergoing diapedesis[32]. Both local and distal affects in the important limbic medial temporal lobe area may ensue.

Encephalopathies, related for example, to infectious, inflammatory, hypoxic-ischemic, or traumatic etiologies for an APR may be macrophage-mediated, leading to the final common pathway of secondary psychiatric brain syndromes. In some cases, these secondary brain syndromes will be acute (eg, postcardiotomy delirium) and in others, they will be chronic (eg, AIDS Dementia, Alzheimer's). The latter conditions may be related to the persistence of the APR precipitant. Thus, we would hypothesize that for AIDS Dementia, a neurotrophic virus causes persistent chronic Mϕ activity that is irreversibly pathogenic and for Alzheimer's, an irritant in the CNS (eg, β-amyloid protein) causes persistent chronic Mϕ activity that is also irreversibly pathogenic. For delirium, a temporary insult causes time-limited acute macrophage activity that is reversibly pathogenic; for schizophrenia, a genetic and/or viral insult during vulnerable periods of neurodevelopment destabilizes Mϕ effects on histogenesis and cytoarchitecture, thus creating a vulnerability to the schizophrenic syndrome, which may be activated by future APRs that are macrophage-mediated and lead to cytokine-neurotransmitter interactions; and for depression, an aberrant, timelimited APR might lead to Mϕ cytokine effects on CRH and the HPA axis, which would contribute to the hypersensitive stress response system associated with depression[6].

New pharmacological research may provide benefit in Mϕ driven neuropsychiatric disorders. For example, lignan phytoestrogens and novel synthetic dithiolane analogs of lignans have been shown to inhibit interferon-γ and lipopolysaccharide induced nitric oxide production in macrophages[33].

NEUROIMMUNOLOGY RESEARCH

We will briefly review recent neuroimmunology research efforts in depression, schizophrenia, autoimmune disorders, cancer, and chronic fatigue syndrome.

Neuroimmunology and depression — research findings Several studies have reported that patients hospitalized for a major depression (MDD) have diminished lymphocyte response to mitogen as compared to normal non-depression controls[34]. Schleifer *et al* found significantly decreased mitogen responses in drug free major depressive hospitalized patients compared with controls[35]. They found no differences between controls and ambulatory major depressive subjects. In a follow-up study of 91 hospitalized and ambulatory MDD patients and 91 matched controls, no significant overall differences on any immune measures were found, although data suggested that, with increasing age, patients with MDD have a decrease in T4 cell number and decreased lymphocyte proliferation in response to mitogen[36]. Also, an effect on the Hamilton Depression (Ham-D) scale score

was seen. The higher the score indicating increased severity of depression, the lower the mitogen response. Hospitalized MDD patients had lower T4 cell counts than outpatients did[59]. The authors postulate an association between the diagnostic entity of depression and an age-dependent change in mitogen activity, perhaps related to changes T-helper cell subpopulation. Older age and increased severity have also been associated with increased probability of an altered neuroendocrine axis[60]. In another example of interaction, Maes *et al* (1993) found statistically significant positive correlations between IL-1β production and post dexamethasone suppression test-DST cortisol levels in depressed as well as normal subjects, suggesting that cortisol non suppression in depression is positively correlated with enhanced IL-1β activity[57]. While they acknowledge that a common mechanism such as psychological stress may produce HPA hyperactivity as well as IL-1β enhancement, they seem to prefer the explanation that proposes an increase in HPA axis activity secondary to cytokine stimulation. This is because of IL-1's stimulating effect on the HPA axis which we discussed earlier[12].

Other studies have focused on natural killer (NK) cell activity. Reduced NK number in hospitalized MDD patients compared with other psychiatric patients has been found[58]. Total lymphocyte number was also reduced in MDD patients. Irwin and colleagues reported reduced NK cell activity in MDD psychiatric inpatients compared to normal controls[59]. Studies of T-cell subpopulations in MDD patients have yielded mixed results. Evans and colleagues have looked at the effect of MDD on NK cell phenotype and activity[60]. They found that in depressed men, but not depressed women there were significant reductions in CD16NK effector cells and NK cell activity.

These results, suggesting an association of depression with immunosuppression, may not be surprising if we keep in mind the stress response systems effects as described by Chrousos and Gold (1992). Indeed there is evidence that CRH suppression of NK activity is dissociated from the pituitary-adrenal axis since CRH reduces NK activity even when P-A axis effects are significantly antagonized[61].

The finding by Nemeroff and his colleagues, revealing computerized tomographic evidence of adrenal hypertrophy in 12 out of 38 patients with MDD, is concordant with the idea that chronic CRH hypersecretion occurs in MDD[62]. There is also now evidence to suggest that HPA axis and autonomic hyperactivity, perhaps related to CRH hypersecretion, is a long term sequela of childhood abuse[63]. This might lower the threshold for psychopathological states like depression.

To summarize, there is considerable evidence suggesting that depression is associated with altered immunity. Leukocytosis, accounted for by increased numbers of monocytes and neutrophils, has been found; however, it is not a consistently seen finding[64]. An alteration in NK cell activity (NKCA), although not a universal phenomenon, appears to be perhaps the most reproducible finding[65]. Although alterations in function have not been consistent, the bulk of studies also show decreased mitogen-stimulated responses. Many cytokine changes in depression have been noted, and include increased interleukin secretion and increased soluble interleukin-2 receptor levels in serum[66,67]. However, many studies show an inconsistency in results, which may have a number of possible causes.

Firstly, a range of confounding variables (sleep, hospitalization, gender, stress, nutrition, alcohol, age, smoking, and family history), some difficult to control for, can affect findings. Secondly, methodologic concerns, including sample size, control group composition and variability in immunologic assays have limited the interpretation of some studies[66,67]. Thirdly, the spectrum of depressive illness may comprise a variety of biologically distinct populations (such as melancholic, psychotic, endogenous subtypes). Fourthly, an alternative explanation could account for the apparent inconsistencies in results of studies on depression. The general understanding is that depression results in a state of immunosuppression. This was prompted and supported by the fact that cortisol, levels of which are raised in many depressives, is the most potent endogenous immunosuppressant in man[17]. A revisionist theory proposes that depression causes an overall increase, not decrease, in immune response. However, multiple feedback effects secondary to this lead to self regulatory inhibition. It is detection of this inhibition which leads to the findings of simultaneous activation and suppression of the immune system[68].

Neuroimmunology and chronic fatigue syndrome (CFS) — research findings CFS features pathological fatigue, with at least four of the following: memory problems, sore throat, tender lymphadenopathy, myalgia, arthralgia, headaches, unrefreshing sleep, and post exercise myalgia, in the absence of medical, alcohol/substance abuse, or psychiatric causes[69]. A sizeable proportion of patients with CFS have concurrent de-

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pression[69]. As well as sharing some symptomatology with depressed patients, many CFS sufferers also show similar altered parameters of immune function. Specifically, decreased NKCA and decreased mitogen induced proliferation are often observed[70].

However, important differences exist. Raised antibody levels to a wide variety of viruses, and circulating antibody complexes, are often reported[71]. Unlike in depression, there can be seen hypothalamic underproduction of CRH and consequent decreases in urinary free cortisol and plasma glucocorticoids have been found[68]. The expansion of a population of activated CD8 + cytotoxic T lymphocytes is another immunological difference[70]. Komaroff and colleagues have found abnormal single photon emission tomography in CFS (and not depression) with reduced cortical perfusion and/or neuronal activity resulting in a moth-eaten appearance which may be related to abnormal immune functioning[72].

Many theories have been advanced to explain the association between CFS and immune system dysfunction. CFS has been viewed as a persistent and inappropriate immune response, or a result of persisting cytokine activity. Support for a cytokine theory includes the finding of symptoms of fatigue, fever and myalgia following high dose interleukin 2 (IL-2) administration[73]. Dysfunction of the HPA axis, possibly at or above the level of the hypothalamus, has also been proposed[74]. A possible unifying theory suggests that an individual may have immunological perturbations compounded by stress which in conjunction with an external insult such as a viral infection, lead to a prolonged illness and chronic immune activation[75].

Neuroimmunology and schizophrenia — research findings A number of hypotheses link schizophrenia and the immune system. Autoimmunity has been proposed as an etiological mechanism for the disease. Direct evidence (in the form of specific antibodies) has not been found; the levels of antibody could be too low to easily detect[76]. Indirect evidence of autoimmune disease as a cause includes the frequently reported findings of decreased IL-2 and increased serum interleukin 2 receptors (SIL-2Rs)[77]. Various autoantibodies have been reported, eg, to smooth muscle, thyroglobulin, and parietal cells[78]. Further evidence includes over two dozen studies showing antibrain antibodies in the sera of schizophrenic patients; conversely, at least six studies have shown no such antibodies, and also such antibodies have been shown in healthy controls. Varying results could be explained if the autoimmune hypothesis applies only to a subgroup of patients[79]. Viral theories have pointed towards the involvement of various viral agents in the disease, including herpetic, retro, and slow viruses[80]. However, no "schizovirus" has been identified. HLA theories have attempted to link schizophrenia with specific immunologic markers. The most consistent reported finding is an association between schizophrenia and HLA-A9 though an association with other HLA markers, eg, HLA DR6, has also been seen[79].

The macrophage-T-lymphocyte theory proposes that chronic Mφ activation, with resultant T cell over secretion of IL-2 and SIL-2Rs, may contribute to schizophrenia[81].

Neuroimmunology and autoimmune — disease findings Recent research has sought to define the relationship between the nervous and immune systems and autoimmune diseases. The contributory role of stress in these illnesses is becoming more apparent. Graves' disease may be precipitated by stress in susceptible individuals[82]. Stress factors are important contributors to the etiology and maintenance of rheumatoid arthritis, particularly sero-negative disease[83]. Ulcerative colitis sufferers who experience more recent life events show increased mucosal damage, even if clinically asymptomatic[84].

Inflammatory bowel disease has traditionally been viewed as a "psychosomatic" illness, with psychological factors, eg, personality and interactive style, contributing to the disease process[85]. This theory had fallen out of favor, however, recent discoveries have brought the role of higher central nervous system control back into focus. The lymphoid cells of the intestinal mucosae are regulated by the neuropeptides of the enteric nervous system, principally substance P, vasoactive intestinal protein (VIP) and somatostatin[86]. Extrinsic nerves serving the gastrointestinal tract connect the enteric nervous system to the central nervous system CNS through sympathetic and parasympathetic pathways[87]. Thus, it is through these pathways that psychological factors may result in causation and propagation of inflammatory bowel disease[88].

SUMMARY

In this paper we have reviewed how the nervous system and immune system are linked in bi-directional neuroimmunologic communication. A major role in this regulatory linkage is played by the stress response systems. This is supplemented by more localized autoimmunoregulations. Pharmacologic approaches to immu-

nologic dissonance will grow out of more intensive research into these regulatory mechanisms and the interrelationship of the stress response and the immune response. For example, the phenolic antioxidant subidatum has shown immunosuppressive effects in mice through effects on phagocytic cells[39]. The macrophage is a candidate cell for investigation given its central role both in bidirectional neuroimmune regulatory feedback as well as in autoimmunoregulation. Immune system modulation is of key importance in our understanding of many neuropsychiatric and psychophysiologic conditions.

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神经免疫对神经精神性和心理生理性紊乱的影响[1]

关键词 精神神经免疫学；精神病学；心理生理学；应激；神经免疫调节；细胞因子类

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