



MIND AND BODY

Psychoneuroimmunology — mind-brain-immune interactions

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Psychoneuroimmunology (PNI) is the study of interactions between psychological, neuroendocrine and immune processes under basal, disease and therapeutic conditions. It expands the understanding of disease, recognising that psychological phenomena and social context can influence the aetiology and progression of and recovery from illness. While debate continues regarding the way in which intangible mental processes and identifiable physiological ones interact, there can be little argument that these psychological processes require an evolved nervous system, with certain neural networks — identified through imaging studies and neurological disease affecting the mind — related to mental and emotional functions.¹

The extension of the mind/brain relationship to include the immune system is predicated on the presence of multiple neuropeptides and their receptors in cells of the immune system, where they are produced and expressed *de novo* with high sequence homology to their neuroendocrine relatives, as well as structural links between lymphoid organs and noradrenergic and peptidergic nerve fibres.² Furthermore many immunopeptides and their receptors are produced *de novo* in discrete regions of the brain, most specifically the limbic-hypothalamic axis, where they may exert a neuromodulatory effect.² The functionality of the immune-brain-behavioural pathway has been well described during the acute phase or sickness response. The acute behavioural and physiological changes that regularly accompany infectious illness include, for example, fever, depression, social withdrawal, increased desire for sleep, decreased interest in food and perceptual changes. As part of the immune response to infection, interleukin-1 (IL-1) acts on IL-1 receptors in the vagus nerve and in the brain to mediate such sickness behaviours.³

The neuroendocrine and immune systems share a common molecular language which serves to integrate the two systems

primarily involved in systemic homeostasis, providing a network of communication between 'mind', brain and body. Because the central nervous system (CNS) and immune systems are central to homeostasis, it is implicit that functional neuroendocrine-immune interactions are constantly established. Further, changes in immunity often give rise to disease, implying that the immune system, and by extension the psychoneuroimmune network, operates at a diffuse border between physiological and pathophysiological processes. This forms a basis on which psychosocial phenomena and interventions may influence disease, immunity and health.

Psychoimmune interaction

The earliest objective evidence suggesting that processes of the mind may influence immune function was demonstrated through classical conditioning. Using a taste aversion paradigm researchers were able to demonstrate modification of both non-specific immune responses and antibody production by pairing saccharin-flavoured water with an injection of cyclophosphamide. Conditioned animals that were re-exposed to the sweetened water after one pairing with the immunosuppressive chemotherapeutic agent showed an attenuated antibody response reflecting conditioned immunosuppression. Moreover, in susceptible animals, behaviourally conditioned immunosuppression modified the development of autoimmune disease (murine lupus) such that the rate of development of proteinuria and mortality were significantly retarded in conditioned mice relative to untreated controls and unconditioned animals.⁴

Of generally greater significance in humans is the extensive literature linking emotions, psychosocial stress and immune function. Negative mood adversely affects immune markers that, directly or indirectly, may contribute to poorer health. For example, in healthy women, those reporting negative mood had lower levels of circulating natural killer (NK) cell activity than those who had no negative mood, while in a group of newlywed couples, those who exhibited more hostile behaviours during a 30-minute discussion of marital problems showed a greater decrease in NK cell activity and proliferative responses of T lymphocytes. Highly negative subjects also had higher antibody titres to latent Epstein-Barr virus than low-negativity individuals.⁵

Significantly, therapeutic emotional expression has been

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shown to affect immune function as well as chronic diseases associated with immune system dysfunction. For example, college students writing about traumatic events for 20 minutes for 3 or 4 consecutive days, demonstrated higher mitogen-induced lymphocyte proliferative responses and developed significantly higher antibody levels against various hepatitis B antigens following vaccination compared with controls who wrote about mundane topics.⁶ In a randomised trial, Smyth and colleagues⁷ have shown that patients with asthma or rheumatoid arthritis (RA), writing about the most stressful events in their lives for 20 minutes a day for 3 consecutive days, had clinically improved health changes 4 months later compared with a control group who wrote descriptively about mundane topics. Of patients evaluated after treatment, asthma patients in the experimental group showed significant improvements in lung function 4 months after the intervention as measured by forced expiratory volume in 1 second (FEV₁) (63.9% versus 76.3%) whereas controls showed no change, while RA patients showed improvement in overall disease (28%) at 4 months compared with controls, as assessed by a rheumatologist.

A well-cited study of women with metastatic breast cancer by Spiegel and colleagues⁸ described a year-long intervention, consisting of weekly supportive group therapy for the interventional group (in addition to standard oncological care) with an emphasis on emotional expression and support between group members. At 10-year follow-up, survival from time of randomisation and onset of intervention was double that of the control group (36 months versus 18 months). Similar structured interventions by Cunningham and colleagues⁹ failed to replicate these results; however those patients who become involved in trying to help themselves do much better than medically expected, with the effects of this minority of motivated individuals being lost when group medians are calculated.

The pervasive human experience of stress provides a fruitful arena for elucidating psychoneuroimmune interactions. Stress may be understood as a threat (real, implied or perceived) to homeostasis, and the integrated, multisystem mechanisms needed to maintain a stable internal milieu in the face of the perturbation. The stress response, while adaptive in the short term, can be deleterious when activated chronically, particularly in the face of psychological stressors where demands exceed the individual's capacity to cope. Under conditions of chronic stress, an inefficient inactivation of stress-induced molecules results in cellular overexposure to these substances, which over time, has pathophysiological consequences.¹⁰

While the relationship between psychosocial stress and immunity in humans is well recognised, the complex and individualised perceptual processes make quantification of this relationship difficult.¹⁰ However certain models have been described offering greater validation of this interaction. The

most broadly described short-term naturalistic stressor has been the effect of academic stress (writing examinations) on immune function in medical students, with changes correlated to health-related self-report data. The data suggest that examination stress results in significant suppression of various parameters including both cellular and humoral immune cell effectiveness and cytokine/receptor production.⁶

Chronic stressors, including both major life events and the 'wear and tear' of daily living, are generally more important determinants of disease risk than are acutely stressful events. The impact of long-term care of patients with Alzheimer's disease (AD) has been utilised as a reproducible model of chronic psychosocial stress, given the progressive decline associated with the disease and the increasing need for supportive care over an extended period. Longitudinal data suggest that caring for a family member with AD is associated with downregulation of the immune response, which was still apparent 3 years after the death of the AD patient. For example, caregivers showed poorer antibody and virus-specific T-cell responses following vaccination with the influenza virus and demonstrated lower levels of *in vitro* virus-specific-induced IL-1 and IL-2 compared with matched controls.⁶ In another study, wound healing from a punch biopsy took significantly longer in caregivers than controls.⁶ An association between stress-induced immune dysregulation and progression to immune-related illness in humans is not invariable. However, certain groups — such as the elderly, or those with pre-existing immune suppression — are recognised to have greater health-associated vulnerability and may manifest the greatest clinical consequences related to stress.^{6,10} Notwithstanding these subgroups, direct evidence also exists for the potential for stress-associated immune modulation to precipitate infectious disease in the general population, where in healthy subjects, psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness following standardised intranasal inoculation.¹¹

Significantly, one of the most effective buffers to psychological stress-induced immune suppression and/or infection is the presence of social support.⁶

Conclusion

The identification of functional physiological pathways between the neuroendocrine and immune systems and the models of research examining the manner in which psychological states influence and interact with immunity provide the foundation on which this field continues to evolve.⁶ Moreover, the molecular biological mechanisms underpinning neuroendocrine-immune interactions are equally applicable to other physiological systems, thereby expanding the potential clinical ambit implicit in the PNI model to diseases of the



cardiovascular, gastrointestinal and dermatological systems. While the growing body of evidence of mind and body interactions is reaching acceptance within mainstream medicine, the debate as to whether the therapeutic corollary of these data — whether psychosocial interventions can improve clinical outcomes in organic disease — continues, with equally vociferous voices at both ends of the spectrum.⁶ Psychosocial interventions also offer a means to modify unhealthy lifestyle behaviours (such as smoking, poor nutrition and lack of exercise) which themselves influence illness.¹⁰ Furthermore, the participation of patients in treatment and validation of their subjective experience, particularly in the face of chronic illness, will enhance quality of life and offer comfort in the face of distress, a therapeutically desirable situation whether or not the intervention influences disease outcome.

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