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Psychoneuroimmunology – Cross-talk between the immune and nervous systems

■ **Abstract** Psychoneuroimmunology is a relatively new field of study that investigates interactions between behaviour and the immune system, mediated by the endocrine and nervous systems. The immune and central nervous system (CNS)

maintain extensive communication. On the one hand, the brain modulates the immune system by hardwiring sympathetic and parasympathetic nerves (autonomic nervous system) to lymphoid organs. On the other hand, neuroendocrine hormones such as corticotrophin-releasing hormone or substance P regulate cytokine balance. Vice versa, the immune system modulates brain activity including sleep and body temperature. Based on a close functional and anatomical link, the immune and nervous systems act in a highly reciprocal manner. From fever to

stress, the influence of one system on the other has evolved in an intricate manner to help sense danger and to mount an appropriate adaptive response. Over recent decades, reasonable evidence has emerged that these brain-to-immune interactions are highly modulated by psychological factors which influence immunity and immune system-mediated disease.

■ **Key words** psychoneuroimmunology · autonomic nervous system · neuroendocrinology · stress · behavioural intervention

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Introduction

Psychoneuroimmunology (PNI) is the scientific field of study investigating the link between bidirectional communications among the nervous system, the endocrine and immune system as well as the implications of these linkages for physical and mental health, thereby focussing on the measurable interaction between psychological and physiological processes. The CNS and the immune system are the two major adaptive entities of the body. Although the immune system has often been regarded as autonomous, the last two to three decades have provided strong evidence that the CNS receives messages from the immune system [10]. Vice versa there is substantial evidence for a brain-derived information outflow to the immune system [3, 18].

Thus, the brain and the immune system are involved in functionally relevant cross-talk, with homeostasis being the main function. These two systems communicate

through intricate chemical messengers that are able to breach their independent and often sequestered anatomical locations. The CNS is without ‘classical’ lymphatic drainage, meaning that in some ways it is devoid of the immune surveillance that is available for the rest of the body. In health there are mechanisms to exclude poten-

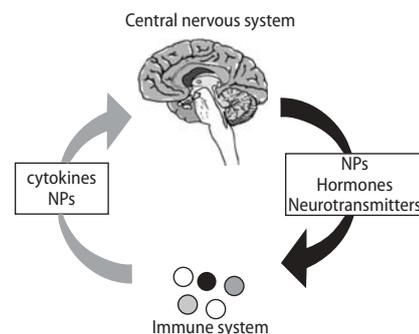


Fig. 1 Reciprocal relationship between the CNS and immune system

tially destructive lymphoid cells from the brain, spinal cord and peripheral nerves. However, multiple anatomic and physiological connections exist between the CNS and the immune system, including 'hardwiring' of the autonomic nervous system. Multiple chemical messengers, ranging from small molecules such as nitric oxide to neuroendocrine peptides such as corticotrophin-releasing hormone (CRH) to large proteins including cytokines and growth factors and their respective receptors, also tie these systems together. Thus, these two elaborate systems relevant for sensing danger and mounting a counterattack to these threats are inextricably linked.

Historical review

Neuroscience and immunology developed independently for many years. Thus, the question how the brain communicates with the immune system remained enigmatic until comparatively recently. In the 1970s and the 1980s, due to the pioneering work of Hugo Besedovsky and co-workers, it became clear that classic hormones and newly described cytokines are involved in functionally relevant cross-talk between the brain and the immune system [3–5]. They have shown that an immune response induces an increase of plasma corticosteroid levels [5], alters the activity of hypothalamic noradrenergic neurones [2], and drops the content of norepinephrine in the spleen [3]. Also in the 1970s, the first hormone receptor on lymphocytes was described functionally, when it was reported that adrenergic agents modulate lymphocyte proliferation [15]. In the 1970s and 1980s, the first comprehensive morphological studies provided evidence that both primary and secondary lymphoid organs are innervated by sympathetic/noradrenergic nerve fibres [22]. Furthermore, altered immune function has been induced by classical behavioural conditioning, by stressful stimuli, or by lesions in specific regions of the brain [1, 9]. Finally, evidence was obtained in experimental animals that the susceptibility to autoimmune diseases is modulated by the activity of the stress system and that stress mediators may exert both pro- and anti-inflammatory effects [18, 23]. Thus,

in the last two decades we witnessed the explosive growth of a new interdisciplinary research area that studies the neuroimmune communication (Table 1).

Pathway links: the autonomic nervous system and the neuroendocrine axis

Two major pathways link the brain and the immune systems: the autonomic nervous system (ANS) via direct neural influences, and the neuroendocrine humoral outflow via the pituitary gland.

The ANS regulates the function of all innervated tissues and organs throughout the vertebrate body with the exception of skeletal muscle fibres. Thus, it forms the major efferent component of the peripheral nervous system, containing integrative neuronal connections and even complete reflex arcs. The ANS is largely autonomous in that its activities are not under direct conscious control. The ANS consists of three components: the sympathetic (noradrenergic) and parasympathetic (cholinergic) systems, which originate in the CNS (with cell bodies in the brainstem and spinal cord), and the enteric system, which lies within the wall of the gastrointestinal tract.

There is evidence for rich neural connections with lymphoid tissue [22]. Receptors for various neurotransmitters beyond acetylcholine and norepinephrine are also present on lymphocytes. Whereas the parasympathetic neurotransmitter acetylcholine potently modulates several classical immune reactions via the vagus nerve, the sympathetic nervous system can alter the TH1/TH2 balance through stimulation of the beta-adrenergic receptor for example [13].

The hypothalamic-pituitary-adrenal axis (HPA axis) comprises the neuroendocrine system that controls reactions to stress and has important functions in regulating various body processes such as digestion, the immune system and energy mobilisation [8, 20]. Species from humans to the most ancient organisms share components of the HPA axis. The key element of the HPA axis is the hypothalamus, which contains parvocellular and magnocellular neurones that synthesise and secrete

Table 1 Besedovsky's criteria for neuroimmune interaction

- Hormones and neurotransmitters must modify immune-related events.
- Immunological cells must express receptors for hormones and neurotransmitters.
- Immune function must be altered by manipulation of endocrine and CNS functions.
- A dynamic immune-neuroendocrine relationship must exist, such that
 - (a) fluctuations in neuroendocrine function should result in immune changes, and conversely,
 - (b) fluctuations in immune activity should result in neuroendocrine changes.
- Neural alterations following immune activation must be mediated by chemical messengers produced by activated cells of the immune system.
- Neuroendocrine signals should feedback to alter immune function shortly after immunological activation.
- There should be changes in the neuronal activity of integrative sites within the brain (e. g. hypothalamus), reflecting reception and processing of signals from activated immune system.

vasopressin and CRH. These two peptides regulate the anterior lobe of the pituitary gland. In particular, CRH and vasopressin stimulate the secretion of adrenocorticotrophic hormone (ACTH). ACTH, when released from the pituitary gland, in turn acts on the adrenal cortices, which produce glucocorticoid hormones (mainly cortisol in humans). Glucocorticoids in turn act back at the hypothalamus and pituitary in an inhibitory fashion (negative feedback) [16].

Inflammation – pain pathways and the immune system

The intimate relationship between neural pathways that mediate pain and the immune regulation of inflammation are extensive. Sensory nerves, especially those mediating pain reflexes, are afferent nerves connecting the peripheral organs such as skin to the spinal cord. These nerves, conveying the sensation of pain, are stimulated by tryptase produced in mast cells. Mast cells are mobile lymphoid cells that act as sentinels of immune brain interactions. They pack secretory granules filled with neurotransmitters, such as histamine, and enzymes, such as tryptase, which can directly activate sensory neural fibres. Activation of these nerves as part of the pain reflex stimulates the release of both calcitonine-gene related peptide (CGRP) and substance P from C-type sensory nerve fibres in both peripheral tissues and spinal cord. Neural release of CGRP and substance P also causes oedema and widespread inflammation in the skin [6, 21]. Tryptase triggers this nerve-mediated inflammatory response, involving CGRP and substance P, through proteinase activated receptor 2 in dorsal root ganglion neurones. These dorsal root ganglia just outside the spinal cord contain the cell bodies for the sensory neurones in the skin [6, 21].

Stress – cross-talk between CNS and immune system

The systemic sympathetic nervous system (SNS) and the HPA axis are the peripheral limbs of the stress system, whose main function is to maintain both basal and stress-related homeostasis. At rest, catecholamines (CAs) maintain homeostasis as major regulators of fuel metabolism, heart rate, blood vessel tone, and thermogenesis. When homeostasis is disturbed or threatened by internal or external challenges, both the SNS and HPA axis become activated, resulting in increased peripheral levels of CAs and glucocorticoids that act in concert to keep the steady state of the internal milieu. Any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor, i. e., under certain conditions an immune response can activate the stress sys-

tem (long feedback loop between the immune system and the brain) to prevent an overshoot or self-destructive reaction of the immune system (Table 1).

Almost all immune cells have receptors for one or more of the hormones that are associated with the HPA axis and the ANS [22]. Immune modulation by these hormones might proceed through two pathways: directly, through binding of the hormone to its cognate receptor at the surface of a cell; or indirectly – for example, by inducing dysregulation of the production of certain cytokines. Cytokines such as interferon- γ have many functions and affect different target cells. Therefore, there are secondary effects of many stress hormones on the immune response. Moreover, communication between the CNS and the immune system is bidirectional. For example, interleukin 1 influences the production of CRH by the hypothalamus [12]. In turn, CRH can affect the HPA axis and thereby trigger increases in stress hormone levels, which result in suppression of immune function [18]. In addition, lymphocytes can synthesise hormones such as ACTH, prolactin and growth hormone [23]. Furthermore, studies proving the existence of nerve fibres reaching the spleen and the thymus provide evidence of direct connections or ‘hard-wiring’ between the SNS and lymphoid organs.

Therefore, there are many pathways through which stressors might influence immune function. Most recently, there has been a trend toward a focus on immune system-to-brain communication and the question on how the activation of inflammatory-cytokine networks might shape mood, cognition and behaviour [17].

Translation of psychoneuroimmunology into the clinical field

Psychoneuroimmunological research has demonstrated that immune regulatory mechanisms are part of a complex network of adaptive responses. This new knowledge of interactions between the brain and the immune system holds considerable promise for expanding our understanding of the mechanisms underlying health and illness, and the role emotions and stress play in this equation. Thus, one focus of psychoneuroimmunological research concerns stress-related immune impairment in humans and the clinical significance of psychosocially induced changes in immune function. Affective instances which are perceived stressful in nature are accompanied by autonomic and neuroendocrine changes capable of influencing immune function and thus probably susceptibility to a variety of diseases [7]. Conversely, behavioural interventions that reduce anxiety or distress decrease the intensity or duration of neuroendocrine responses [14], thereby effecting a change in immune function that promotes wellness and recovery from disease [11].

Given the complexity of feedback and forward mechanisms within and between the immune and nervous systems, it is unreasonable to expect that psychosocial circumstances alone could perturb the immune system to an extent that exceeds homeostatic limits. Therefore, when we speak of the role of stress in susceptibility to disease, we are in almost all cases speaking of effects on the expression or progression of disease, not on the induction or cause of disease. The best way to adapt this model is to include the consideration and exploitation of several classes of variables such as vulnerable or at-risk populations, individual differences, qualitative and quantitative dimensions of stressful life experiences and immunogenic challenges and, as a common denominator, outcome measures that are biologically relevant to specific disease processes. Individuals with genetic predisposition to particular diseases like autoimmune diseases and individuals currently in remission from chronic disease also constitute these vulnerable populations in which

one can investigate the effect of psychosocial factors on the progression, recurrence and exacerbation of existing disease rather than the development of new disease.

Clinical significance of behavioural interventions

Many different kinds of behavioural interventions are more or less effective in improving mood, quality of life, health behaviour and in altering neuroendocrine and immune functions [19]. However, the question remains as to whether these latter effects are sufficiently large or last long enough to contribute to one's health status, or if they are even relevant to the development of a specific disease. Unfortunately, we have not yet reached the stage where the selection of a behavioural intervention is based on its ability to change those parameters of physiological function that are relevant to the progression of specific disease processes.

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