Biochemical and Biophysical Research Communications 370 (2008) 531–535

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

On the mechanisms and putative pathways involving neuroimmune interactions

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ARTICLE INFO

Article history:
Received 1 April 2008
Available online 14 April 2008

Keywords:
Brain
CNS
Cytokine
HPA
Inflammation
Neuroimmunology
Neuropeptide
Neurotransmitters

ABSTRACT

Bidirectional interdependence between the immune system and the CNS involves the intervention of common cofactors. Cytokines are endogenous to the brain, endocrine and immune systems. These shared ligands are used as a chemical language for communication. Such interaction suggests an immunoregulatory role for the brain, and a sensory function for the immune system. Interplay between the immune, nervous and endocrine systems is associated with effects of stress on immunity. Cytokines are thus capable of modulating responses in the CNS, while neuropeptides can exert their effects over cellular groups in the immune system. One way is controlled by the HPA axis, a coordinator of neuroimmune interactions that is essential to unravel in order to elucidate vital communications in a manner that this crosstalk remains a cornerstone in perpetuating a stance of homeostasis.

Neuroimmune interactions, pathways and putative mechanisms

Burgeoning research has shown that the immune, nervous and endocrine systems are tightly linked via specialized, homeostatic pathways [1]. This platform is bolstered by evidence that nervous system output can modulate immune function [2].

Neuroimmune interactions are not unidirectional. This bidirectional influence ensures that the immune system can affect the nervous system [1,2]. Anomalies of immune function can cause diseases of, or relating to, the nervous system. Effective defense mechanisms require a complex coordination of the activities of the nervous and immune systems, and abnormalities in the relationships between the two of them can instigate pathophysiologic aberrations [3].

Classically, the brain has been regarded as an 'immunologically' privileged site [1,4]. This evasion of systemic immunological recognition confers a privilege property that is so unique and, in many ways, plays a major role in shaping the grounds for neuroimmune interactions. The nervous system, in fact, has a number of attributes that influence local immune responses, hence the 'bidirectional' effect canopy [1,2].

Neuroimmune interactions can be summarized as follows: (i) alterations in immune responses can be conditioned and regulated; (ii) electrical stimulation or lesions of specific brain sites can modulate immune functions; (iii) stress (and the HPA axis) affects immune responses and infections in experimental and physiological models; and (iv) activation of the immune system is correlated with altered neurophysiological, neurochemical and neuroendocrine activities of brain tissue [5].

The relationship between the nervous and immune systems

Immune signaling and activation crosswalks are communicated to the nervous system via specific pathways [1]. This essentially occurs through the release of peripheral soluble factors (cytokines) by cells of the immune system (lymphoid vs. myeloid), and cells of non-immune origin. These factors function as hormones or modifiers to modulate the responses of the CNS; they can affect the CNS directly by crossing the BBB or indirectly by stimulating the vagus nerve.

Bidirectional influence: immune system effects on the nervous system

Cytokines can influence the electrophysiological function of neurons; this is evident during the ensuing of inflammation in the CNS or PNS [1,2]. Chemokines resemble a family of proteins associated

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0006-291X/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2008.04.012

with the emigration of leukocytes in physiological immune surveillance and inflammatory cell recruitment in normal host defense mechanisms. Chemokines also play an integral role in the CNS. They are constitutively expressed by microglial cells (or macrophages of the brain), astrocytes and neurons, and their expression can be induced by inflammatory mediators. Chemokines can also modulate neuronal signaling via the regulation of the flow of Ca^{2+} [6].

Immunologically active molecules can affect voltage-dependent and transmitter receptor-operated ion currents of peripheral/central neurons [1]. Cytokines can influence cognitive processes, for example, and thus modify central neurotransmission and the function of PNS. In addition, cytokines and neuropeptides secreted by peripheral immune cells may have effects on behavioral aspects of the CNS. Pro-inflammatory cytokines, furthermore, can activate the HPA axis and may induce sickness behavior during the inflammatory acute phase response [1–5].

Nervous system components associated with and/or affected by immune responses

Neurons can counter-regulate brain immunity in the CNS. For example, microglia are kept in a quiescent state by interactions between the microglia receptor cluster of designation (CD)200 and its ligand, which is inducibly expressed on neurons [7]. Furthermore, neurons can downregulate MHC expression in glial cells. Certain chemokines are also associated with the surface of neurons (e.g., fractalkine is bound to the outside of neurons in the dorsal horn of the spinal cord). Microglia, moreover, are shown to express fractalkine receptors (CX3CR1). When spinal cord dorsal horn neurons are activated by pain producing stimuli, for instance, they release fractalkine, which binds to the microglial receptors and stimulates the microglia, causing the release of cytokines [1]. This seems to be a vital mechanism in the generation of chronic pain [8,9].

Glia can form an innate immune system offshoot, within the 'immune privileged' CNS, which has the potential to initiate immune responses to exogenous antigens or endogenous degenerative processes [7]. Oligodendrocytes (CNS) and Schwann cells (PNS) are sensitive to injurious and/or pharmacologically active agents including antibodies, complements and cytokines. Astrocytes, on the other hand, affect neuronal function by the release of neurotrophic factors, guide neuronal development physiologically, contribute to the metabolism of neurotransmitters, and regulate extracellular pH and K^+ currents. The astrocyte, specifically, is an immunocompetent cell in the CNS. The reason is that these cells can express MHC class II and co-stimulatory molecules that are critical for antigen presentation and subsequent T cell activation [1].

Nervous system influence on the immune system––unidirectional or bidirectional effect?

Converging evidence has demonstrated that the immune system is not regulated in an autonomous fashion, but is influenced by external factors particularly mediated by the nervous system. What are the major connecting mechanisms mediating neuroimmune interactions? There are at least three putative pathways: (i) ANS route via direct nerve fiber connections; (ii) sensory portion of the nervous system via primary afferent nerve fibers; and (iii) neuroendocrine output via the HPA axis. In particular, neural control in immunological phases range from induction and activation to effector functions and inactivation zones [1–6,10].

Influence of hypothalamic/pituitary neuroendocrine hormones on the immune system

The pituitary gland is essential in the regulation of immune system development and activity. Following surgical removal, Gisler and Schenkel-Hulliger [11] observed reduced antibody responses; growth hormone (GH) treatment restored antibody production. These observations implicate neuroendocrine hormones in immune regulation [1].

Adrenocorticotrophic hormone (ACTH)

ACTH stimulates the adrenal glands to release glucocorticoid hormones. These hormones are anti-inflammatory in nature, reduce edema, and influence other aspects of inflammation. Synthetically produced glucocorticoids, which can be directly administered without the use of ACTH, are potent, cause less Na^+ retention and less K^+ loss, and are longer-acting than ACTH [1–5].

Gonadal steroids

Several lines of evidence implicate sex steroids in immune regulation [12] and in the regulation of neuronal gene expression [1,8]. In general, androgens exert suppressive effects on humoral and cellular-mediated immune responses, and seem to represent natural anti-inflammatory hormones; in contrast, estrogens exert immuno-enhancing activities, at least on humoral responses [1].

Immunological surveillance of the nervous system by lymphocytes

Studies on the migration of T cells have shown that activated lymphocytes of rather myriad specificity enter the normal CNS parenchyma [13]. T cell traffic in the CNS appears to be governed by the same principle as applies to other organs, namely that activated cells preferentially migrate from the blood into tissues, whereas resting cells exit in lymph node high-endothelial venules (HEVs) [1–5]. T cells are consistently demonstrable in the brain, indicating that the CNS is patrolled by activated lymphocytes.

Conditioning of the immune response

Compelling evidence for the influence of the nervous system on the immune system arises from studies that indicate that behavioral conditioning can modify immune responses. A study [14] indicated that after the immunosuppressive drug, cyclophosphamide, had been paired with the taste of saccharin, subsequent ingestion of saccharin prevented the production of antibodies in response to sheep red blood cells (SRBC). Conditioning, therefore, can alter immune responses, but the immunological specificity of the effects is not clear, and the mechanisms are yet to be unraveled. It is possible that at least some of the immunosuppressive effects are from a conditioning of hormone and neurotransmitter secretion [1–5].

Effects of brain lesions on immune function

Although it is indicated that brain lesions may have effect on immunity, consistent coherence is, at best, fragmented, incomplete and complex. Effective lesions are most commonly located in the hypothalamus and are generally inhibitory. Lesions in other limbic areas may also be effective, notably in the septum, hippocampus and amygdala. Some studies have indicated that cortical lesions can affect immune responses and that the effects depend upon the laterality of the lesion [1].

There is evidence that lesions of the left cortex, but not the right, can produce pronounced immune deficits in spleen cell number, lymphocyte proliferation, and NK cell activity [15]. The lateral specificity indicates that the aforementioned observation cannot be from nonspecific effects of the lesion, and it could account for the greater number of left-handed individuals who exhibit diseases of the immune system. Lesions of the central noradrenergic systems have also been shown to impair aspects of the immune response [1].