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Neural–immune interactions: An integrative view of the bidirectional relationship between the brain and immune systems

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Abstract

This review briefly summarizes a part of the relevant knowledge base of neuroimmunology, with particular emphasis on bidirectional neural–immune interactions. These complex systems interact at multiple levels. Both neuroendocrine (the primary hormonal pathway is hypothalamic–pituitary–adrenal axis) and neuronal (direct sympathetic innervation of the lymphoid organs) pathways are involved in the control of the humoral and cellular immune responses. Although, the recent evidence has been made on immunosuppressive effect of acetylcholine-secreting neurons of the parasympathetic nervous system. The immune system, in turn, influences the central nervous system primarily through cytokines. At the molecular level, neuro- and immune signal molecules (hormones, neurotransmitters, neuropeptides, cytokines) or their receptors are member of the same superfamily which enable the mutual neuroimmune communication. Most extensively studied are cytokine-neuropeptide/neurotransmitter interactions and the subcellular and molecular mechanisms of these interactions. At the system (neuroanatomical) level, advances in neural–immune communication have been made in the role of discrete brain areas related to emotionality. The immunoenhancement, including the antiviral and antitumor cytotoxic activity, related to the "brain reward system", limbic structures and neocortex, offers a new directions for therapy in immune disorders.

Keywords: Neuroimmune modulation; Brain structures; Immune response; Lesion; Stimulation

1. Introduction

Over the past 20 years, the functional autonomy of both the immune and central nervous systems has been successfully challenged. Advances in the field of neuroimmunology and more recently in psychoneuroimmunology have shown that the central nervous system (CNS) and the immune system are intimately linked and do not function as independent systems (Felten et al., 1987; Blalock, 1989; Madden and Felten, 1995; Jiang et al., 1998; Dantzer, 2004). The CNS can have widespread effects on the immune system following activation of the hypothalamic–pituitary–adrenal (HPA) axis (Berczi, 1986; Berczi and Nagy, 1991; Haddad et al., 2002) and the sympathetic nervous system (SNS) (Hori et al., 1995; Madden et al., 1995; Madden, 2003). Glucocorticoids released from the adrenal cortex have many important effects on metabolism but also have potent anti-inflammatory and immunosuppressive effects (Munck and Guyre, 1991; Auphan et al., 1995; Meier, 1996; Barnes, 1998; Sternberg, 2001; Webster et al., 2002). Activation of SNS can occur during the classic fight-or-flight response (Stoddard et al., 1986a,b) and results in the release of catecholamines from the adrenal medulla and sympathetic nerve terminals. The effects of catecholamines are mediated through adrenoceptors and result in a wide range of physiological changes that best serve an animal in the face of imminent danger. However, lymphocytes and other cells of the immune system also express adrenoceptors (Fuchs et al., 1986; Madden et al., 1995; Sanders, 1998; Tayebati et al., 2000; Dong et al., 2003) and may, therefore, be influenced by circulating catecholamines. The SNS may also affect more specific aspects of the

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immune system, since lymphoid tissues are innervated with noradrenergic postganglionic sympathetic fibers that are very closely associated with lymphoid cells and may even form synaptic connections with individual lymphocytes (Felten and Olschowka, 1987; Stevens-Felten and Bellinger, 1997; Elenkov et al., 2000). The presence of such a close association between sympathetic nerve fibers and cells of the immune system could provide a direct mechanism enabling the CNS to regulate specific aspects of the immune response. Thus, it appears that the CNS can communicate with the immune system in a general sense via endocrine outflow from the CNS (i.e., hypothalamically or pituitary controlled hormones such as corticotropine (CRH), adrenocorticotropine (ACTH), glucocorticoids to the periphery (Munck and Guyre, 1991) but also more directly by means of sympathetic innervation of both primary and secondary lymphoid organs (Shimizu et al., 1994). Although, recent evidence shows an important role of the parasympathetic cholinergic pathway in the bidirectional communication between the brain and the immune system (Tracey, 2002; Pavlov et al., 2003; Saeed et al., 2005; Zimring et al., 2005). The immune system, in turn, may communicate with CNS through immune products, primarily cytokines leading to the direct CNS activation (Berkenbosch et al., 1987; Sapolsky et al., 1987) or to release of CNS-derived cytokines. Recent findings (Rivest, 2003) indicate that CNS responds to systemic bacterial infection with innate immune reaction without pathogen's direct access to the brain. In addition, immunocytes synthetize and secrete hormones, neurotransmitters and neuropeptides, similar to those released from the CNS, which react with common immune and central nervous systems receptors.

2. The nervous system communication with the immune system

2.1. The endocrine and autonomic system routes

Both endocrine and autonomic (primarily sympathetic) system routes allow biologically active molecules (hormones, neurotransmitters, neuropeptides, and cytokines), which constitute the largest groups of chemical messengers in the brain to interact with lymphocytes and their associates (macrophages, epithelial cells, dendritic cells) via specific receptors on immunocompetentent cells. T- and B-lymphocytes, monocytes/macrophages, NK cells, and granulocytes possess adrenoceptors (Fuchs et al., 1986; Felten et al., 1987; Madden et al., 1995; Dong et al., 2003) for the hormones, neurotransmitters, and neuropeptides including epinephrine (E), norepinephrine (NE), dopamine (DA), histamine, acetylocholin (Ach), substance P (SP), prostaglandins, somotostatin (SOM), vasoactive intestinal peptide (VIP), prolactin (PRL), growth hormone (GH), corticosterone, testosterone, CRF, ACTH, and endogenous opioids (Bellinger et al., 1997; Basu and Dasgupta, 2000; Dorshkind and Horseman, 2000). The interaction between neuroendocrine factors and their receptors on immunocompetentent cells could alter cellular activity through the activation of a variety of second messengers including cAMP and cGMP (Murgo et al., 1986). Alternatively, neuroendocrine factors may modulate immune response indirectly by affecting the production of lymphokines and monokines (DeRijk and Berkenbosch, 1991).

2.1.1. Noradrenergic pathway: catecholamines (NE, E)

In response to sympathetic stimulation, NE is released from noradrenergic sympathetic nerve fibers of the spleen (Shimizu et al., 1994; Madden, 2003), allowing for paracrine effects. Altering catecholamine levels, either by stimulation with NE or other catecholamines, or by denervation may result in altered immune function (Ackerman et al., 1991). Rice et al. (2002) demonstrated that chemical sympathectomy increases the percentages of neutrophils in the spleen and the number of peritoneal macrophages in mice. Recent studies of Bellinger et al. (2005) demonstrate that, although noradrenergic innervation in the Fischer 344 rat spleen is diminished with the age, sympathetic signaling of the immune system remains intact and SNS can inhibit antibody produced in response to a protein antigen in both young and old animals.

The catecholamines NE and E have been implicated as important efferent immune modulators following exposure to stressors. Catecholamines can enhance (Madden and Livnat, 1991; Schedlowski et al., 1993; Benschop et al., 1996; Dhabhar and Mc Ewen, 1999; Kohm and Sanders, 1999) or suppress (Koff et al., 1986; Cunnick et al., 1990; Dobbs et al., 1993) a range of immune cell activities, including cell proliferation, cytokine and antibody production, lytic activity and migration. For instance, E and NE interacts with β-adrenoceptors on lymphoid organs and increases numbers of leukocytes (Madden and Livnat, 1991; Schedlowski et al., 1993; Madden et al., 1994; Benschop et al., 1996) and enhance the expression of cell-surface differentiation antigens (Singh, 1985). Also, E is reported to inhibit complement activation and macrophage-mediated lysis of tumor or herpes simplex virus infected cells (Koff and Dunnegan, 1986). Moreover, Gan et al. (2002) demonstrated that NE-induced inhibition of NK cytotoxicity is manifested at multiple levels, including a modification of NK cell receptor ligation to target cells, blockade of NK cytokine secretion necessary for NK maturation and differentiation, and inhibition of the target-induced activation of the cytotoxic mechanism(s) in NK cells. The authors concluded that sympathetic activation may profoundly impair natural cellular immunity through varied measurable pathways. The data of Dokur et al. (2004) suggest that NE and beta-adrenergic agonists may inhibit NKCC activity by regulating the production of perforin, granzyme B, and IFN-γ in splenocytes. The crucial role played by central and peripheral catecholamines in modulating immune function was also supported by Pacheco-Lopez et al. (2003) who